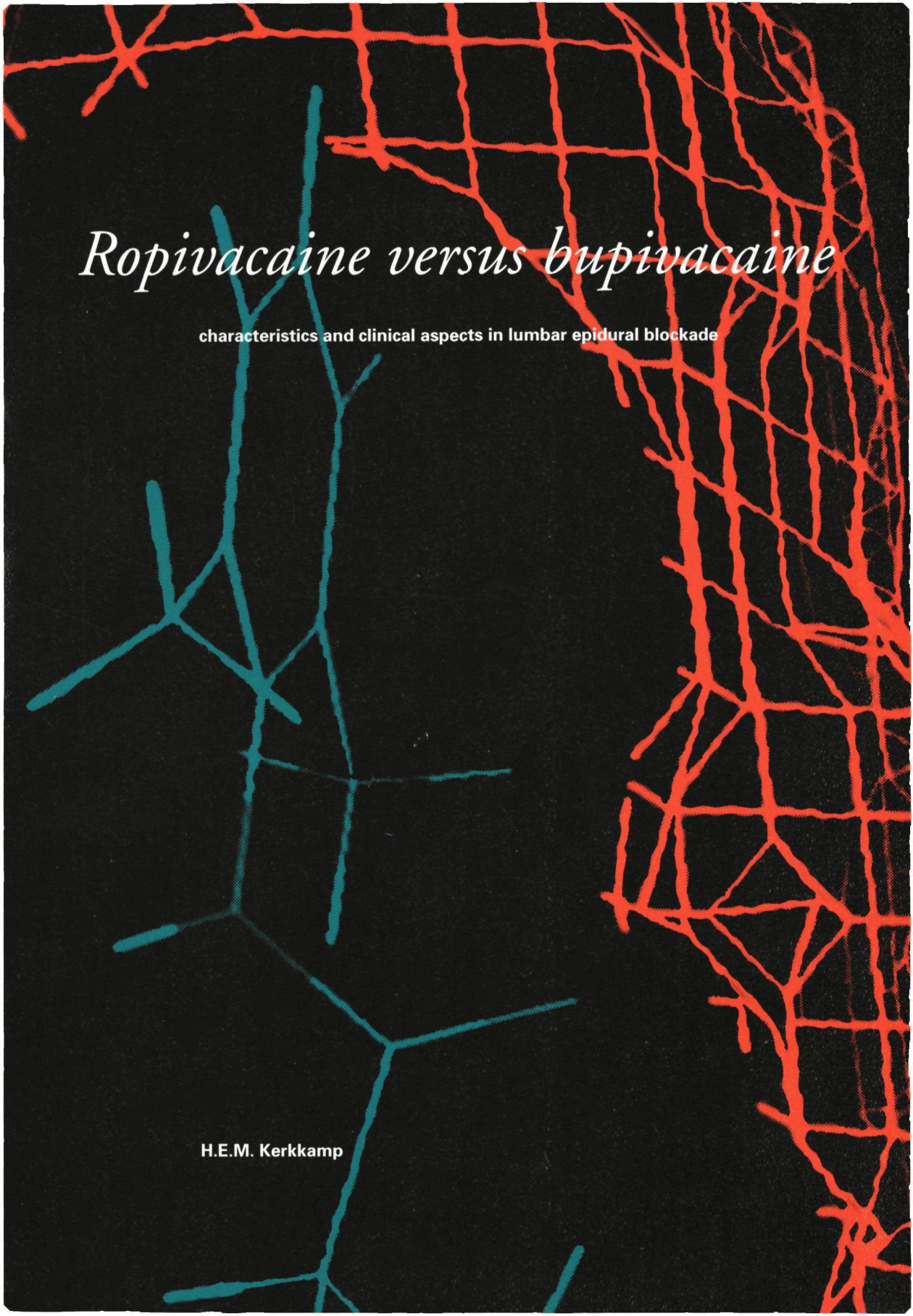

Ropivacaine versus bupivacaine

characteristics and clinical aspects in lumbar epidural blockade

H.E.M. Kerkkamp

Ropivacaine versus bupivacaine

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Een wetenschappelijke proeve op het gebied van
de geneeskunde en de tandheelkunde in het bijzonder de geneeskunde

Proefschrift ter verkrijging van de graad van doctor aan de Katholieke Universiteit
te Nijmegen, volgens besluit van het College van Decanen
in het openbaar te verdedigen op woensdag 21 november 1990
des namiddags te 3.30 uur

door

HANS EDDE MICHAEL KERKKAMP
geboren op 8 maart 1956 te 's-Gravenhage

Druk SSN, Nijmegen 1990

promotor: Prof. Dr. L.H.D.J. Booij
co-promotor: Dr. M.J.M. Gielen

aan: Ella
Pim
Karlijn

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Aims and objectives of the studies

The lumbar approach to the epidural space was first described by the Spanish surgeon Fidel Pages (1921). Its main attractions over the spinal blockade are that it never causes headache and that it allows the possibility of extending the sensory blockade into the postoperative period, either by repeated injections or by continuous infusion.

Several local anesthetics are used for epidural anesthesia. Today the most used drug is bupivacaine, especially for postoperative pain relief. However accidental intravenous injection of bupivacaine may cause sudden cardiovascular collapse (Albright 1979, Moller 1988). To ensure safe and optimal perioperative treatment new drugs have been introduced.

The development of local anesthetic drugs is facilitated by molecular engineering. Differences in chemical structure of the various compounds relate to anesthetic properties. The determination of crystal structures of closely related drugs is used to understand and explain the phenomenon that minor changes in structural formula may cause severe differences in physiochemical characteristics.

Ropivacaine, n-propyl-1-dimethyl-2′,6′-piperidine-carboxanilidine-2, is the latest long acting local anesthetic agent of the amide type. Animal studies have indicated that ropivacaine is less cardiotoxic than bupivacaine (Åkerman 1988). The cardiovascular effects of local anesthetics can be studied by invasive monitoring. The risks associated with this kind of monitoring pose a significant hazard to the research patient. Noninvasive assessment of cardiovascular function offers the anesthesiologist techniques that limit the risks.

This thesis covers the above mentioned aspects of the local anesthetics bupivacaine and ropivacaine. The main objectives of this thesis are:

- To determine the crystal structure of ropivacaine and bupivacaine (chapter 3).
- To assess the cardiovascular effects of addition of epinephrine to bupivacaine for epidural blockade (chapter 6).
- To assess cardiovascular effects after epidural injection of either ropivacaine or bupivacaine (chapter 7).
- To determine the dose-response relationship after epidural or intrathecal injection of ropivacaine and bupivacaine in rats (chapter 8).
- To evaluate the clinical efficacy of ropivacaine in different concentrations for epidural anesthesia (chapter 9).
- To evaluate the differences in neural blockade characteristics of ropivacaine and bupivacaine following epidural administration in humans (chapter 10).

These studies are accompanied with brief surveys of the general pharmacology and neurophysiology of local anesthetics, the method of noninvasive cardiovascular monitoring by thoracic electrical bioimpedance and the cardiovascular effects of epidural blockade (chapter 2, 4 and 5).

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Moller RA, Covino BG Cardiac electrophysiologic effects of lidocaine and bupivacaine Anesth Analg 1988 67 107-114

Pages F Anestesia metamerica Rev Sanid Milit Argent 1921 11 351-365

Local anesthetics

History of ester type local anesthetics

The first local anesthetic discovered was cocaine, an alkaloid extracted from the coca plant. The Incan people thought that the coca leaf was a gift from their Sun God, Manco Capac (Gay 1976). The leaves were initially used among the religious and political aristocracies of Incan society. After the destruction of Incan civilization in the sixteenth century, the lower classes and slaves were paid in coca leaves. Coca served as a stimulating tonic to the people working in the Andes.

In 1860 Albert Niemann (1834-1861) isolated cocaine from the leaves of Erythroxylon coca (Niemann 1860). Von Anrep reported the physiologic and pharmacologic effects of cocaine in an extensive article (Anrep 1880). Large doses of this alkaloid, administered in warm blooded animal, caused psychic agitation and excitation, acceleration of respiration and heart rate, a rise in blood pressure and dilatation of pupils.

Karl Koller, a resident in ophthalmology, was intent upon finding a drug to anesthetize the cornea. In 1884 he was the first person to use the drug for topical anesthesia in the human eye (Koller 1884). James Leonard Corning (1885), a neurologist, was the first who used cocaine to generate a central neural blockade (epidural).

The strong toxicity, the short duration of anesthesia and the impossibility of sterilizing the solution, stimulated chemists to find a substitute which was free of these disadvantages. Cocaine in high doses produces tremors, seizures, tachycardia, vasoconstriction, and elevation of body temperature.

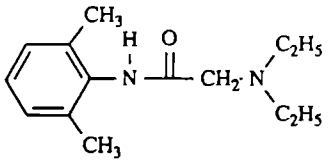
Presumably around 1904, Einhorn synthesized procaine. This drug was the first synthetic ester type local anesthetic. Procaine was found to elaborate few central nervous effects. Following the introduction of procaine, numerous ester type local anesthetics were synthesized. Tetracaine, the most potent ester of the benzoic acid series, was synthesized in 1928 by Eisler. The least toxic ester type local anesthetic, chloroprocaine, was discovered in 1949. The major drawback to these drugs has been, unfortunately their propensity for producing allergic reactions.

History of amide type local anesthetics

The first amide type local anesthetic was discovered by Meischer (1932) in 1925. Dibucaine was extremely potent and highly toxic. It was discovered while preparing an antipyretic agent related to quinine. In 1935, two Swedish chemists, von Euler and Erdtman, tried to elucidate the structure of an alkaloid, gramine. In the course of the investigations they synthesized a compound which was isomeric with gramine but, as opposed to gramine, exhibited a local anesthetic action. Other related compounds, the so called alkylaminoacylanilides, were synthesized by Erdtman and Löfgren.

From subsequent investigations Löfgren and Lundqvist discovered, in 1943, the compound diethylaminoaceto-2,6,-xylidine (figure 2.1), which today is known as

lidocaine (Löfgren 1948). This local anesthetic was more stable in solution, had a shorter onset of sensory blockade and a longer duration of action, than the amino ester agents. The amide type local anesthetics proved to be less allergenic than the ester type anesthetics (Incaudo 1978, DeShazo 1979, Brown 1981, Fisher 1982).



Lipophilic | Intermediate chain | Hydrophilic

Figure 2.1: The chemical formula of lidocaine, showing the three essential portions of a local anesthetic molecule.

Although the clinical profile of lidocaine (relatively fast onset, good sensory and motor blockade, low toxicity) was satisfactory, its duration of action was short. So the need for a long-acting local anesthetic was the main reason for further research. A large part of the initial clinical investigations of bupivacaine was performed by Widman (1964). Table 2.1 gives the chronology of some ester type and amide type local anesthetics, including the years of synthesis and clinical application.

Even with the wide range of agents, there is a need for more safety, versatility, and other modes of use of local anesthetics. Over the past two decades sudden cardiovascular collapses have been reported after accidental intravenous injection of a large dose of bupivacaine in patients (Albright 1979). This indicates the need for the development of an equally effective, but less toxic local anesthetic agent.

Chemical structure of local anesthetics

Local anesthetics are chemicals which consist of a lipophilic and hydrophilic portion separated at a distance of 6 to 9 Ångstroms by an intermediate chain (figure 2.1). The total length of the molecules varies between 13-18 Ångstroms. The hydrophilic group is usually a tertiairy amine, while the lipophilic portion is usually an unsaturated aromatic ring such as para-aminobenzoic acid. The intermediate chain contains either an ester (-COO) or an amide (-CONH) linkage. Local anesthetics therefore are classified as ester or amide compounds. Ester type agents include cocaine, benzocaine, procaine, chloroprocaine and tetracaine; while amide type agents include dibucaine, lidocaine, prilocaine, etidocaine, mepivacaine, bupivacaine, articaine andropivacaine (figure 2.2a/b) (Tucker 1988). Ropivacaine and bupivacaine are structurally related:

the former is the active (L) form of 1-propyl-2′,6′pipecoloxylidide, and the latter is racemic (DL) 1-butyl-2′,6′-pipecoloxylidide.

Table 2.1· Chronology of local anesthetic agents.

Drug	Year of synthesis	Discovered by	Clinical introduction	Clinical use
Esters				
Cocaine	1860	Niemann[1]	1884	Koller[2]
Benzocaine	1895	Salkowski[3]	1904	Einhorn[4]
Procaine	1904	Einhorn[4]	1905	Braun[5]
Tetracaine	1928	Eisler	1932	*
Chloroprocaine	1949	Marks	*	*
Amides				
Dibucaine	1925	Meischer[6]	1930	Uhlmann
Lidocaine	1943	Lofgren[7]	1947	Gordh
Mepivacaine	1956	Ekenstam[8]	1957	Dhuner
Prilocaine	1959	Lofgren[9]	1960	Wielding
Bupivacaine	1957	Ekenstam[8]	1963	Widman[10]
Etidocaine	1971	Takman	1972	Lund
Articaine	1974	Muschaweck[11]	1974	Bader[12]
Ropivacaine	1957	Ekenstam[8]	1988	Kerkkamp[13]

[1]Niemann 1860
[2]Koller 1884
[3]Salkowski 1895
[4]Einhorn 1899
*Not known
[5]Braun 1905
[6]Meischer1932
[7]Lofgren 1948
[8]Ekenstam 1957
[9]Lofgren 1960
[10]Widman 1964
[11]Muschaweck1974
[12] Bader1974
[13]The first epidural injection of ropivacaine in humans was on 24th february 1988 at the University Hospital of Nijmegen, The Netherlands

Physicochemical properties

Small changes in the chemical structure of local anesthetics produce profound changes in physicochemical properties and in clinical profile. Differences in pharmacology of local anesthetics such as onset, duration of action and potency are associated with physical and chemical properties (Concepcion 1984). Duration of action is related to protein binding and lipid solubility. The lipid solubility also determines the intrinsic anesthetic potency.

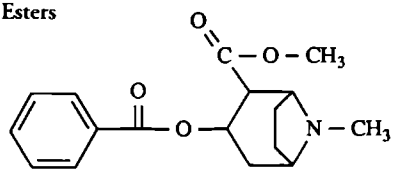
Molecular weight

The molecular weights of the amide type local anesthetics vary from 220-325. The molecular weight determines the rate of diffusion into the sodium channel of the nerve membrane (Courtney 1980). Transdural transfer is also dependent on molecular weight.

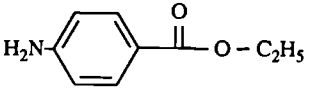
Structure-activity relationships in series of homologous local anesthetics were studied by Åberg (1977). He demonstrated that when the number of carbon atoms on

the piperidine-nitrogen of the mepivacaine molecule was increased to up to four or five carbons, the toxicity of the compounds and the duration of their local anesthetic effects were increased.

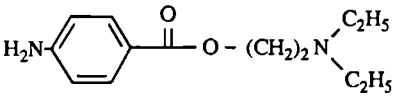
Esters



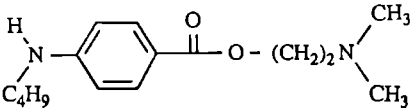
Cocaine



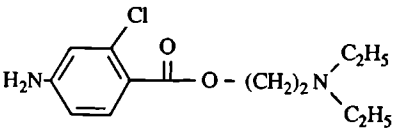
Benzocaine



Procaine



Tetracaine



Chloroprocaine

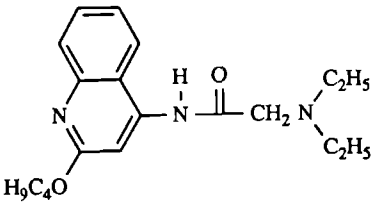
Figure 2.2a: Chemical structures of currently available ester type local anesthetic agents.

Lipid solubility

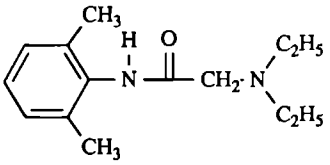
The lipophilic portion of the molecule is essential for anesthetic activity. A high lipid solubility would be expected to promote diffusion through membranes, thereby decreasing the onset time of action, and to enhance interaction with hydrophobic components of receptor sites.

Therapeutically useful local anesthetics require a delicate balance between lipid solubility and water solubility. Partitioning between n-heptane and phosphate buffer (pH 7.4 at 37°C) is often referred to when comparing the lipid solubilities of local anesthetics (Tucker 1980). Investigations of the relative partitioning of four amide local anesthetics (see table 2.2) in n-heptane/phosphate buffer, rat sciatic nerve tissue, human extradural fat and human subcutaneous fat showed that the ratios of relative mean uptake of bupivacaine and ropivacaine were lower than the theoretical n-heptane/

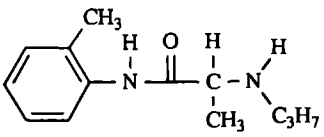
Amides



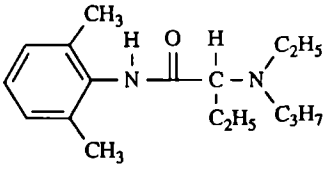
Dibucaine



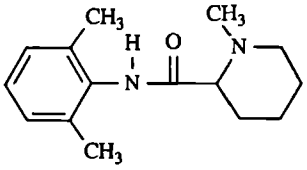
Lidocaine



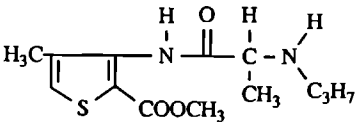
Prilocaine



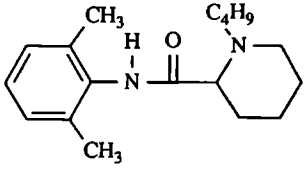
Etidocaine



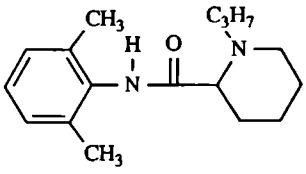
Mepivacaine



Articaine



Bupivacaine



Ropivacaine

Figure 2.2b: Chemical structures of currently available amide type local anesthetic agents.

buffer ratios (Rosenberg 1986). The variation in the absorption of bupivacaine and ropivacaine into fatty tissues is much less than in n-heptane/phosphate buffer. Therefore the solubility in a pure organic solvent is not an optimal predictive test of clinical differences between local anesthetics.

Table 2 2· Ratios of relative partitioning and mean relative uptake of four amide local anesthetics in a pure organic solvent and in biological tissues

	B	E	L	R
n-Heptane/phosphate buffer	10 0	39 0	1	2 9
Human extradural fat	4 1	8 3	1	2 3
Human subcutaneous fat	3 8	10 6	1	1 9
Rat sciatic nerve	3 3	4 0	1	2 3

B =bupivacaine E =etidocaine
L =lidocaine R =ropivacaine

From Rosenberg (1986)

pKa

The pKa of a compound determines the extent of ionization. The greater the pKa of a base, the smaller the fraction of nonionized compound at any pH. Because the nonionized form of the agent is responsible for diffusion across the nerve sheat and membrane (Ritchie 1965), the pKa values of local anesthetics are related to the onset of anesthesia.

The esters have higher pKa values (8.46-9.05) than the amides (7.76-8.16) and will, therefore, be less ionized at physiological pH (7.4). To ensure the stability of the ester-type agents they are dispensed in acid solutions. Hence the pH of plain ester solutions is low (2.8) compared with the pH of the amides (4.4-6.4). Consequently a less nonionized ester drug is available initially to diffuse to action sides.

Protein binding

The degree of protein binding has important pharmocokinetic and pharmocodynamic implications. A high degree of binding to plasma and tissue proteins of a local anesthetic exhibits a high potency and long duration.

The two plasma proteins that bind amide local anesthetics are α_1-acid glycoprotein and albumin (Routledge 1980). α_1-Acid glycoprotein has a high affinity for local anesthetics, but has a limited capacity, whereas albumin has a low affinity but a large capacity.

Metabolism

The ester compounds are metabolized in blood and the liver. They are hydrolyzed by

pseudocholinesterases. Plasma half life times in normal adults vary from 10-20 seconds for chloroprocaine to several minutes for tetracaine (Foldes 1965, O'Brien 1979). The clinical implication of the rapid clearance of esters is that if a toxic concentration is attained after accidental intravenous injection, the ensuing reaction is of short duration.

The amide type local anesthetics are stable in blood. The metabolism of amide types is more complex and slower; these drugs undergo varying rates of metabolism by microsomal enzymes located primarily in the liver (Boyes 1975, Covino 1976). The rate of hepatic degradation varies between the compounds. Plasma half life times vary from 93-96 minutes for prilocaine and lidocaine to 111-162 minutes for ropivacaine and bupivacaine (Lee 1989). Table 2.3 summarizes the physicochemical properties of local anesthetics.

Table 2 3 Physicochemical properties of local anesthetics

Agent	Mol weight (Base)	Pka[1]	Partition coeffitient[2]	Percent plasma[3] protein binding
Esters				
Procaine	236	9 05	0 02	6
Chloroprocaine	271	8 97	0 14	*
Tetracaine	264	8 46	4 1	76
Amides				
Lidocaine	234	7 91	2 9	64
Prilocaine	220	7 90	0 9	55
Mepivacaine	246	7 76	0 8	77
Etidocaine	276	7 70	141 0	94
Bupivacaine	288	8 16	27 5	95
Ropivacaine	274	8 07	8 7	85

[1]At 25°C
[2]n-Heptane/phosphate buffer (µg ml^{-1}/µg ml^{-1}) at 37°C, pH 7 4
[3]The percentage binding relates to concentrations of a drug around 1 µg local anesthetic ml^{-1} plasma (Tucker 1975)
* Not known

Mechanism of action

Local anesthetics interfere with the conduction of action potentials along the peripheral nerve fibers. They generally do so by impairing the function of sodium channels within the region where the drug has been applied (Strichartz 1973).

Resting membrane potential

Nerve fibers possess a lipoprotein membrane that separates the intracellular matrix from the extracellular phase. An electrolyte concentration gradient between the intracellular fluid, containing mainly potassium, and the extracellular fluid, containing

sodium, is maintained by an active metabolic process. The concentration gradient for potassium is the major determinant of the transmembrane potential (-70 to -90 mV). The membrane is polarized. The resting potential exists because there are more anions than cations within the cell. The high extracellular sodium concentration is maintained because at rest the membrane is impermeable to sodium ions (Guyton 1986).

The nerve action potential

Nerve signals are transmitted by action potentials, which are rapid changes in the transmembrane potential. The membrane suddenly becomes permeable to sodium ions, allowing the migrations of sodium ions to the interior of the axon and of potassium to the outside. This is called depolarisation. The normal rest potential of -70 to -90 mV is lost, with the potential rising rapidly in the positive direction (+20 mV). This is quickly followed by repolarization back to the resting value. The process occupies 1-2 ms. The principal actor in causing depolarization of the nerve membrane during the action potential is the voltage-gated sodium channel. The channels contain charged or dipolar regions that slide, twist or turn when changes in the membrane's electric field (corresponding to the transmembrane potential) alter the energy differences between different conformations of the channel. Through such "voltage-gated" changes in shape, ion channels are "activated" to ion-conducting (open) states by membrane depolarization (Catterall 1988). The depolarizing phase of impulses follows from the activation of Na^+ channels and the resulting flow of Na^+ ions into the cell (Hodgkin 1952).

The voltage change associated with the depolarizing phase opens the sodium channels in the next section, so that the action potential is propagated along the nerve (Guyton 1986).

Site of action of local anesthetics

Local anesthetics act by interfering with the ability of the membrane to undergo the specific change in permeability to sodium in response to partial depolarization. Three distinct sites have been proposed where local anesthetics might exert their effect on sodium conductance (Seeman 1972, Ritchie 1975, Lee 1976):

1 On the membrane surface, involving alteration of the fixed negative charge and hence transmembrane potential, without change in resting intracellular potential.
2 Penetrating the membrane, to cause a conformational change in lipoproteins, thereby causing distortion of the sodium channel.
3 Binding to specific intracellular receptors at the cell membrane and preventing the opening of sodium channels.

During the past decade much evidence has accumulated to support the specific receptor binding hypothesis(Hille 1980). Nevertheless, the membrane distortion theory still provides part of the explanation for anesthetic actions.

Differential blockade

The ability of local anesthetics to block impulse conduction in certain nerve fibers, while sparing conduction in others, has generated much attention. This situation is called a differential block. This term, when defined as selective block of specific nerve fibers, implies that motor and sensory characteristics depend on activity in specific nerve fiber groups.

Nerve fibers are classified as A, B, and C fibers, on the basis of their diameters and velocity of conduction of nerve impulses (table 2.4). The diameter and myelinization of a nerve fiber determine its sensitivity to local anesthetics (Wildsmith 1975).

Bupivacaine and etidocaine provide an interesting contrast in terms of their differential sensory/motor blocking activity, although they are both potent long acting anesthetics (Scott 1980). Bupivacaine is widely used to provide adequate sensory analgesia with minimal blockade of motor fibers. On the other hand etidocaine shows little separation between sensory and motor blockade.

The factors responsible for differential sensory/motor separation are not known precisely. The concept that the small myelinated fibres are more susceptible than the larger fibres to be blocked by local anesthetics has been questioned and a reverse fiber sensitivity was found in animal nerves (Gasser 1929, Gissen 1980). The slow blockade of A-fibers by bupivacaine is believed to be a result of the relatively high pKa of this agent. Other factors found to modulate the degree of blockade include: temperature, pH, nerve activity, nerve type, duration of drug exposure, CO_2 tension, and so forth (Raymond 1987).

Table 2.4 Classification of peripheral nerve fibers.

Fibre type	Diameter (μm)	Myelin	Conduction speed (ms^{-1})	Function
A- alpha	12-20	+++	70-120	somatic motor
beta	5-12	+++	30-70	touch, pressure
gamma	3-6	++	15-30	proprioception
delta	2-5	++	12 30	fast pain, touch, temperature
B	<3	+	3-15	preganglionic autonomic
C	0 3-1 3	-	0 5-2 3	slow pain, reflexes, temperature

+++ heavily myelinated ++ moderately myelinated
+ lightly myelinated - nonmyelinated

Conclusion

The most important clinical properties of local anesthetic agents are potency, onset, duration of action and relative blockade of sensory and motor fibres. These qualities are related to physicochemical characteristics of the drugs. On the basis of anesthetic activity in man the agents are classified as follows:

1 Low anesthetic potency and short duration of action: procaine and chloroprocaine.
2 Intermediate anesthetic potency and duration of action: lidocaine, mepivacaine, prilocaine.
3 High anesthetic potency and prolonged duration of action: tetracaine, etidocaine, bupivacaine and ropivacaine.

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Crystal structure determinations of the local anesthetics ropivacaine and bupivacaine

H.J. Bruins Slot[1], H.J. Behm[2], H.E.M. Kerkkamp[3]

1 CAOS/CAMM Center, University of Nijmegen, The Netherlands.
2 Crystallography Laboratory, University of Nijmegen, The Netherlands.
3 Institute for Anesthesiology, University of Nijmegen, The Netherlands.

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A prerequisite for the complete physicochemical interpretation of the processes involved in neural blockade by local anesthetics is, that the structures of the appropriate components be known to atomic detail

From the structure/activity relationships obtained by Åberg and others (1977), it appears that by increasing the number of carbon atoms on the piperidine nitrogen on the mepivacaine molecule, the physicochemical and biological effects of these amide type local anesthetics are changed Since the theory of the action of local anesthetics is, at present, not unambiguously determined (Hille 1980, Strichartz 1987), the need for 3-dimensional information of both local anesthetics and the excitable tissues is put forward The axonal membrane is similar to the plasma membrane of other cells, and is complex and comprise many different molecules such as, carbohydrates, proteins and lipids

X-ray crystallography is the most powerful method of deriving structure information This chapter, starting with a brief summary on the basic principles of X-ray diffraction by single crystals, deals with the elucidation of the 3-dimensional structure of the active forms of both ropivacaine and bupivacaine The 3-dimensional structures of the molecules of the excitable cell membrane remain to be determined to clarify the mechanism of action.

X-ray diffraction

A single crystal can be thought of as a three dimensional repeating pattern of identical units, the so called unit cells. A unit cell is described by three base vectors, **a**, **b** and **c** Because of its three dimensional grating, a single crystal diffracts X-rays in discrete directions Each diffracted beam is called a reflection **h**, and its direction is related to the reciprocals of the three base vectors of the unit cell A physical explanation of the diffraction of X-rays was given by W L Bragg in the second decade of this century (Bragg 1913) He showed that the diffracted beams behave as if they are reflected from discrete planes passing through the crystal lattice Intensity maxima are only observed when angle of the incident X-ray with a set adjacent planes obey Bragg's law (figure 3 1)·

$$2\, d_h \sin(\theta) = n\lambda \qquad (3.1)$$

From X-ray diffraction theory it follows that the intensity I of a reflection **h**, is proportional to the squared amplitude of a complex quantity known as the structure factor F_h.

$$I_h = \text{constant} \, |F_h|^2 \qquad (3.2)$$

When the atomic structure of the crystal is known, the structure factor F_h can be calculated from

$$F_h = \sum_{j=1}^{N} f_{j,h} \exp[2\pi i \mathbf{h}.\mathbf{r}_j] \qquad (3.3)$$

where N is the number of atoms in the unit cell, $f_{j,h}$ is the atomic scattering factor of atom j for reflection **h**, and $\mathbf{r}_j$ is the position of atom j. If the atomic structure of the crystal is represented by a continuous electron density function $\sigma(r)$, its periodicity allows $\sigma(\mathbf{r})$ to be written as a Fourier series:

$$\sigma(\mathbf{r}) = V^{-1} \sum_{\mathbf{h}} F_h \exp[-2\pi i \mathbf{h}.\mathbf{r}] \qquad (3.4)$$

where V is the volume of the unit cell and **r** is the position of a point in the unit cell.

Thus, if structure factors F_h are known, $\sigma(r)$ can be calculated directly, and the three dimensional arrangement of atoms in the unit cell can be obtained. Unfortunately, the complex structure factors F_h are known only in magnitude from equation 3.2; their phases are unknown. This is the 'phase problem' in crystallography. Each method to solve a structure by X-ray diffraction data involves finding the phases of structure factors. Once phases are found, the electron density function is calculated using equation 3.4, and from its local maxima the arrangement of atoms in the unit cell can be deduced.

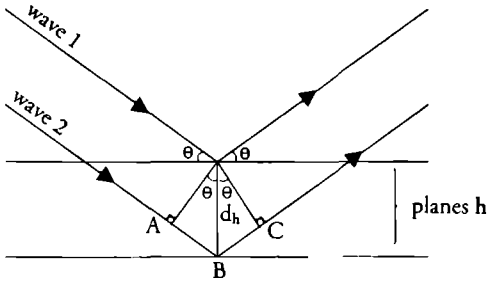


Figure 3.1: Two waves are incident on the **h** set of planes. A phase difference between the two waves exists and an intensity maximum occurs if the geometrical path difference (AB+ BC = 2 d_h sin (θ) between the waves is an integral number of wavelengths (n.λ).

X-ray structure determination

Raw material for both (1) n-propyl-1-dimethyl-2′, 6′-piperidine-carboxanilide-2-(ropivacaine) and (2) n-butyl-1-dimethyl-2′,6′-piperidine-carboxanilide-2 (bupivacaine) was supplied by Astra Alab, Södertälje, Sweden. Only for (1) a diastereomeric salt was provided. Recrystallization from 1:1 ethanol/water (1) and from 1:1 ethanol/acetone (2) yielded needle-shaped crystals. Datasets were collected on an

Enraf-Nonius CAD-4 diffractometer using graphite monochromatized CuKα radiation (λ=1.54184Å) using the ω-2θ scan technique (0°< θ <70°) with a scan angle of 1.5° and a variable scan rate with a maximum scan time of 20s per reflection. Profile analysis was performed on all reflections (Lehman 1974, Grant 1978). Normal Lorentz-polarization corrections and empirical absorption corrections using psi-scans (North 1968) were applied. Crystal data and experimental data are summarized in table 3.1. As opposed to the straightforward data collection on bupivacaine (2), the crystals of ropivacaine (1) appeared to be twinned. From CAD-4 data collected to determine the

Table 3 1 Crystal and experimental data

	Ropivacaine	Bupivacaine
Structural formula	$C17H27N2O^+$ Cl H2O	$C18H29N2O^+$ Cl $^1/_2$C2H6O
M_r	328 881	347 927
Crystal system	monoclinic	monoclinic
Spacegroup	$P2_1$	$P2_1/n$
a (Å)	9 5508(14)	9 220(3)
b (Å)	7 3287(6)	11 0417(17)
c (Å)	13 1784(7)	20 392(6)
ß (°)	97 429(15)	102 85(4)
volume ($Å^3$)	914 7(2)	2024(1)
Z	2	4
D_x (gcm^{-3})	1 194	1 142
radiation (Å)	(λCuKα)=1 54184	(λCuKα)=1 54184
μ (cm^{-1})	19 23	17 43
F(000)	355 95	755 89
T (K)	293	293
Crystal dimensions (mm)	0 19x0 18x0 07	0 48x0 22x0 18
No of reflections to determine lattice parameters	25	25
θ range (°)	19 35	20 35
Max (sin(θ)/λ)($Å^{-1}$)	0 588	0 609
hkl range		
h	-11,11	-11,11
k	8,8	0,13
l	-15,15	-24,24
No of standard reflections	3	3
Drift correction range	1 031 0 981	1 120-0 989
Emp abs correction range	1 000-0 897	0 999 0 894
Total data measured	6206	8082
Unique data	1688	3827
Rint=$\Sigma(I - \langle I \rangle)/\Sigma I$	0 023	0 017
Data used in refinement	2062	2318
Parameters refined	189	244
R	0 056	0 064
R_w [$w^{-1}=\sigma^2(F)+gF^2$]	0 053	0 069
S	0 294	2 805
Weighting-scheme parameter g	0 001	0 004
Max shift/error in last cycle	0 015	0 084
Final difference Fourier map peaks ($eÅ^{-3}$)		
min	-0 27	-0 30
max	0 23	0 45

unit cell dimensions it appeared that the two indiviuals (I and II) of the crystal share their ab plane. The twinning operation is the reflection in this ab plane. The resulting angle between a_I^* and a_{II}^* is 165.14(2)°. Fig. 3.2 shows the hol zone, in which indices for both lattices are given. Reflections with h=0 coincide for the two lattices. Again, there is a hypothetical coincidence for h=2.8, therefore the reflections 3n,k,l are excluded from the least-squares refinement.

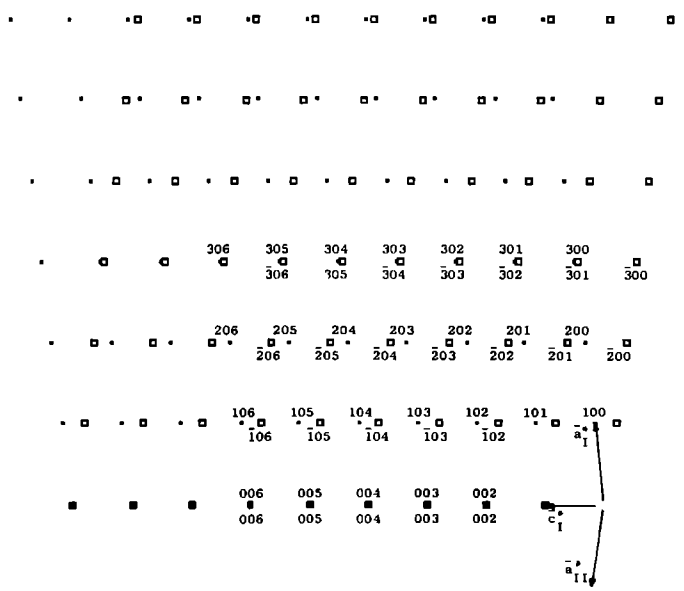


Figure 3.2: Indexed h0l zone of (1) ropivacaine. (For individual I, points with indices given above: for individual II, squares with indices given below).

The structures were solved using the automated Patterson search methods of the DIRDIF system (Beurkens 1984, Beurkens 1987). For the orientation and translation searches the non-hydrogen fragment depicted in fig.3.3 was used. Coordinates for this fragment were obtained from molecular mechanics calculations using MacroModel (Mohamadi 1990). In the DIRDIF Fourier synthesis, all non-hydrogen atoms for both (1) and (2) were found. The structures were refined isotropically.

The phenyl groups were treated as regular hexagons, with C-C distances of 1.395Å. During the isotropic refinement, a peak in the difference Fourier map was assigned a water oxygen (O2) for ropivacaine, and three peaks in the difference Fourier map of bupivacaine were assigned C19 with full occupancy, and C20 and O21 with half occupancy, to form disordered acetone. H atoms were located from subsequent difference Fourier maps. H positions were refined with fixed isotropical temperature factors, which were taken from the atoms they are bonded to. Except the H atoms bonded to

N, the H atoms were refined, riding on the atoms they are bonded to. No positional parameters for the amino proton H2 in ropivacaine (1) could be obtained. Isotropic refinement of H2, placed at a calculated position, using 'riding mode' resulted in an unacceptable large temperature factor, and therefore H2 was omitted. No hydrogen atoms could be located for the solvent molecules in both structures. After an additional empirical absorption correction using DIFABS (Walker 1983), the nonhydrogen atoms were refined anisotropically, except for the solvent molecules which were refined isotropically.

At this stage an examination of the temperature factors of the atoms C19, C20 and O21 revealed that the initial assignment was not correct and that a description as disordered ethanol with occupancies of 1., 0.25 and 0.25 for the renamed atoms C19, O20 and O21 respectively, was more appropriate than disordered acetone. Isotropic refinement of this model with fixed site occupancy factors showed a consistent set of temperature factors.

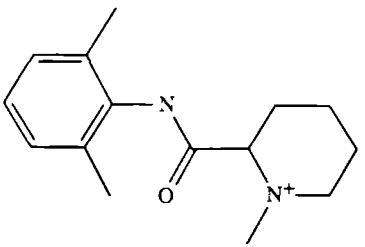


Figure 3 3 Non-hydrogen skeleton used for orientation and translation searches of the DIRDIF system.

The H atoms of the methyl groups in (2) appeared to be disordered. From a difference Fourier map alternative positions for the methyl H atoms were located. Of all methyl H atoms, the positional parameters and the site occupancy factors were refined with fixed isotropical temperature factors using distance constraints. For refinements and as a source of atomic scattering factors, SHELX (Sheldrick 1976) was used. The absolute configuration of (1) was confirmed using BIJVOET (Beurskens 1980), B=0.9933(3). Positional parameters for all atoms are given in table 3.2 for both (1) and (2).*

*Lists of structure factors, complete lists of positional and (an)isotropic thermal parameters and full lists of bond lengths, angles and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England

Table 3 2 Atomic coordinates with site occupancy factors and equivalent isotropic temperature factors (Å^2) for (1) ropivacaine and (2) bupivacaine

($U_{eq} = {}^1/_3 \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* a_i a_j$)

(ropivacaine first line, bupivacaine second line)

	x/a	y/b	z/c	sof	U_{eq}/U_{iso}
N1	-0 7671(4)	0 0996(5)	-0 3652(3)	1	0 0451(13)
	0 7305(4)	0 0228(3)	0 6344(2)	1	0 0543(11)
N2	-0 8471(3)	-0 0841(4)	-0 1261(2)	1	0 0354(9)
	0 6978(3)	0 0098(3)	0 8056(2)	1	0 0507(11)
O1	-0 7853(4)	-0 1960(4)	-0 3215(2)	1	0 0570(12)
	0 7078(3)	0 1767(2)	0 7052(1)	1	0 0638(11)
C1	-0 7769(3)	0 0723(5)	-0 4723(1)	1	0 0434(13)
	0 7074(3)	0 0942(2)	0 5758(1)	1	0 0565(13)
C2	0 6559(3)	0 0803(5)	-0 5211(1)	1	0 0565(15)
	0 8278(3)	0 1207(2)	0 5472(1)	1	0 0668(16)
C3	0 6665(3)	0 0604(5)	0 6271(1)	1	0 0689(19)
	0 8062(3)	0 1883(2)	0 4880(1)	1	0 0858(22)
C4	0 7982(3)	0 0324(5)	-0 6842(1)	1	0 0681(19)
	0 6642(3)	0 2294(2)	0 4574(1)	1	0 0928(24)
C5	-0 9192(3)	0 0244(5)	-0 6354(1)	1	0 0575(15)
	0 5438(3)	0 2029(2)	0 4860(1)	1	0 0809(21)
C6	-0 9086(3)	0 0444(5)	-0 5294(1)	1	0 0493(14)
	0 5654(3)	0 1353(2)	0 5452(1)	1	0 0655(17)
C7	-0 5115(6)	0 1043(10)	-0 4575(4)	1	0 0784(23)
	0 9807(5)	0 0784(5)	0 5806(3)	1	0 0881(22)
C8	-1 0417(5)	0 0410(6)	-0 4769(4)	1	0 0575(19)
	0 4332(5)	0 1084(4)	0 5746(2)	1	0 0805(18)
C9	-0 7721(4)	0 0338(5)	0 2981(3)	1	0 0410(12)
	0 7346(4)	0 0690(3)	0 6947(2)	1	0 0495(12)
C10	-0 7537(4)	0 0268(5)	0 1854(3)	1	0 0353(12)
	0 7859(3)	-0 0159(3)	0 7541(2)	1	0 0497(12)
C11	-0 5999(4)	-0 0011(8)	0 1399(3)	1	0 0469(12)
	0 9508(4)	0 0095(4)	0 7835(2)	1	0 0703(16)
C12	-0 5779(4)	0 0598(6)	0 0277(3)	1	0 0522(14)
	1 0094(5)	0 0590(4)	0 8484(2)	1	0 0790(18)
C13	-0 6786(4)	-0 0422(6)	0 0314(3)	1	0 0487(14)
	0 9164(5)	0 0310(4)	0 8978(2)	1	0 0793(18)
C14	-0 8302(4)	-0 0186(6)	-0 0163(3)	1	0 0438(12)
	0 7544(5)	0 0602(3)	0 8692(2)	1	0 0646(16)
C15	-1 0020(4)	-0 0904(6)	0 1705(3)	1	0 0429(13)
	0 5327(4)	0 0040(3)	0 7799(2)	1	0 0623(14)
C16	-1 0759(6)	0 0893(7)	0 1854(4)	1	0 0534(16)
	0 4785(4)	-0 1298(4)	0 7617(3)	1	0 0811(19)
C17	-1 2303(5)	0 0571(8)	0 2247(4)	1	0 0697(17)
	0 3110(5)	-0 1304(5)	0 7367(3)	1	0 0982(21)
C18	-				
	0 2403(6)	-0 2511(5)	0 7314(3)	1	0 1202(30)
CL1	-0 8230(1)	-0 5000	-0 0817(1)	1	0 0509(3)
	0 8372(1)	0 2487(1)	0 6220(1)	1	0 0757(4)
O2	-0 6746(4)	-0 5502(4)	-0 2763(3)	1	0 0663(13)
	-				
C19	-				
	0 4381(8)	-0 0234(8)	0 9736(4)	1	0 149(3)
O20					
	0 4235(16)	0 0564(15)	0 9191(8)	0 25 0	113(5)

O21					
	0 3219(20)	-0 0895(17)	0 9851(9)	0 25	0 137(6)
H1	-0 736(5)	0 198(7)	0 342(3)	1	0 0429
	0 762(4)	-0 048(4)	0 635(2)	1	0 0671
H2					
	0 712(4)	0 080(4)	0 821(2)	1	0 08(1)
H3	-0 5729(3)	0 0665(5)	-0 6649(1)	1	0 0621
	0 8925(3)	0 2073(2)	0 4675(1)	1	0 0791
H4	-0 8065(3)	0 0170(5)	0 7663(1)	1	0 0655
	0 6487(3)	0 2779(2)	0 4150(1)	1	0 0893
H5	-1 0212(3)	0 0028(5)	0 6796(1)	1	0 0562
	0 4420(3)	0 2324(2)	0 4641(1)	1	0 0763
H71	-0 4305(6)	0 1076(10)	0 5076(4)	1	0 0843
	0 992(8)	-0 004(4)	0 601(5)	0 51(9)	0 0844
H72	-0 4920(6)	0 0083(10)	0 4047(4)	1	0 0843
	1 029(7)	0 140(7)	0 615(5)	0 51(9)	0 0844
H73	-0 5099(6)	0 2307(10)	-0 4152(4)	1	0 0843
	1 029(9)	0 080(9)	0 541(3)	0 51(9)	0 0844
H74					
	1 003(8)	0 084(11)	0 631(5)	0 49(9)	0 0844
H75	-				
	1 063(6)	0 118(7)	0 563(5)	0 49(9)	0 0844
H76					
	0 973(8)	-0 009(3)	0 567(6)	0 49(9)	0 0844
H81	-1 0134(5)	0 0582(6)	0 3955(4)	1	0 0693
	0 464(10)	0 101(17)	0 625(9)	0 33(9)	0 0787
H82	-1 0950(5)	0 0881(6)	0 4917(4)	1	0 0693
	0 392(13)	0 029(8)	0 555(8)	0 33(9)	0 0787
H83	1 1110(5)	0 1505(6)	-0 5064(4)	1	0 0693
	0 355(10)	0 173(9)	0 562(8)	0 33(9)	0 0787
H84					
	0 435(7)	0 163(7)	0 614(3)	0 67(9)	0 0787
H85					
	0 344(3)	0 127(8)	0 538(2)	0 67(9)	0 0787
H86					
	0 429(7)	0 022(2)	0 589(4)	0 67(9)	0 0787
H10	-0 7824(4)	0 1690(5)	0 1812(3)	1	0 0312
	0 7716(3)	-0 1026(3)	0 7398(2)	1	0 0488
H111	-0 5732(4)	0 1438(8)	-0 1444(3)	1	0 0421
	0 9640(4)	0 0983(4)	0 7926(2)	1	0 0662
H112	-0 5325(4)	0 0784(8)	-0 1827(3)	1	0 0421
	1 0093(4)	0 0152(4)	0 7498(2)	1	0 0662
H121	-0 5976(4)	0 2046(6)	-0 0235(3)	1	0 0466
	1 1146(5)	0 0342(4)	0 8676(2)	1	0 0794
H122	-0 4706(4)	0 0312(6)	0 0050(3)	1	0 0466
	1 0056(5)	0 1480(4)	0 8390(2)	1	0 0794
H131	-0 6676(4)	0 0091(6)	0 1089(3)	1	0 0467
	0 9525(5)	0 0804(4)	0 9394(2)	1	0 0760
H132	-0 6523(4)	-0 1855(6)	0 0323(3)	1	0 0467
	0 9261(5)	0 0570(4)	0 9094(2)	1	0 0760
H141	0 8983(4)	0 0972(6)	0 0263(3)	1	0 0412
	0 6948(5)	0 0380(3)	0 9028(2)	1	0 0623
H142	-0 8587(4)	0 1238(6)	-0 0145(3)	1	0 0412
	0 7437(5)	-0 1488(3)	0 8593(2)	1	0 0623
H151	1 0570(4)	0 1711(6)	0 1196(3)	1	0 0404
	0 5025(4)	0 0477(3)	0 7389(2)	1	0 0643
H152	-1 0091(4)	0 1567(6)	0 2442(3)	1	0 0404
	0 4830(4)	0 0260(3)	0 8156(2)	1	0 0643

H161	1 0675(6)	0 1612(7)	-0 1134(4)	1	0 0486
	0 5258(4)	-0 1613(4)	0 7255(3)	1	0 0826
H162	1 0278(6)	0 1697(7)	0 2403(4)	1	0 0486
	0 5064(4)	-0 1829(4)	0 8023(3)	1	0 0826
H171	1 2841(5)	0 1866(8)	-0 2356(4)	1	0 0660
	0 2871(5)	-0 0923(5)	0 6910(3)	1	0 0999
H172	-1 2782(5)	-0 0233(8)	-0 1698(4)	1	0 0660
	0 2673(5)	-0 0805(5)	0 7684(3)	1	0 0999
H173	-1 2385(5)	-0 0149(8)	-0 2968(4)	1	0 0660
	-				
H181	-				
	0 1304(6)	-0 2421(5)	0 7147(3)	1	0 1189
H182	-				
	0 2614(6)	-0 2905(5)	0 7767(3)	1	0 1189
H183	-				
	0 2812(6)	-0 3023(5)	0 6994(3)	1	0.1189

Discussion of the x-ray structures

Plots of the numbering schemes used for both ropivacaine (1) and bupivacaine (2) are shown in fig.3.4. Selected bond lengths, valence angles and torsion angles, obtained using PARST (Nardelli 1983), are tabulated in tables 3.3, 3.4 and 3.5. Table 3.6 lists the geometry of the disordered ethanol in (2) bupivacaine. No anomalous geometric values are observed. A geometric feature of interest of both local anesthetics is the molecular conformation as compared to, for example, the closely related lidocaine derivatives (fig.3.5). The related compounds were found using a connectivity search on the Cambridge Crystallographic Database (CSD) (Allen 1979) using 2,6-acetoxylidide as search fragment. This search gave 7 structures with 9 unique fragments. In the CSD use is made of so called reference codes to identify entries. The 7 structures found are designated BEFLUT (Faggiani 1982), BEVMOE (glowka 1981), LIDCAN10 (Hanson 1974), LIDNPP (Yoo 1975), LIDOCA10 (Hanson 1972), LIDOCN (Hanson 1972) and LIPFAZ (Germain 1977). The fragments are characterized by 2 planar groups: the 'phenyl-group' consisting of the atoms C1 to C8 and N1, and the 'amide-group' consisting of the atoms C1, N1, C9, O1, C10 (averaged deviations from l.s. planes in the retrieved entries vary from 0.002 to 0.034Å). In table 3.7 the angles between the phenyl groups and amide groups are given. Also, extending the comparison of lidocaine derivatives by Yoo et al (1975) in table 3.7, the conformation along the main chain (i.e. C1-N1-C9-C10-N2) is given, together with relevant crystallographic characteristics of the structures extracted from the CSD.

In order to compare these structures correctly, it was necessary to generate symmetry releated (inverted) fragments for bupivacaine, BEFLUT, one of the unique fragments of BEVMOE and LIDOCA10. Inclusion of the conformation along the main chain for LIPFAZ is questionable since it's spacegroup symmetry prohibits inversion. The conformation along the main chain of the inverted structure of LIPFAZ was added to table 3.7 because the resemblence of this conformation with the conformation of ropivacaine is striking.

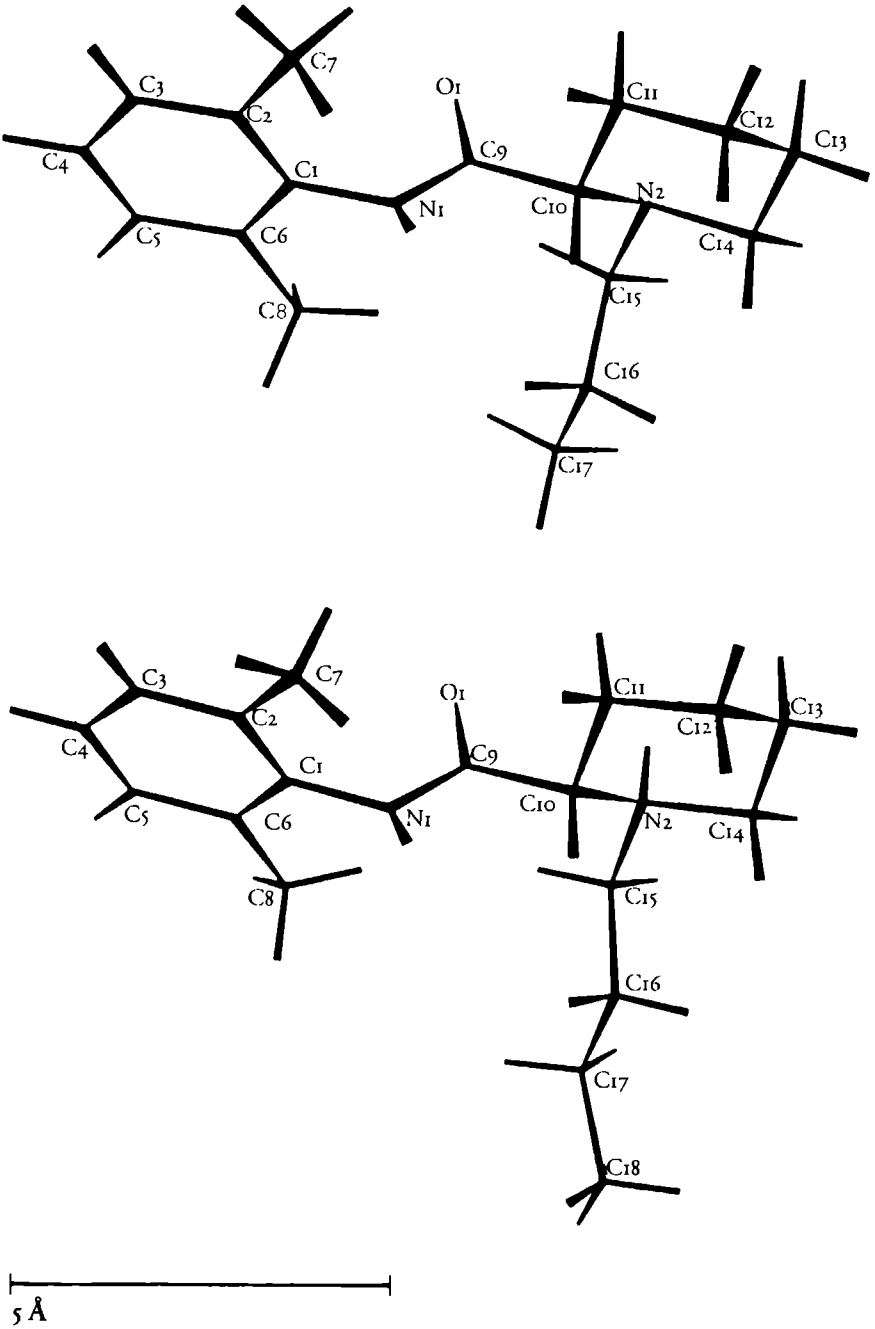
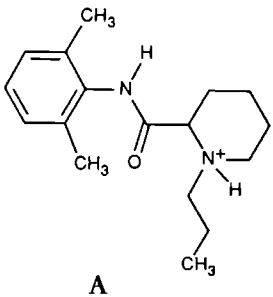


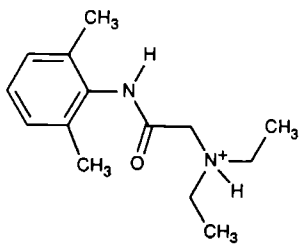
Figure 3.4: Perspective drawings of ropivacaine (upper) and bupivacaine (under).

Table 3.3:Bond lenghts (Å) for non-H atoms of (1) ropivacaine and (2) bupivacaine.

	(1) Ropivacaine	(2) Bupivacaine
C1-C2	1 395(4)	1.394(4)
C1-C6	1.395(4)	1.395(4)
C1-N1	1.416(4)	1.409(4)
C2-C3	1.395(2)	1.395(3)
C2-C7	1.529(6)	1.498(5)
C3-C4	1.395(4)	1.395(4)
C4-C5	1.395(4)	1 395(4)
C5-C6	1.395(2)	1.395(3)
C6-C8	1.524(6)	1 503(6)
C9-C10	1.538(5)	1.521(5)
C9-O1	1.230(5)	1 243(4)
N1-C9	1.323(5)	1.324(5)
N2-C15	1.520(5)	1.503(5)
C10-C11	1 527(5)	1.531(5)
C10-N2	1 499(5)	1.491(5)
C11-C12	1 533(6)	1.516(6)
C12-C13	1 511(6)	1.494(7)
C13-C14	1 511(6)	1.513(6)
C14-N2	1.513(5)	1.500(5)
C15-C16	1 495(7)	1.495(5)
C16-C17	1.517(7)	1.515(6)
C17-C18		1.477(7)



A



B

Figure 3.5: Schematic drawings of ropivacaine (A) and lidocaine (B) active forms.

Table 3.4: Valence angles (°) for non-H atoms for (1) ropivacaine and (2) bupivacaine.

	(1) Ropivacaine	(2) Bupivacaine
C1-C2-C3	120 0(2)	120 0(3)
C1-C2-C7	119 6(3)	120 0(3)
C1-C6-C5	120 0(2)	120 0(3)
C1-C6-C8	120 3(2)	121 4(3)
C1-N1-C9	123 9(3)	122.8(3)
C2-C1-C6	120 0(2)	120 0(2)
C2-C1-N1	120 1(3)	119 2(3)
C2-C3-C4	119 9(2)	120 0(3)
C3-C2-C7	120 3(3)	120 0(3)
C3-C4-C5	120 0(1)	120 0(2)
C4-C5-C6	120 0(2)	120.0(3)
C5-C6-C8	119 7(2)	118 6(3)
C6-C1-N1	119 8(3)	120 7(3)
C9-C10-C11	108 9(3)	107 7(3)
C9-C10-N2	110 2(3)	108 7(3)
N1-C9-C10	115 0(3)	116 2(3)
N1-C9-O1	123 9(4)	124 2(3)
N2-C15-C16	116 2(4)	115 9(3)
O1-C9-C10	121 1(3)	119 5(3)
C10-C11-C12	110.2(3)	112 4(3)
C10-N2-C14	109 2(3)	111.8(3)
C10-N2-C15	115 5(3)	113.8(3)
C11-C10-N2	109 2(3)	109 8(3)
C11-C12-C13	109 7(4)	109 8(4)
C12-C13-C14	111 6(3)	111 2(4)
C13-C14-N2	109 9(3)	110 4(3)
C14-N2-C15	110 9(3)	112 3(3)
C15-C16-C17	109.2(4)	110 3(4)
C16-C17-C18	-	115.4(4)

Table 3 5 Torsion angles (°) for non-hydrogen atoms for (1) ropivacaine and (2) bupivacaine

	(1) Ropivacaine	(2) Bupivacaine
C1-C2-C3 C4	-0 0(4)	0 0(4)
C1-N1 C9-C10	177 8(3)	-170 1(3)
C1-N1-C9-O1	0 2(6)	5 6(6)
C10 C11 C12-C13	56 3(5)	-55 2(5)
C10-N2-C15-C16	-57 5(5)	66 8(4)
C11 C10 N2 C14	61 9(4)	-55 6(4)
C11-C10-N2-C15	-172 3(3)	175 9(3)
C11-C12 C13-C14	-55 5(5)	56 6(5)
C12-C13-C14-N2	57 9(4)	-58 2(5)
C13-C14-N2-C10	-60 7(4)	57 9(4)
C13-C14-N2-C15	170 9(3)	-172 8(3)
C14-N2-C15-C16	67 4(5)	-61 5(4)
C15-C16-C17-C18	-	-167 0(4)
C2-C1-C6 C5	0 1(4)	0 1(4)
C2-C1 C6-C8	-178 2(3)	-180 0(3)
C2-C1-N1 C9	-103 1(4)	104 3(4)
C2-C3-C4 C5	0 0(4)	0 0(4)
C3-C4 C5 C6	0 0(4)	0 0(4)
C4-C5-C6-C1	-0 0(4)	-0 0(4)
C4-C5-C6-C8	178 2(3)	-180 0(3)
C6 C1 C2-C3	-0 0(4)	-0 1(4)
C6-C1-C2 C7	-177 9(4)	178 9(3)
C6-C1-N1-C9	79 4(5)	77 4(4)
C7-C2-C3-C4	177 9(4)	-179 0(3)
C9-C10-C11-C12	179 5(3)	172 8(3)
C9-C10-N2-C14	-178 5(3)	-173 2(3)
C9 C10 N2-C15	-52 7(4)	58 3(4)
N1-C1-C2-C3	-177 5(3)	178 2(3)
N1 C1 C2 C7	4 6(5)	-2 8(4)
N1-C1-C6-C5	177 6(3)	-178 2(2)
N1 C1 C6 C8	-0 7(5)	1 8(4)
N1-C9-C10-C11	-97 3(4)	98 1(4)
N1 C9 C10-N2	142 9(3)	-143 0(3)
N2-C10-C11-C12	-60 1(4)	54 6(4)
N2-C15-C16-C17	-177 0(4)	-179 9(4)
O1-C9-C10-C11	80 3(5)	-77 8(4)
O1-C9-C10-N2	-39 5(5)	41 1(4)

Table 3 6 Geometry of the disordered ethanol in (2) bupivacaine (Symmetry code. ' 1-x,-y,2-z)

C19-O20	1 401(18) Å
C19-O21	1 359(21) Å
C19-C19'	1 477(10) Å
O20-C19-O21	122 3(11) °
O20-C19-C19'	106 2(9) °
O21 C19 C19'	125 0(10) °

Table 3 7 Conformational comparison of (1) Ropvacaine and (2) Bupivacaine with selected related compounds

Name[$]	Space	R	angle[1]	T11[2]	T12	T21	T22	T31	T32	T41	T42	Hbnd[3]
(1) Ropi*	P21[+]	0 056	78 4	-103 1	79 4	0 2	177 8	142 9	39 5	-178 5	-52 7	1
(2)Bupi*	P21/n	0 064	71 9	-104 3	77 4	-5 6	170 1	143 0	-41 1	173 2	-58 3	1
BEFLUT	P21/c	0 043	82 6	-98 6	82 3	0 7	-179 8	157 0	-23 5	168 6	-68 3	-
BEVMOE1*	P21/c	0 114	88 8	-89 4	93 4	0 4	177 8	143 6	-39 0	168 1	63 9	1
LIDOCA10*	C2/c	0 044	65 5	-111 1	70 1	-5 6	173 3	168 0	-13 0	153 4	-78 1	1
LIPFAZ	P212121	0 090	71 4	-73 5	106 9	4 4	-179 2	141 9	-41 9	170 0	66 1	-
LIDNPP*	P21/c	0 067	62 4	-113 6	67 9	6 2	172 2	149 7	-31 8	79 0	-50 4	-
LIDOCN	P21/c	0 110	71 9	-105 6	76 9	-4 9	173 8	131 5	-49 8	72 9	57 0	-
LIDCAN101	P21/c	0 110	76 3	-80 7	102 9	5 1	-177 1	5 2	-177 0	-128 8	107 0	2
LIDCAN102	P21/c	0 110	82 1	-82 4	98 3	0 0	-179 4	1 8	178 8	-131 1	115 9	2
BEVMOE2*	P21/c	0 114	80 8	-101 0	79 0	3 5	-177 7	168 8	-12 4	-123 5	118 5	1

[$]) For references of structures see text
*) Protonated at N2
[+]) Absolute configuration known
[1]) Angle (°) between l s plane through C1 to C8 and N1 and l s plane through C1, N1, C9, O1 and C10
[2]) Torsion angles Tij (°) according to Klyne and Prelog (Klyne 1960)

T11=C2-C1-N1 C9 T12=C6-C1-N1-C9 T21=C1-N1-C9 O1
T22=C1-N1-C9-C10 T31=N1-C9-C10 N2 T32=O1-C9-C10-N2
T41=C9-C10-N2 C14 T42=C9-C10 N2 C15

[3]) Intramolecular hydrogen bond between
1 N2-H O1
2 N1-H N2
- none

From this comparison it is very likely that the structure of LIPFAZ as published by Germain et al. (1977) should be inverted. Yoo et al. (1975) compared the conformations of the main chain of LIDNPP, LIDOCN and LIDOCA10, and reported a different conformation for LIDOCA10 compared to LIDNPP and LIDOCN. Ropivacaine and bupivacaine resemble the conformation of LIDOCA10. Also, from the structures extracted from the CSD, the conformations of the main chain of BEFLUT, of one of the independent molecules of BEVMOE and of LIPFAZ can be regarded as belonging to the same group. A totally different conformation is found for both molecules in LIDCAN10, where the intramolecular N1-H...N2 hydrogen bond dominates the conformation of the main chain.

The conformation of the main chain of the other independent moiety in BEVMOE is different from all of the other conformations found. It should be noted that intermolecular hydrogen bonds play a role in the conformation of the main chain. For the conformations listed in table 3.7, all nitrogen atoms N1 act as intermolecular hydrogen bond donors, as do the protonated nitrogen atoms N2. For the entries in which the nitrogen atoms N2 are not protonated (BEFLUT, LIPFAZ, LIDOCN and LIDCAN10), N2 atoms do not take part in intermolecular hydrogen bonding as acceptors. For the amide oxygen atoms O1, intermolecular hydrogen

bonds are found for the entries BEVMOE (for only one independent molecule), LIDOCA10, LIDOCN and both independent molecules of LIDCAN10, and ropivacaine.

Although the conformations of the ropivacaine and bupivacaine cations are very similar (for a l.s. fit of all common non-hydrogen atoms, fig.3.6; mean deviation = 0.22Å), the molecular packing arrangements are quite different. In (1) ropivacaine, adjacent ropivacaine cations are joined by strong hydrogen bonds to water, i.e. between O1...H-O2 and O2...H1′-N1′, to form chains parallel to **b**. Also, the anionic chlorine participates in the hydrogen bonding by accepting a waterproton and an amino-proton. The amino-proton could not be located, but distances and angles involved in the assumed hydrogen bonding scheme are acceptable. The rather weak intramolecular hydrogen bond between O1 and N2 as described by Hanson (1972) is less favourable than the N2...C11 hydrogen bond.

Table 3.8 summarizes the distances and angles involved in hydrogen bonding. Fig. 3.7 shows the packing along the a-axis for (1) ropivacaine. Fig.3.8 shows a perspective drawing of the crystal packing along the a-axis for (2) bupivacaine.

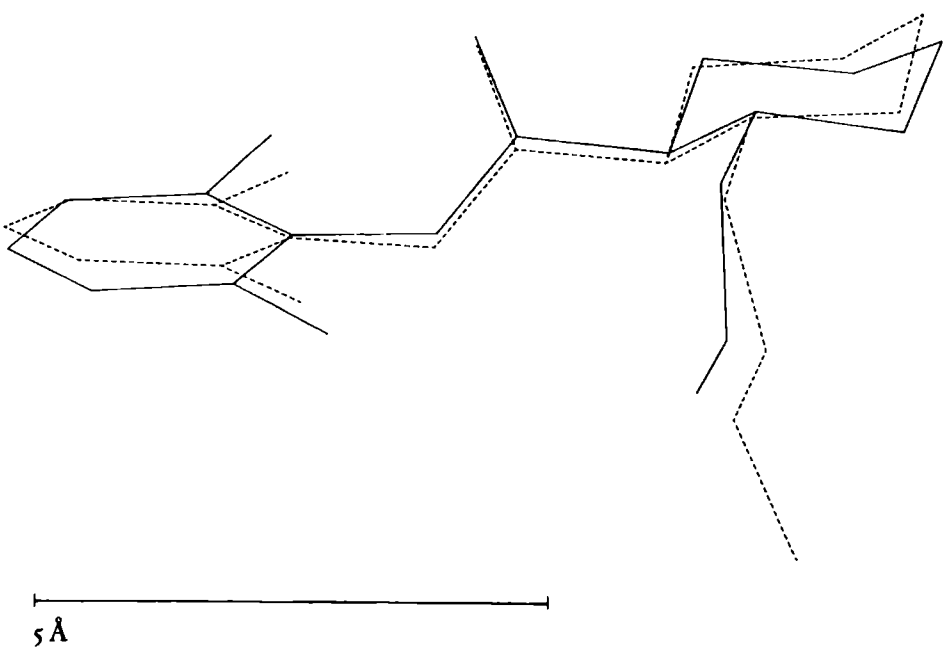


Figure 3.6: Stick drawing of the ropivacaine and bupivacaine cations (non-hydrogen atoms only) showing their similar overall conformation. Solid lines ropivacaine; dashed lines bupivacaine.

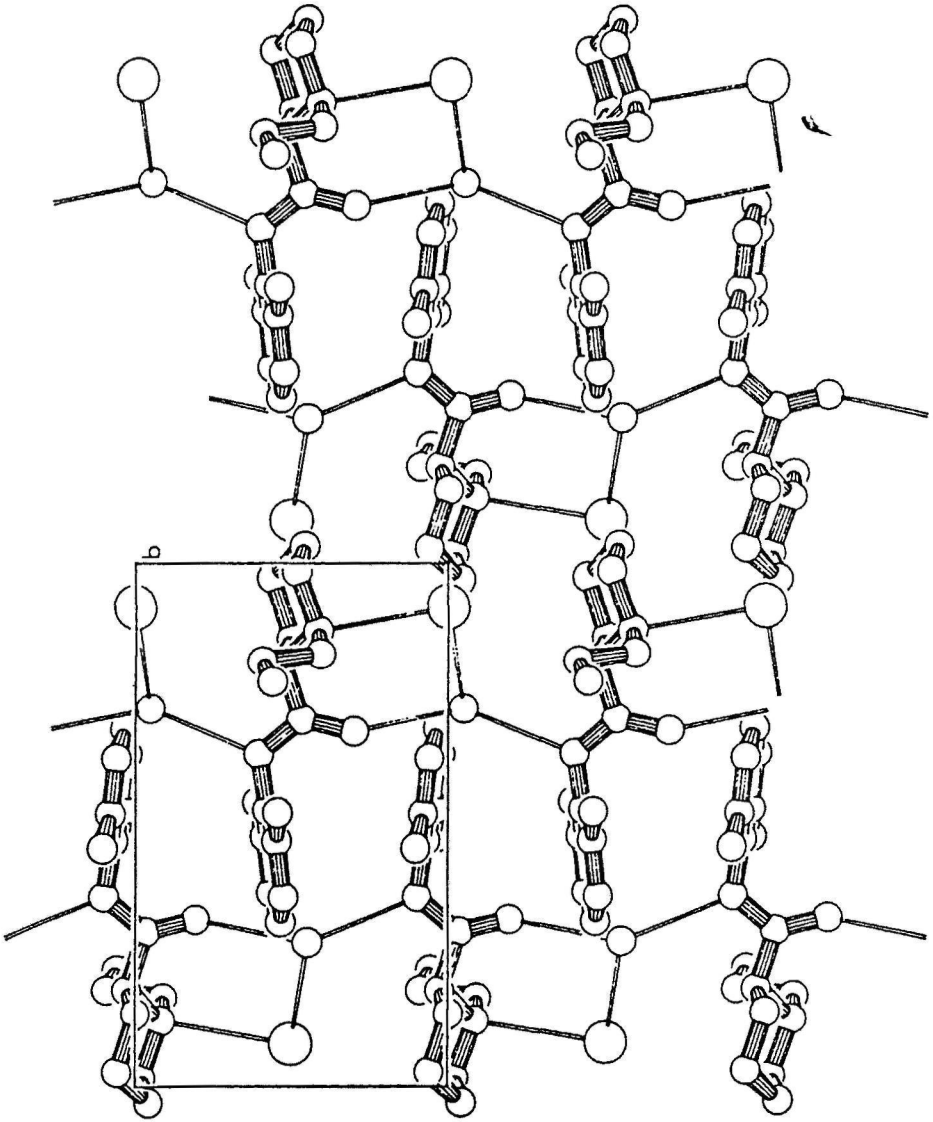


Figure 3.7: Hydrogen bonded chains in (1) ropivacaine, viewed perpendicular to b, c,-plane.

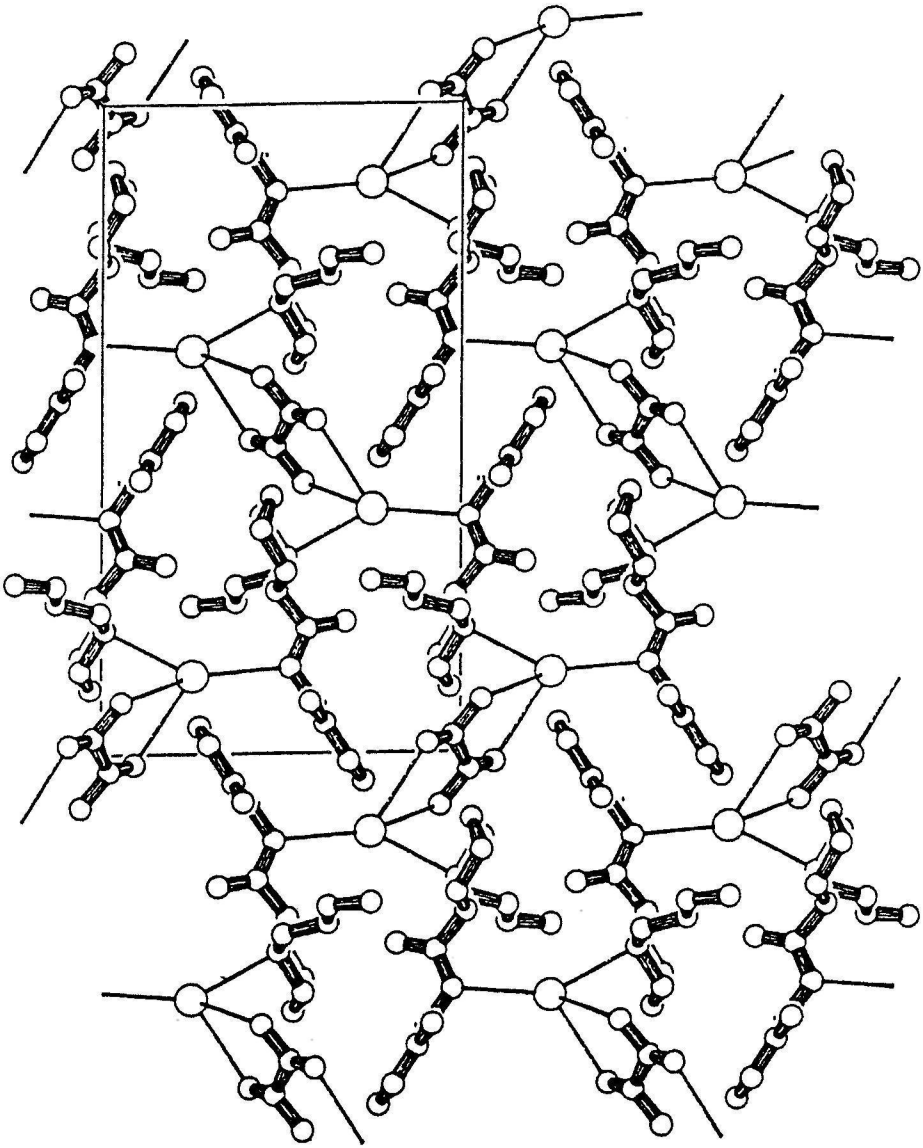


Figure 3.8: Hydrogen bonded chains in (2) bupivacaine, viewed perpendicular to b, c-plane.

Table 3.8: Distances (Å) and angles (°) involved in hydrogen bonding for (1) ropivacaine.

CL1...N2	3.107(3)
CL1...O2	3.109(4)
O1...N2	2.836(4)
O1...O2	2.838(4)
N1...O2a	2 910(5)
H1...O2a	2.09(5)
N1-H1...O2a	175(4)

Symmetry Code
None: x,y,z;
a: x,y+1,z

Table 3.9: Distances (Å) and angles (°) involved in hydrogen bonding for (2) bupivacaine.

CL1...N1	3.183(3)
CL1...H1	2.35(4)
N1-H1...CL1	173(4)
O1...N2	2 771(4)
O1...H2	2.58(4)
N2-H2...O1	94(4)
CL1...N2a	3.100(3)
CL1...H2a	2.32(4)
N2a-H2a...CL1	156(4)
CL1...O20a	3.321(17)
CL1...O21b	3.291(19)

Symmetry code
None. x,y,z ;
a:-x+3/2,y-1/2,-z+3/2;
b:x+1/2,-y-1/2,z-1/2

Bupivacaine cations, chlorine anions and the disordered ethanol molecules are held together by hydrogen bonds and van der Waals contacts to form layers parallel to the plane characterized by the 'Miller indices' 101. All positions of the disordered ethanol are shown to illustrate the connection in the total hydrogen bonding scheme. As in (1) ropivacaine, the hydrogen bond between Cl1 and N2 is stronger than the intramolecular hydrogen bond between O1 and 2, because of the unfavourable angles involved in the latter. Table 3.9 summarizes the hydrogen bonding scheme in terms of distances and angles. The layers perpendicular to the 'Miller plane' 101 show a nonpolar interaction between the inversion related adjacent phenyl rings of the bupivacaine cations (Fig. 3.8). The distance between the least-squares planes through the adjacent phenyl rings is only 3.08Å. Adjacent layers are held together by van der Waals contacts.

Ropivacaine and bupivacaine crystallize in the same conformation, although their crystallographic packing schemes are quite different. This conformation of active (protonated) form of both molecules was recognized earlier in related lidocaine derivatives.

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Cardiovascular effects of epidural blockade

Corning has been credited with being the first to use epidural analgesia in 1885 (Corning 1885). Epidural analgesia has been practiced since 1901 with the use of several techniques. Sicard and Cathelin popularized the caudal approuch. In 1921 Fidel Pages renewed interest in the midline lumbar approach (Pages 1921). The introduction of the Tuohy's needle and the epidural catheter, managed to escape the genera decline in use of regional techniques (Fink 1988).

During the 1960s, epidural blockade became the most widely used technique of neural blockade for postoperative and obstetric pain relief. The development of long-acting local anesthetics and increasing knowledge of the physiology of regional anesthesia have ensured that epidural anesthesia is safe and practical.

However, the administration of local anesthetic drugs into the epidural space affects the cardiovascular system in a number of ways. The cardiovascular effects associated with epidural blockade are related to:

1 The type and dosage of the local anesthetic agent.
2 The addition of vasoconstrictors.
3 The level of sympathetic blockades.
4 The blood volume status of the patient.

Toxicity of local anesthetic agents

Local anesthetic agents are relatively free from side effects if they are administered in an appropriate dosage and in the appropriate anatomical location. However, systemic and localized toxic reactions may occur.

Local anesthetics when employed clinically, rarely produce localized nerve damage. In recent years, prolonged sensory deficits have been reported in some patients following the normal extradural or intrathecal administration of large doses of chloroprocaine (Reisner 1980). The cause of the potential neurotoxicity is believed to be related to the low pH and the presence of sodium bisulphite, an antioxidant. Skeletal muscle appears to be more sensitive to the local irritant properties of local anesthetic agents than other tissues. In general, the more potent and longer acting agents cause a higher degree of damage than the less potent and shorter acting agents. This effect on skeletal tissue is reversible and regeneration occurs within 2 weeks.

Systemic reactions to local anesthetics primarily involve the central nervous and the cardiovascular systems. These reactions are due to the inappropriate use of local anesthetics, such as accidental intravascular or intrathecal administrations of an excessive dosage.

In general the central nervous system is more susceptible to local anesthetics than the cardiovascular system (Scott 1981). The most common manifestation of central

nervous system toxicity is related to central nervous excitation (dizziness, tinnitus and convulsions). This central nervous excitation also results in cardiovascular changes: hypertension, tachycardia and dysrhythmias (Heavner 1986).

Considerable interest in cardiotoxicity of local anesthetics has developed over the last decade. This interest stemmed from cardiac deaths induced by bupivacaine and etidocaine (Albright 1979). Direct local anesthetic induced cardiovascular depressions occur less frequently than central nervous system reactions. However, adverse effects involving the cardiovascular system tend to be more serious and more difficult to manage. Administered local anesthetics can exert a direct action both on cardiac muscle and on vascular smooth muscle.

Cardiac effects: cardiodepression and cardiac dysrhythmias

The mechanism of direct cardiac depression by local anesthetics involves effects of ionic conductance in myocardial conducting membranes and in the myocardial conducting system. A decrease in maximum rate of depolarization is believed to be due to an interaction with the fast sodium channels in the cardiac membrane, which results in a decreased rate of depolarization(Clarkson 1985). The ability of local anesthetic drugs to depress the contractility of cardiac muscle is proportional to their ablility of cardiac muscle to suppress conduction in peripheral nerves.

However, death following administration of local anesthetics is due to severe cardiac dysrhythmias: ventricular arrhythmias and ventricular fibrillation (Kotelko 1984). The electrophysiological changes produced by bupivacaine suggest that reentry phenomena may cause severe ventricular arrhythmias (Moller 1988). Several studies have been performed to compare the electrophysiological effects of ropivacaine and bupivacaine. In all these studies ropivacaine appears to provide a greater margin of safety than bupivacaine (Pedigo 1988, Nancorrow 1989, Reiz 1989, Moller 1990).

Vascular effects

Local anesthetic agents can exert significant effects on peripheral blood vessels. Studies have demonstrated that local anesthetic agents have a biphasic action on smooth muscle of peripheral blood vessels (Blair 1975). Low concentrations of local anesthetics causes an increase in basal tone of the vascular smooth muscle. By increasing the dose of the local anesthetic agent, the stimulatory or vasoconstrictor action changes to inhibition and vasodilatation. All of the local anesthetic agents which have been studied exert this biphasic effect with the exception of cocaine and ropivacaine. In a comparative study with bupivacaine, ropivacaine appeared to be an effective vasoconstrictor for the cutaneous microvasculature (Kopacz 1988). Dahl et al (1990)

demonstrated that epidural blood flow decreased 37% after administration of ropivacaine, compared to a 17% increase with bupivacaine.

Vasoconstrictors

Vasoconstrictors are frequently added to local anesthetic solutions to reduce toxicity, prolong duration and improve the intensity of blockade. Local anesthetic solutions usually contain a 1:200.000 (5 $\mu g.ml^{-1}$) concentration of epinephrine. Vasoconstrictors are less effective in prolonging the anesthetic properties of long acting drugs (Covino 1976). In extradural blockade duration of adequate analgesia was only improved when epinephrine 1:200.000 was added to 0.125% and 0.25% bupivacaine. The value of adding epinephrine to long acting drugs is the reduction of the potential danger of systemic toxic local anesthetic reactions, by a reduction of peak plasma concentrations (Burm 1985). However, the addition of epinephrine to local anesthetics also exerts systemic circulatory effects by stimulating both alpha and beta adrenergic receptors. Bonica and associates describe the effects of epinephrine (Bonica 1971).Chapter 6 of this thesis describes the effects of 100 µg epinephrine added to 20 ml 0.5% bupivacaine used in epidural blockade.

Sympathetic blockade in epidural blockade

Epidural blockade results in sympathetic nerve block. The cardiovascular effects depends on the site and level of the block. Lumbar epidural blockade up to T5 causes arteriolar and venous dilatation in the pelvis and lower limbs. This results in a decrease in venous return and consequently a reduced cardiac output. Blockade above T5 affects not only sympathetic vasoconstrictor fibres but also the sympathetic innervation of the heart. This results in a reduction in heart rate and cardiac output. The reduction in cardiac output is related to the inhibition of myocardial sympathetic fibres resulting in a decreased cardiac contractility and also in a decrease in venous return from venodilatation and expansion of capacitance vessels (Ward 1965). The effects of sympathetic blockade may be exaggerated in certain cardiac conditions. However, Baron showed that decrease in left ventricular loading induced by lumbar epidural anesthesia may improve left ventricular function in patients with stable mild related angina (Baron 1987).

Blood volume status of the patient

Cardiovascular changes are more pronounced in hypovolemic patients (Bonica 1972). Epidural anesthesia in hypovolemic volunteers is associated with profound hypoten-

sion. The addition of epinephrine to the local anesthetic solution usually results in a less profound hypotension.

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Noninvasive hemodynamic monitoring by thoracic bioimpedanc

Blood transports oxygen and nutrients to the tissues and removes waste products from the tissues that have been produced in metabolic processes. The circulatory system consists of three main components: the heart, the blood vessels and the blood.

The heart provides the pumping force necessary to circulate the blood throughout the bloodvessels. As the body's need for oxygen and nutrients alters, tissue perfusion changes through central and local modulation, i.e. vasoconstriction-vasodilatation and change in cardiac output.

Cardiac output is defined as the volume of blood ejected by the heart per unit of time (minute). Cardiac output is the product of heart rate and stroke volume. Cardiac output measurements are used to monitor cardiovascular performance and to assess the response of patients to drugs.

The stroke volume is the volume of blood ejected by the heart during each contraction. Over a period of time cardiac output must equal venous return. Under normal circumstances the major factor determining the stroke volume is the rate of venous return (Guyton 1959). The intrinsic ability of the heart to adapt to changing venous return is described by Frank and Starling (1895). Basically, the Frank-Starling law states that the force of cardiac contraction increases in proportion to the degree of diastolic stretch (preload) of the myocardial fiber (Noble 1978).

Preload is defined as the initial ventricular muscle fiber length at end-diastole. Clinically, preload is determined by the ventricular end-diastolic volume. Changes in left ventricular end-diastolic volume will alter left ventricular end-diastolic pressure, which is reflected by the pulmonary capillary wedge pressure (Swan 1970).

Ejection fraction, defined as the ratio of stroke volume to end diastolic volume, is a global index of the extent of ventricular fiber shortening. The ejection fraction has the advantage of being dimensionless; therefore, it does not require correction for body size.

Cardiac output measurements

Today, numerous methods are available for the measurement of cardiac output. One way to categorize the methods of cardiac output is based on their invasiveness (Ehlers 1986). The majority of techniques are invasive, requiring entrance into the body (dilution technique, electromagnetic flow probe and Fick). This increases the risk of infection, thrombosis, vessel perforation and air embolism (Shah 1984). Several techniques exist which allow cardiac output measurement without entering the body; hence, they are classified as noninvasive. Transthoracic bioimpedance and doppler ultrasound methods are two noninvasive techniques presently used.

The ideal method would be noninvasive, continuously, easy to perform, safe and inexpensive. In the discussion of any technique two characteristics must be considered: accuracy and reproducibility.

Administration of local anesthetics influences the cardiovascular system leading to hemodynamic alteration. Monitoring of patients during regional anesthesia is done to determine the change in the hemodynamics and to evaluate the response to administered vasoactive drugs.

The indications for cardiovascular monitoring in patients undergoing epidural anesthesia are:

1 Measurements of quantitative alterations in cardiovascular functions (blood pressure, heart rate, cardiac output).
2 Monitoring of changes in hemodynamics during surgery caused by blood loss and body position.
3 Evaluation of cardiovascular function after administration of new local anesthetics.
4 Evaluation of the treatment of the hemodynamic changes (bradycardia, hypotension), which often involves administration of potent drugs with specific cardiovascular effects.

The effects of epidural blockade on physiologic parameters have been discussed in chapter 4. In general, cardiovascular depression is related to the level of the sympathetic blockade, the dose and the cardiotoxicity of the administered drug.

The minimal standards for basic peri-operative monitoring are continuous ECG tracing, plethysmography and arterial blood pressure measurement (Gezondheidsraad 1978). When cardiovascular parameters are measured, the intervention-related risk to the patient must always be carefully balanced against potential benefit. Hence the use of non-invasive methods are most desired.

Thoracic bioimpedance monitoring

When a high frequency alternating current is applied across the chest, changes in the thoracic impedance can be recorded. In the early decades of this century many authors used this principle to study the volume changes of the heart. The method used for calculating stroke volume is based on spontaneous rhythmic variation in thoracic electrical bioimpedance. Such variation is induced by fluctuations in the caliber of the large vessels, which in turn are caused by the cardiac cycle. For this reason the method was called impedance plethysmography (Nijboer 1950).

In 1966, Kubicek developed a noninvasive method to estimate the cardiac output by thoracic bioimpedance, yielding acceptable correlation with invasive methods but reliable only in healthy men (Kubicek 1966). The empirically derived formula to calculate stroke volume is:

$$SV = \tau \frac{L^2}{Z_0^2} (dZ/dt)_{max}.T \qquad (5.1)$$

SV = stroke volume, ml
τ = specific resistivity of blood, ohm.cm^{-1}
L = length of measured segment, cm
Z_0 = basic impedance, ohm
T = ventricular ejection time, seconds
dZ/dt_{max} = the maximum inflection of the first derivative (dZ/dt) of impedance changes, ohms.s^{-1}

In several studies the method of measuring cardiac output by Kubicek's impedance equation , when compared with other techniques (thermodilution, Fick, radionuclide angiocardiography), showed a good correlation (Kubicek 1966, Muzi 1985, Williams 1985, Hatcher 1986). However, at that time expansion of the technology to patients with severe illnesses produced poor correlations.

One of the major problems in equation 5.1 is the measurement of τ (resistivity of blood). Other limitations in the equation are: it assumes the thorax to be a cylinder, it overestimates stroke volume in wet-lung patients and it requires a period of apnea.

The problems and deficiencies of the Kubicek equation were reevaluated by Sramek and Bernstein (Bernstein 1986). They proposed a new set of equations to obviate the false assumptions of the Kubicek equation. The Sramek-Bernstein equation has since then been incorporated into the software of a microprocessor (the NCCOM-3, BoMed Medical Manufacturing, Ltd, Irvine, CA). The bioimpedance cardiac output monitor NCCOM-3 calculates stroke volume for every heart rate according to equation 5.2.

Figure 5.1 shows the time relationships between the electrocardiogram, arterial pressure, and dZ/dt waveform. The thoracic bioimpedance change is an approximate image of arterial pressure (middle curve in figure 5.1). The change in thoracic bioimpedance originates in two pressure related phenomena: the volumetric change in blood in the thoracic segment due to arterial pressure compliance and the alignment of red cells due to variation in velocity. By magnitude, the cardiovascular impedance change is approximately 0.5% of base impedance or 10% of ventilation impedance change.

$$SV = VEPT \times VET \times \frac{EVI}{TFI} \qquad (5.2)$$

SV = stroke volume, ml
VEPT = physical volume of electrical participating thoracic tissue, ml

$$VEPT = \frac{L^3}{4{,}25} \qquad L = 17\% \text{ of the patients height (cm)}$$

VET = ventricular ejection time, seconds
EVI = $(dZ/dt)_{max}$ = ejection velocity index ohms.sec^{-1}
TFI = Z_0 = thoracic fluid index, an indication of thorax fluid content, ohm

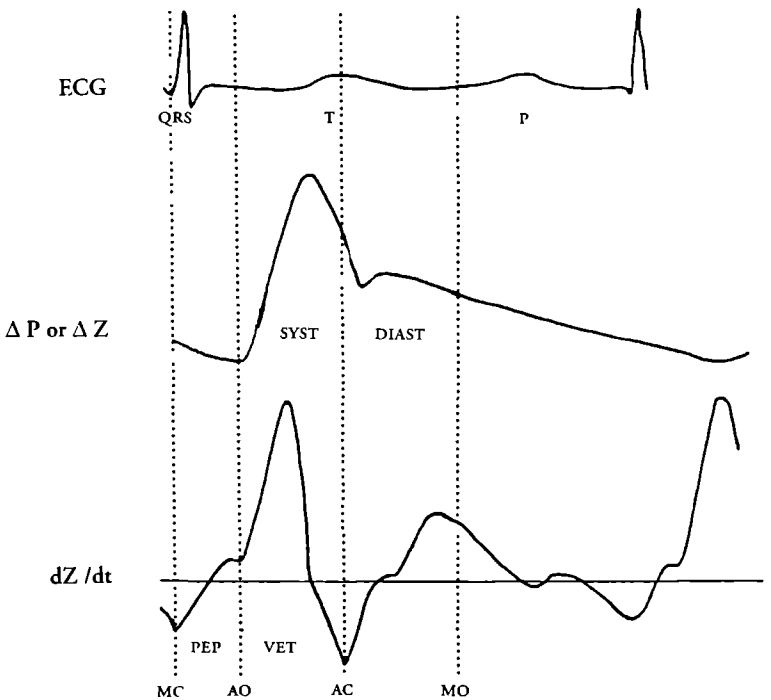

Figure 5 1 Simultaneously recorded electrocardiogram (FCG), change in arterial pressure (ΔP) or change in cardiovascular impedance change (ΔZ), and the first derivative of the thoracic impedance dZ/dt syst= systole, diast= diastole, PEP= pre-ejection period, VET= ventricular ejection time, MC= mitral valve closed, AO= aortic valve open, AC= aortic valve closed, MO= mitral valve open

The TFI (thoracic fluid index) measured in ohms represents the total resistance of the thorax to the flow of electric current (2.5 mA., 70KHz). Thus the TFI represents the contribution of the interstitial and intravascular fluids. The VET (ventricular ejection time) is the period in seconds of mechanical systole, measured between the opening and closure of the aortic valve in seconds. The EVI (ejection velocity index) is the maximum value measured in ohms of the rate of thoracic impedance change $(dZ/dt)_{max}$. The VEPT (volume of electrical participating tissue) is the volume in ml of the truncated cone.

The Sramek-Bernstein equation differs from equation 5.1 in that:

1 The thoracic volume conductor is modelled geometrically as a truncated cone rather than as a cylinder.
2 The specific resistivity of blood, τ, is eliminated.
3 The measured thoracic length is replaced in the equation by a volume of electrically participating tissue, calculated by the microprocessor (in the monitor) from the patient's height.

Recent studies allow the comparison of cardiac output measurements by thoracic bioimpedance with several other methods, both in the clinical setting and in experimental models. In the interpretation and discussion of the clinical results in comparisons between the thoracic bioimpedance method and other methods of cardiac output monitoring, we have to keep in mind that no perfect method for measuring cardiac output is available. Most of the studies confirm experimental and clinical findings with acceptable levels of correlation between thermodilution and thoracic bioimpedance cardiac output measurements (Hetherington 1985, Appel 1986, Bernstein 1986, Tremper 1986, Kerkkamp 1988).

Based on changes in the electrical conductivity of the thorax, the NCCOM-3 has the capacity to display several cardiodynamic parameters. The standard, clinically used parameters are: heart rate, stroke volume, cardiac output, end diastolic volume and ejection fraction. As this technique is continuous and noninvasive, there is no harm to the patient. Therefore bioimpedance cardiac output monitoring has particular relevance in research concerning the hemodynamic effects of anesthetic agents or certain procedures which are known to cause cardiovascular disturbance.

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Hemodynamic monitoring in epidural blockade: cardiovascular effects of 20 ml 0.5% bupivacaine with and without epinephrine

H.E.M. Kerkkamp, M.J.M. Gielen

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Parts of this study have been presented at the 14th Annual ASRA Meeting, Boston, USA, March 30-April 2, 1989.

Abstract

Twenty patients scheduled for elective urologic surgery received epidural anesthesia with 20 ml 0.5% bupivacaine. Ten patients received an epinephrine-free solution and ten patients received epinephrine 5 $\mu g.ml^{-1}$ added to the local anesthetic solution. The mean maximum level of sensory blockade was not different between the two groups (T7 and T8). After epidural administration of 20 ml of either solution, the mean arterial blood pressure decreased significantly from pre-blockade values. After administration of 0.5% bupivacaine with epinephrine, cardiac output, stroke volume and end diastolic volume increased significantly from pre-blockade control values. These changes occurred within two to four minutes after injection of the local anesthetic solution and are caused by the systemic effects of epinephrine. After 15 minutes the ejection fraction in the plain bupivacaine group decreased significantly from pre-blockade control values and the bupivacaine with epinephrine group. The differences in hemodynamic effects of the two solutions can be explained by the vasoactive effects of epinephrine and the cardiodepressive effects of bupivacaine.

Introduction

The hemodynamic effects of epidural anesthesia are complex and are related to (1) the level of anesthesia, (2) the amount and type of anesthetic injected, (3) the addition of vasoconstrictors to the local anesthetic solution and (4) the physical status of the patient. Epidural blockade that is restricted to the level of the lumbar region results in peripheral sympathetic blockade with level vascular dilatation in the pelvis and lower limbs. If all splanchnic fibers are blocked (T6-L1), pooling of blood in the abdominal region may also occur. The blockade results in an arteriolar vasodilatation (decreased systemic vascular resistance) and pooling of blood in the venous capacitance vessels (Bonica 1971). Because the capacitance vessels contain 80% of the blood volume, venodilatation can have a dramatic effect on end diastolic volume, cardiac output and blood pressure.

Low doses of local anesthetics decrease peripheral arterial flow without any change in systemic arterial pressure. Higher doses result in an increased blood flow in peripheral arteries indicating a state of vasodilatation.

Since Braun first described the addition of epinephrine to local anesthetics, its pharmacokinetic and pharmacodynamic have been studied widely (Tucker 1975). The advantages of adding epinephrine to local anesthetics are the generation of a more intense block, a longer duration of anesthesia, and a reduction of systemic toxic reactions by reducing the peak plasma concentration (Stanton-Hicks 1973, Tucker 1979, Burm 1986).

In previous studies, the circulatory effects of epidural blockade with lidocaine-epinephrine solutions were studied (Bonica 1971, Stanton-Hicks 1973). Cardiac output was measured with invasive methods: thermodilution or dye dilution techniques. These techniques are expensive, can only be performed intermittently and are not without risk (Foote 1974, Barash 1981, Shah 1984).Bioimpedance cardiac output monitoring has the advantage of being noninvasive and continuous. The continuous nature of the measurements is of great value for detection of changes in circulatory performance (Appel 1986, Hanna 1988, Mcmenemin 1988). The aim of the present study was to measure heart rate, mean arterial blood pressure, stroke volume, cardiac output, end diastolic volume and ejection fraction in response to the lumbar epidural injection of 20 ml 0.5% bupivacaine in contrast to the injection of 20 ml 0.5% bupivacaine with epinephrine 5 $\mu g.ml^{-1}$.

Methods

Twenty patients ASA 1 or 2 scheduled for urologic surgery under epidural anesthesia were studied. The study was randomized and performed in a double blind fashion. The patients were divided into two groups: Group 1 received 20 ml 0.5% bupivacaine, group 2 received 20 ml 0.5% bupivacaine with epinephrine 5 $\mu g.ml^{-1}$.

The study was approved by the local Ethical Committee of the Hospital. Each patient was informed about the purpose of the study and oral consent was obtained. None of the patients had a history of cardiovascular disease or received cardiovascular medication. Premedication consisted of 10 mg diazepam orally, 60-90 minutes before inserting the epidural catheter. Each patient received 500 ml of a balanced electrolyte solution (NaCl-Dextrose), which was administered prior to the epidural catheter insertion.

The epidural space was identified by the loss-of-resistance technique, the patient being in the lateral position, using an 18 gauge Tuohy needle in the 2-3 or 3-4 lumbar epidural interspace via a midline approach. An epidural catheter was inserted to a depth of 3 cm and the patient was turned supine.

Before injecting the local anesthetic solution, a 15-minutes rest period was observed. Systolic, diastolic and mean arterial blood pressure were measured at 1 minute interval with an automatic blood pressure monitor (EME Bristol Gardens, England). Cardiovascular measurements (heart rate, cardiac output, stroke volume, end diastolic volume and ejection fraction) were continuously obtained with the NCCOM-3 cardiodynamic monitor (Bomed Medical Manufacturing, Irvine, California). The cardiovascular parameters obtained five minutes before epidural injection were used as pre-blockade control values.

In order to exclude spinal placement of the catheter, a test dose of 3 ml 0.5% bupivacaine or 3 ml 0.5% bupivacaine with epinephrine 5 $mg.ml^{-1}$ was injected. Approximately three minutes after the test dose, the remaining 17 ml of one of the bupivacaine solutions was injected within one minute. The hemodynamic measurements were continuously monitored started at the end of the bupivacaine injection (t=0), for 30 minutes, with the patient still in the supine position. Sensory analgesia was determinated by the pinprick method using a blunt 27-gauge needle. After 30 minutes, the patient was transported to the operating theatre and surgery was performed.

The data are expressed as relative changes from the pre-blockade control values, taking the pre-blockade values as 0%. Statistical analyses between the control values and the changes in each group were performed using the Student's paired t-test. The significance of the difference between the means of the two solutions were calculated with the unpaired t-test. $P < 0.01$ was considered statistically significant.

Results

Twenty male patients participated in the study. There was no difference between the groups with regard to age, height and weight (table 6.1).

Onset and spread of analgesia

The dermatomal levels reached for the two groups are shown in figure 6.1. For the majority of patients in both groups, the upper analgesic limit reached T7. No signifi-

cant differences in onset times were found between the two groups at any segmental level.

Hemodynamic effects

The absolute figures for the hemodynamic measurements (control values) before injection of the local anesthetic drug are shown in table 6.2. In table 6.3 the relation between mean maximum relative hemodynamic changes from control values and time from the end of epidural injection is given.

Table 6.1: Demographic data (mean + SEM).

	Bupivacaine 0.5% (n=10)	Bupivacaine 0.5% with epinephrine 5 $\mu g.ml^{-1}$ (n=10)
Age (years)	57(6.1)	61(4.8)
Weight (kg)	75(3.8)	73(2.7)
Height (cm)	174(2.6)	173(1.8)

n= number of patients

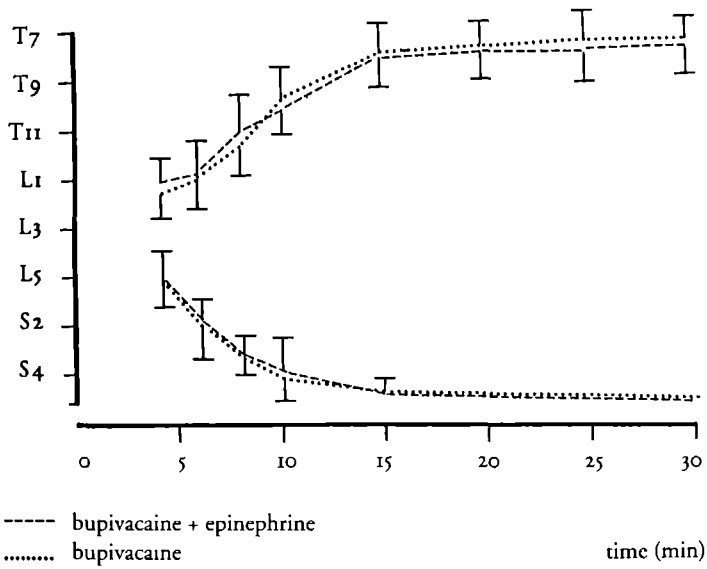

Figure 6.1: The onset of sensory blockade after epidural injection. Values are means ± SEM.

Table 6 2 Mean pre-blockade hemodynamic values with standard deviations between parentheses (control value = 0% change).

	Bupivacaine	Bupivacaine with epinephrine
Heart rate (bpm)	74(16)	78(14)
Mean arterial blood pressure (mm Hg)	100(17)	101(14)
Stroke volume (ml)	67(19)	72(24)
Cardiac output (l/min)	5 0(1 6)	5 7(1 8)
End diastolic volume (ml)	130(35)	110(27)
Ejection fraction (%)	57(10)	61(9)

Table 6 3 Relation between mean maximum relative hemodynamic changes from control values and the time after the end of epidural injection

	Bupivacaine		Bupivacaine with epinephrine	
	change(%)	time(minutes)	change(%)	time(minutes)
HR	+5	20	-6	2
MAP	-17*	20	-11**	15
SV	-16	25	+53*	10
CO	-11	25	+60*	15
EDV	+11	15	+43*	10
EF	-12**	25	+5	10

HR=heart rate, MAP=mean arterial pressure, SV=stroke volume, CO=cardiac output, EDV=end diastolic volume, EF=ejection fraction
Significant change from control * $p < 0.001$, ** $p < 0.01$

Changes in heart rate are illustrated in figure 6.2. The changes in heart rate within the groups were not significant, nor were the changes between the two groups. Mean arterial blood pressure decreased significantly in both groups, five minutes after the end of injection (figure 6.3). No significant differences were found between the two groups with regard to changes in mean arterial blood pressure, although the plain bupivacaine group tended to decrease more. Significant hypotension (defined by >30% drop in pre-blockade systolic blood pressure) requiring administration of intravenous drugs was not observed in this study.

Changes in stroke volume and cardiac output are illustrated in figures 6.4 and 6.5, respectively. Two minutes after injection of bupivacaine with epinephrine, stroke volume and cardiac output increased significantly from control values. Maximum mean relative change in stroke volume was 53%, ten minutes after the end of epidural injection of bupivacaine with epinephrine. Maximum mean relative change in cardiac output was 60% and occurred 15 minutes after epidural injection. Significant differences in stroke volume and cardiac output between the two groups occurred after four and eight minutes respectively. The maximum relative change in end diastolic volume was 43%, ten minutes after the end of the bupivacaine with epinephrine injection (figure 6.6).

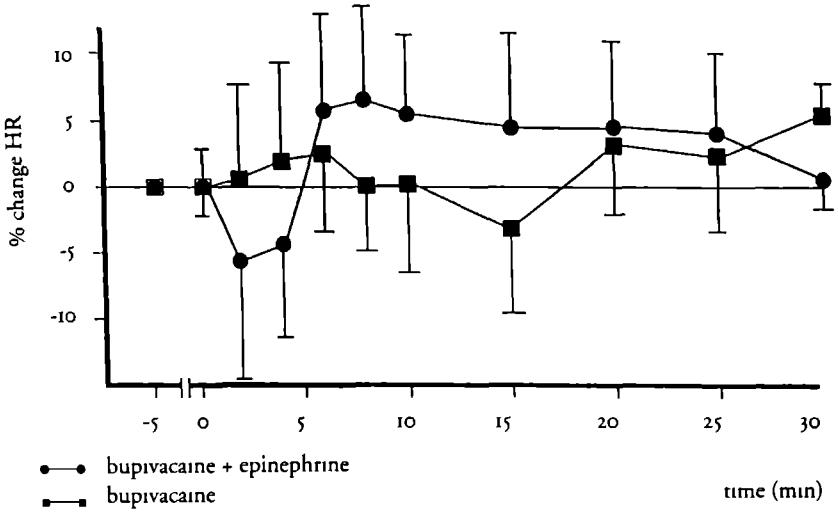

Figure 6 2 Changes in heart rate Each point represents the mean (± SEM) relative change from control values T= -5 represents the mean pre-blockade injection control value T=0 represents the values at the end of the epidural injection

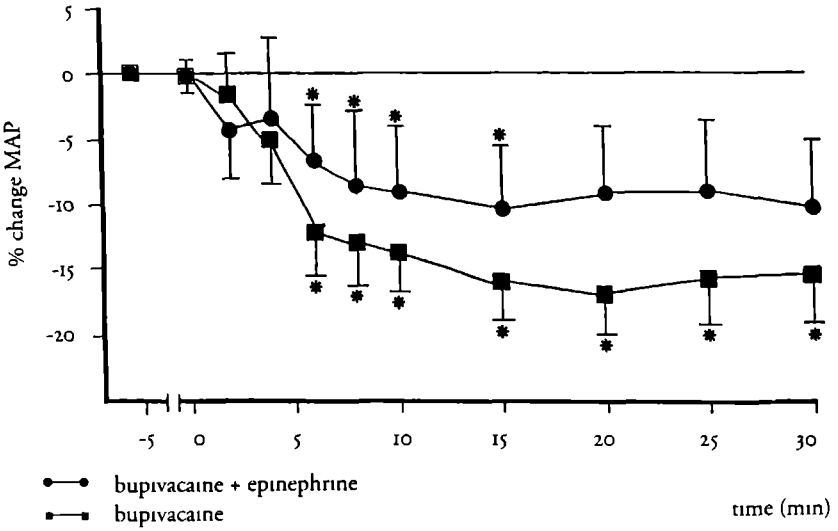

Figure 6 3 Changes in mean arterial blood pressure Each point represents the mean (± SEM) relative change from control values Statistical significant differences within the groups are indicated by *

Comparison of the mean relative change in ejection fraction between the two groups showed a significant difference six minutes after the end of the epidural injection of the local anesthetics (figure 6.7). While no significant changes from control were observed in the bupivacaine with epinephrine group, the ejection fraction for the plain bupivacaine group decreased significantly 15 minutes after injection. The maximum

relative change in ejection fraction was -12% in the plain bupivacaine group and occurred 25 minutes after epidural injection.

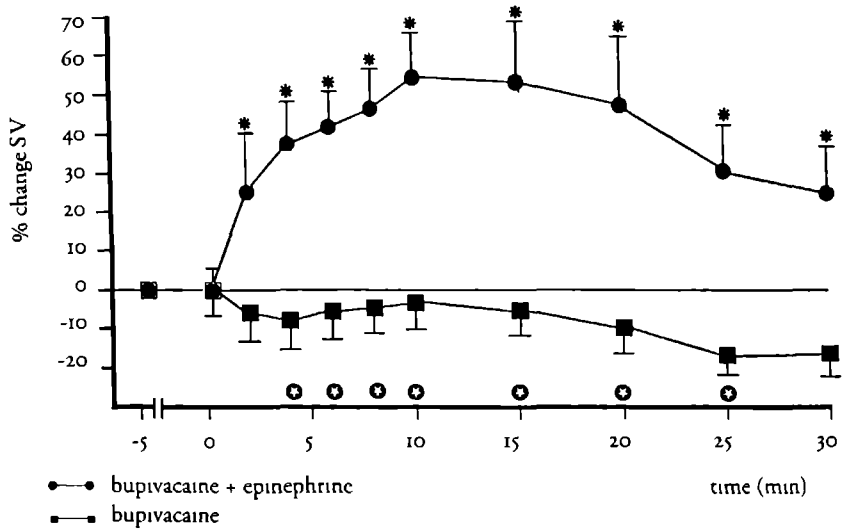

Figure 6 4 · Changes in stroke volume Each point represents the mean (± SEM) relative change from control values. Statistical significant differences within the groups are indicated by * and between the groups by ✪ .

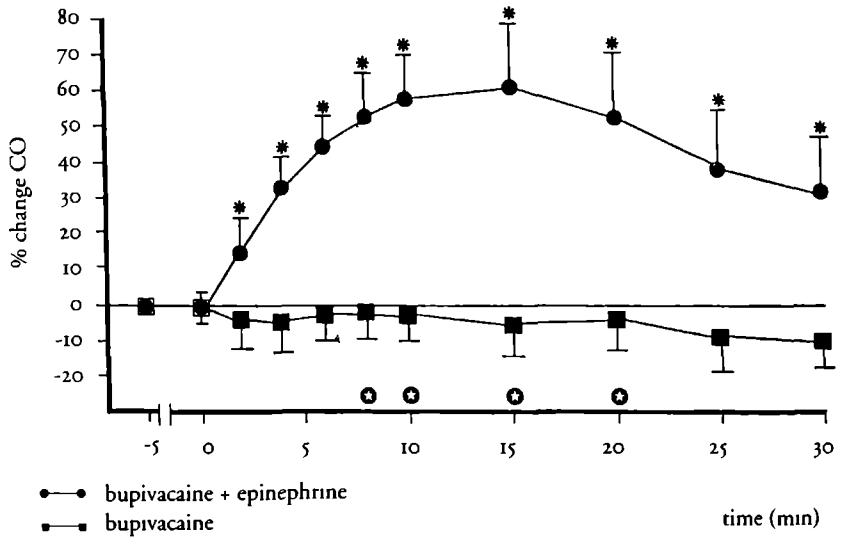

Figure 6 5 · Changes in cardiac output. Each point represents the mean (± SEM) relative change from control values. Statistical significant differences within the groups are indicated by * and between the groups by ✪ .

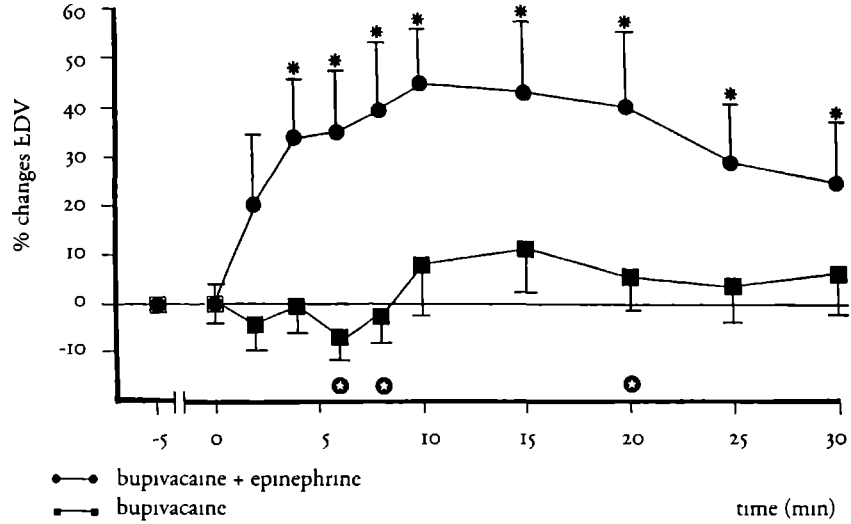

Figure 6 6 Changes in end diastolic volume Each point represents the mean (± SEM) relative change from control values Statistical significant differences within the groups are indicated by * and between the groups by ✪

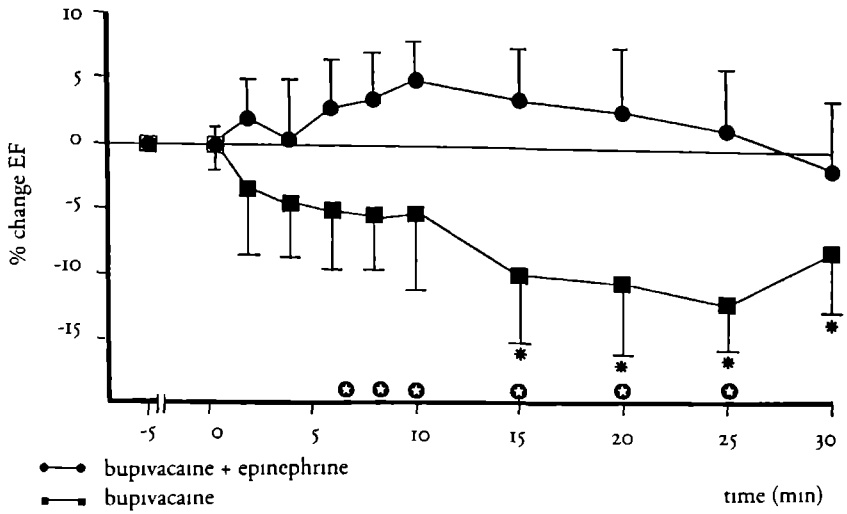

Figure 6 7 Changes in ejection fraction Each point represents the mean (± SEM) relative change from control values Statistical significant differences within the groups are indicated by * and between the groups by ✪

Discussion

In 1971 Bonica et al. described the cardiovascular effects of epinephrine added to lidocaine (Bonica 1971). In contrast to our results, they found a 10% decrease in mean ar-

terial blood pressure in the lidocaine-epinephrine group and a 5% decrease in the plain group. Bonica et al. suggested a synergistic action between the resorption of epinephrine and vasomotor blockade. No significant differences in mean arterial blood pressure were found between the two groups in our study. In contrast to the observations of Bonica et al., we did not find an increase in heart rate. The maximum relative increase in cardiac output was 60% after 15 minutes in the bupivacaine-epinephrine group. Bonica et al. found a 49% increase in cardiac output after 15 minutes. The major factor responsible for these changes is an increased stroke volume. Two minutes after injection of the bupivacaine with epinephrine solution, stroke volumes increased significantly from control and persisted more than 30 minutes. Changes in end diastolic volume (preload) contributed to the increased stroke volume.

In 1958 Guyton et al. showed the effects of epinephrine on the venous return (Guyton 1958). They illustrated that by increasing the rate of intravenous epinephrine infusion under total spinal anesthesia, the venous return to the heart increased progressively with constant right atrium pressures. Guyton concluded that the rise in cardiac output caused by epinephrine is caused mainly by the increased venous return rather than the increased contractility of the heart.

An experimental study in sheep by Ottesen et al., demonstrated that after the induction of lumbar epidural analgesia with mepivacaine, the effect of intravenously injected epinephrine was an increased venous return to the heart (Otteson 1978). In our study, the venous uptake of epinephrine from the epidural space resulted in a venoconstriction followed by an increased end diastolic volume and stroke volume in the first minutes after epidural injection.

Another interesting finding in our study was the decreased ejection fraction in the plain bupivacaine group. Fifteen minutes after epidural injection, the ejection fraction decreased significantly in the plain bupivacaine group, with the maximum decrease after 25 minutes (-12%). In the bupivacaine with epinephrine group the ejection fraction did not change significantly. In previous studies, the cardiodepressive effects of bupivacaine were studied (Nath 1986). Beal et al. showed that a significant reduction in cardiac output already occurred with an intravenous bupivacaine infusion at a rate of 0.2 $mg.kg^{-1}.min^{-1}$ (Beal 1988).

Twenty minutes after epidural administration, a maximum bupivacaine plasma level was observed by Wilkinson and Lund (Wilkonson 1970). The decrease in ejection fraction that also occurred around that time in our study can be explained by the cardiodepressive effects of the absorbed bupivacaine. The epinephrine counteracts these effects in the bupivacaine with epinephrine group.

In conclusion, this study shows that the addition of epinephrine to bupivacaine can partly counteract the vasodilatator effects of sympathetic blockade as well as the effects due to systemic uptake of bupivacaine and their influences on the cardiac contractility.

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Cardiovascular effects after lumbar epidural administration of 0.75% bupivacaine and 0.75% ropivacaine, both with epinephrine

H.E.M. Kerkkamp, M.J.M. Gielen

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Abstract

In a randomized double blind fashion twenty patients received 20 ml of 0.75% bupivacaine or 20 ml 0.75% ropivacaine, both with 5 $\mu g.ml^{-1}$ epinephrine for epidural anesthesia. Onset time and mean maximum level of sensory blockade were not different in the two groups. Cardiovascular measurements were determined by a noninvasive cardiac output monitor, the transthoracic electrical bioimpedance monitor. After epidural administration of 20 ml of either solution, the mean arterial blood pressures decreased significantly from control values, the decrease was more pronounced in the bupivacaine group. Mean maximum decreases for bupivacaine and ropivacaine were 21% and 9.6% respectively, 20 minutes after epidural administration. Stroke volume and cardiac output increased significantly from control values. There were no significant differences between the two groups. The ejection fraction increased significantly from control values, two minutes after epidural administration of 20 ml bupivacaine 0.75% with epinephrine, whereas the changes in the ropivacaine group were not significantly different. The differences in the cardiovascular effects between the two groups are caused by the difference in their own vasoactive properties of bupivacaine and ropivacaine.

Introduction

The potent cardiotoxic effects of the highly lipid soluble local anesthetic agent, bupivacaine, are well documented (Prentiss 1979, Mallampati 1984). This indicates the need for the development of an equally effective, but less cardiotoxic, local anesthetic agent.

Ropivacaine is a new local anesthetic agent, with a chemical structure similar to that of bupivacaine (Rosenberg 1983). Previous studies in animals and humans suggest that the cardiac toxicity of bupivacaine is greater than that of ropivacaine when given in equal doses on mg basis (Arthur 1988, Moller 1986, Reiz 1989, Bowler 1989).

Ropivacaine and bupivacaine with epinephrine 5 $\mu g.ml^{-1}$ are equally potent in terms of onset and duration of analgesia after epidural injection (Kerkkamp 1990[a], chapter 10). However ropivacaine seems to produce less motor blockade after epidural administration than bupivacaine (Feldman 1988, Kerkkamp 1990[a]).
Cardiovascular changes were compatible with those associated with the autonomic blockade of epidural blockade (Kerkkamp 1990[a], Feldman 1989).

The cardiovascular effects of epidural anesthesia are complex and related to the level of anesthesia, the amount of anesthetic injected, the addition of epinephrine to the local anesthetic solution, and the cardiovascular status of the patient.

Transthoracic electrical bioimpedance monitoring is a noninvasive method of measuring cardiac output that has been shown to correlate with cardiac output measured by thermodilution (Appel 1986, Bernstein 1986). The monitor measures the impedance to electrical current flow from the neck to the base of the thorax. This impedance is a function of the blood volume of the chest and fluctuates with the cardiac output. This technique is useful in the research of the hemodynamic effects of anesthetic agents or procedures known to cause cardiovascular disturbances (McMenemin 1988, Kerkkamp 1990[b]).

The aim of the present study is to determine the cardiovascular changes in relation to epidurally administered bupivacaine and ropivacaine.

Materials and methods

Twenty patients (ASA physical status I or II) were entered into a randomized double blind study. The study was approved by the Human Ethical Committee of the University of Nijmegen. Informed consent was obtained from all patients prior to admission to the study. All patients were scheduled for elective surgery under epidural anesthesia. Excluded were patients with a history of neurological, cardiovascular or pulmonary disease and patients using cardiovascular medication. The patients were divided in two groups: group 1 received 20 ml 0.75% ropivacaine with 5 $\mu g.ml^{-1}$ epinephrine and group 2 received 20 ml 0.75% bupivacaine with 5 $\mu g.ml^{-1}$ epinephrine.

Premedication consisted of diazepam 10 mg, given orally 90 minutes before inser-

ting the epidural catheter. All patients received 500 ml of a balanced electrolyte solution intravenously before epidural administration of the local anesthetic agent.

With the patient in the lateral position and after infiltration of the skin with lidocaine 1%, a 18 gauge Tuohy needle was introduced in the L2-3 or L3-4 interspace using the midline approach and the loss of resistance technique with air. An epidural catheter was then inserted 3 cm beyond the needle tip, and the patient was turned supine, after securing the catheter. Before administration of the local anesthetic solution, a 15 minutes rest period was observed. Systolic, diastolic and mean arterial blood pressure were measured at 1 minute interval with an automatic blood pressure monitor (E.M.E. Bristol Gardens, England). Hemodynamic measurements (heart rate, stroke volume, cardiac output and ejection fraction) were continuously obtained with the NCCOM-3 cardiodynamic monitor (Bomed Medical Manufacturing ltd., Irvine California, USA).

Heart rate, blood pressure, stroke volume, cardiac output and ejection fraction measured five minutes before epidural injection, were used as pre-epidural injection control values. A test dose of 3 ml of either 0.75% ropivacaine or 0.75% bupivacaine both with 5 $\mu g.ml^{-1}$ epinephrine was administered. After four minutes a total dose of 17 ml of the same solution was administered in incremental doses over four minutes. The total dose given was 150 mg ropivacaine or 150 mg bupivacaine respectively.

The hemodynamic measurements were continuously monitored during 30 minutes after epidural injection in the supine position. The data are expressed as relative changes from the control values. The upper and lower levels of analgesia were determined bilaterally by pinprick with the blunt end of a Sherwood B400 27-gauge needle at 2 and then every 5 minutes after the end of the injection for 30 minutes. The levels of analgesia are segmentally recorded. All times given are from the end of the epidural injection.

All parameters were compared within and between the two groups. The results were analysed using a t-test for paired or unpaired observations. A p value less than 0.05 was considered statistically significant.

Results

Twenty patients participated in the study. The groups were comparable in age, height and weight (table 7.1).

Onset and spread of analgesia

The development of segmental blockade after the end of epidural administration of the local anesthetics is shown in figure 7.1. Statistical analysis indicate no significant differences for mean onset time and mean maximum cephaled level of analgesia which reached T6 for both groups.

Table 7 1 Demographic data (mean ± SEM)

	Ropivacaine 0 75% with epinephrine n=10	Bupivacaine 0 75% with epinephrine n=10
Age (years)	47(5)	55(6)
Height (cm)	180(2)	176(2)
Weight (kg)	79(4)	75(3)

n= number of patients

Table 7 2 Mean pre-blockade hemodynamic values (control values) with standard deviations between parentheses

	Ropivacaine 0 75% with epinephrine n=10	Bupivacaine 0 75% with epinephrine n=10
Heart rate (bpm)	71(9)	73(12)
Systolic art blood pressure (mm Hg)	132(15)	133(18)
Diastolic art blood pressure (mm Hg)	80(10)	83(9)
Mean art blood pressure (mm Hg)	97(11)	99(11)
Stroke volume (ml)	97(24)	79(24)
Cardiac output (l/min)	6 8(1 6)	5 5(1 5)
Ejection fraction (%)	65(5 7)	60(6 5)

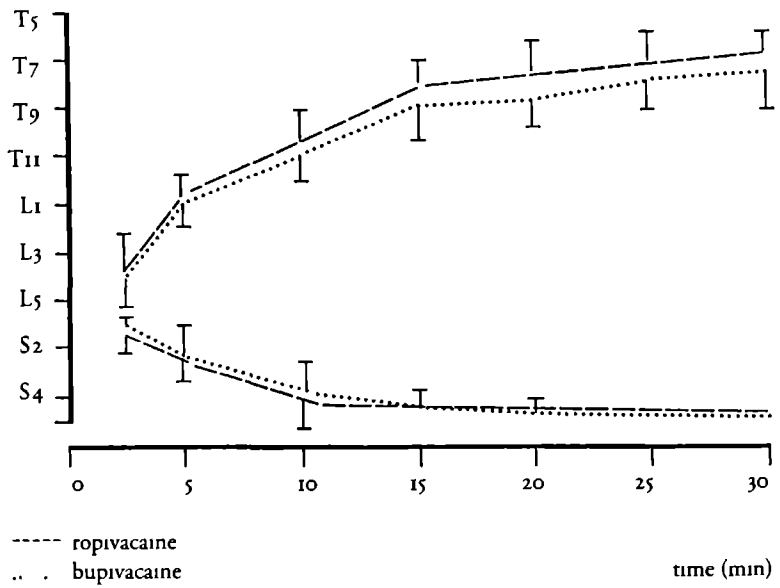

Figure 7 1 The onset of sensory blockade after epidural injection of 20 ml 0 75% ropivacaine and 20 ml 0 75% bupivacaine both with epinephrine. Values are means of segmental dermatomes ± SEM.

Hemodynamic effects

The absolute figures of the hemodynamic measurements (control values) before injection of the local anesthetic drug are shown in table 7.2.

Changes in heart rate are illustrated in figure 7.2. Two minutes after the end of the epidural administration the heart rate increased significantly in the ropivacaine group. In the bupivacaine group, the heart rate increased significantly after 5 minutes after the end of epidural administration. In contrast to the bupivacaine group, in the ropivacaine group the heart rate remained significantly elevated throughout the study period. The mean maximum relative change in heart rate was 22% in the ropivacaine group, 10 minutes after the end of epidural injection. The mean maximum relative change was 12% in the bupivacaine group after 10 minutes. The changes in heart rate between the two groups were not significantly different.

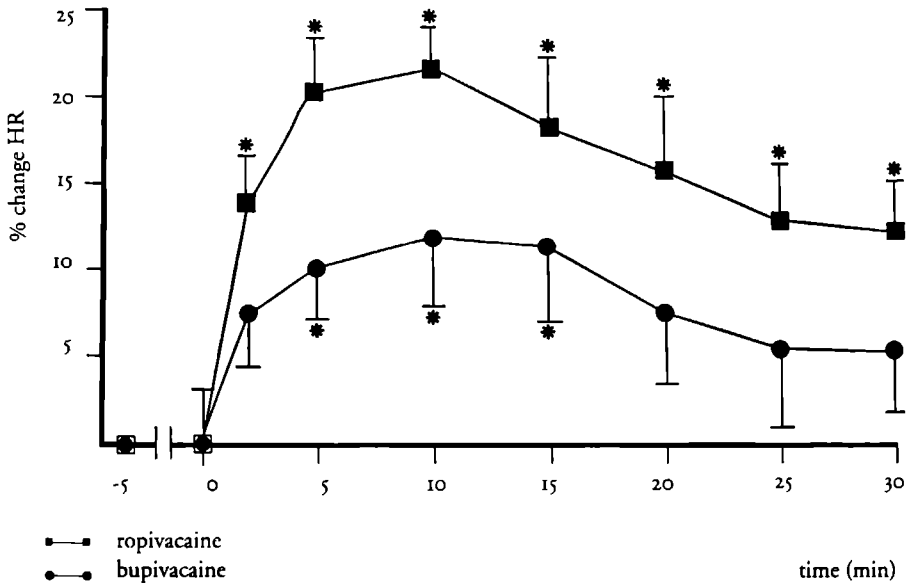

Figure 7.2: Changes in heart rate after epidural injection. Each point represents the mean (± SEM) relative change from control values. T=0 represents the values at the end of the epidural administrations. Significant differences within the groups are indicated by ✱ .

Changes in systolic blood pressure are shown in figure 7.3. Twenty five minutes after injection of the local anesthetic drug the systolic blood pressure decreased significant (-13%) from control values in the bupivacaine group. Clinical relevant hypotension (defined by a > 30% drop in systolic blood pressure from control values), requiring administration of intravenous drugs or supplementary fluid loading, was not experienced in this study, although the decrease in systolic blood pressure was more marked in the bupivacaine group.

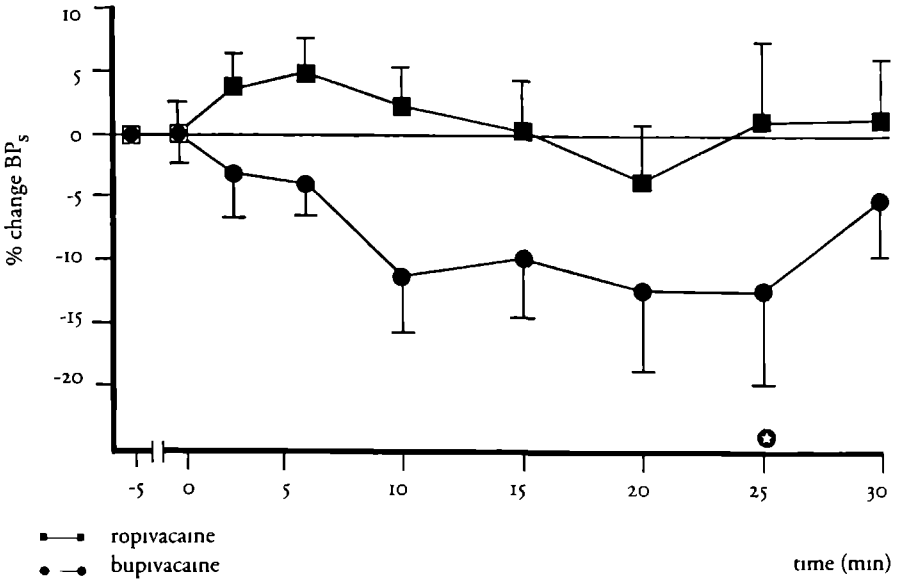

Figure 7 3 Changes in systolic blood pressure after epidural injection Each point represents the mean (± SEM) relative change from control values T =0 represents the values at the end of the epidural injections Significant differences between the two groups are indicated by ✪

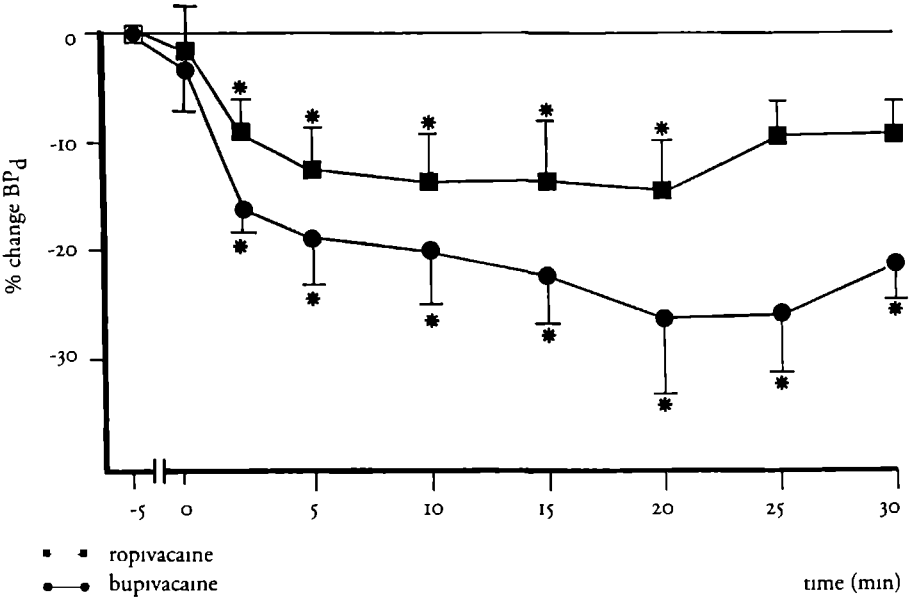

Figure 7 4 Changes in diastolic blood pressure Each point represents the mean (± SEM) relative change from control values T=0 represents the values at the end of the epidural administrations Significant differences within the groups are indicated by ✱

Significant changes in diastolic blood pressure occurred in both groups after 2 minutes. All values remained lower than control in both groups. No significant differences were found in diastolic blood pressures between the groups (figure 7.4). The decrease in the bupivacaine group was more pronounced than in the ropivacaine group. Mean arterial blood pressure changes are given in figure 7.5. In the bupivacaine group the mean arterial blood pressure decreased significantly after 2 minutes, the changes in the ropivacaine group were significant only after 20 minutes.

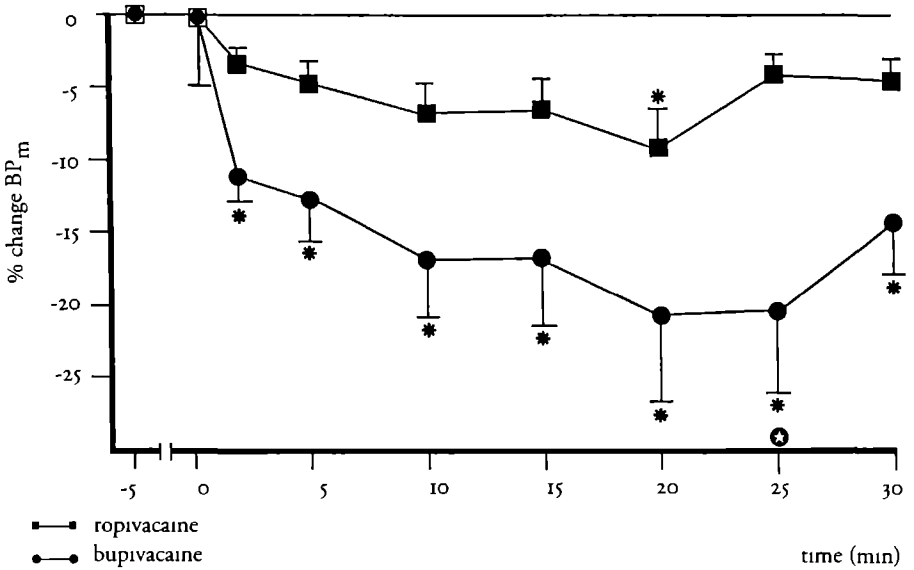

Figure 7.5 Changes in mean arterial blood pressure Each point represents the mean (± SEM) relative change from control values T=0 represents the values at the end of the epidural administrations Significant differences within the groups are indicated by ✱ . Significant differences between the two groups are indicated by ✪

Changes in stroke volume and cardiac output are illustrated in figures 7.6 and 7.7. Stroke volume increased significantly 2 and 5 minutes after the end of epidural administration for the bupivacaine and ropivacaine group, respectively. Two minutes after the end of epidural injection cardiac output increased significantly from pre-blockade values in both groups. Stroke volume and cardiac output remained elevated throughout the study period. Comparison between the two groups for both parameters, showed no significant differences.

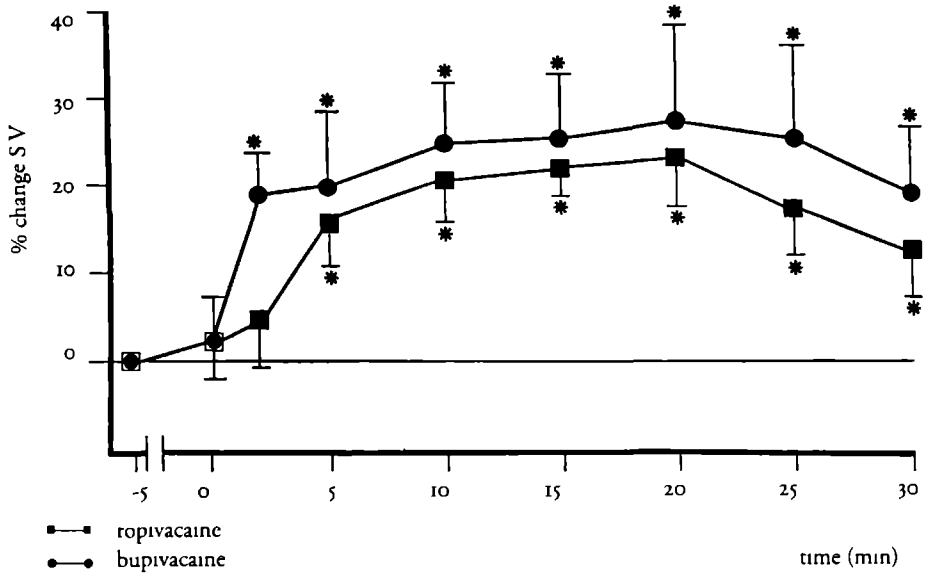

Figure 7 6 Changes in stroke volume Each point represents the mean (± SEM) relative change from control values T=0 represents the values at the end of the epidural administrations Significant differences within the groups are indicated by *

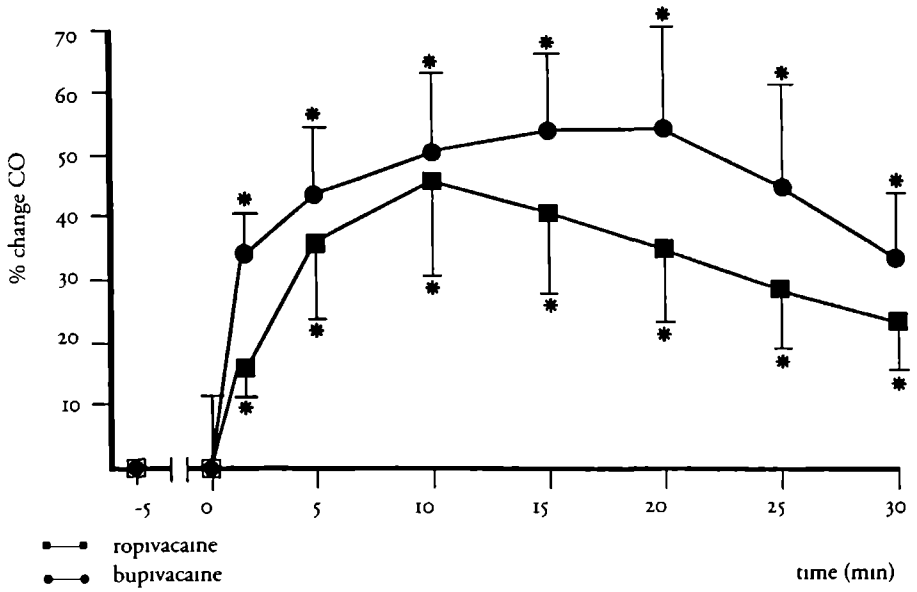

Figure 7 7 Changes in cardiac output Each point represents the mean (± SEM) relative change from control values T=0 represents the values at the end of the epidural administrations Significant differences within the group are indicated by *

Figure 7.8 shows the relative changes in ejection fraction after the end of epidural injection. Two minutes after the administration of bupivacaine with epinephrine the increase in ejection fraction was 5.5%. The maximum relative change in ejection fraction in the bupivacaine group was 9%, which was a significant increase from control. Comparison of the ejection fractions between the two groups showed no significant differences.

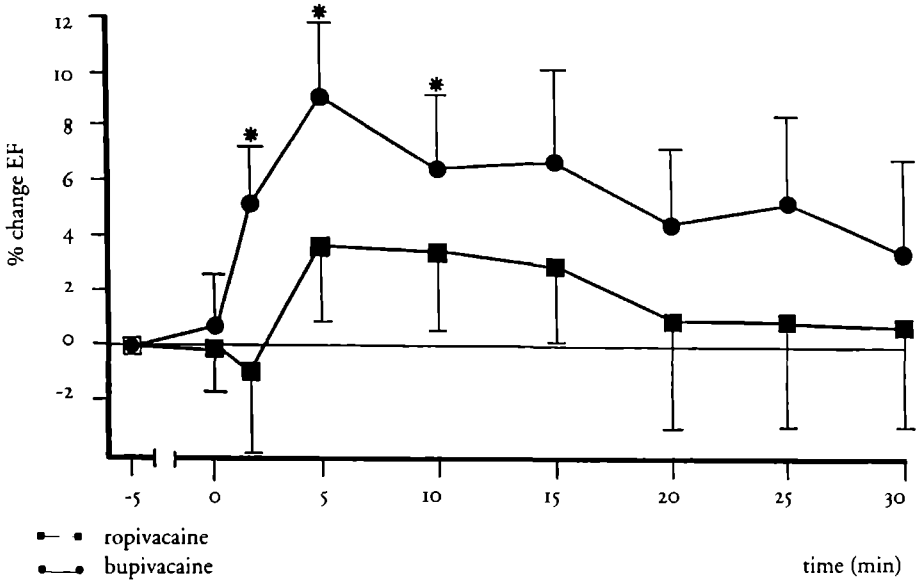

Figure 7.8: Changes in ejection fraction. Each point represents the mean (± SEM) relative change from control values. T=0 represents the values at the end of the epidural administrations. Significant differences within the bupivacaine group are indicated by * .

Discussion

Ropivacaine and bupivacaine are effective local anesthetic drugs when used for epidural anesthesia in man. Onset times for analgesia were similar in both groups. Other studies indicated a good differential blockade with regard to sensory versus motor for ropivacaine (Kerkkamp 1990[a], Whitehead 1990).

Differences in autonomic blockade of epidural anesthesia after administration of bupivacaine or ropivacaine are not known. However, cardiovascular effects associated with epidural anesthesia are not only attributed to a sympathetic blockade, but also to the type and dose of the local anesthetic agent, the added vasoconstrictor and the ability of the vascular system to compensate (Covino 1978).

Although it is not statistically significant, the decrease in blood pressure is more pronounced in the bupivacaine group, compared to the ropivacaine group. The differ-

ences in blood pressure in the current study can be explained by the extent of sympathetic blockade and the direct effects of the absorbed local anesthetics. In contrast to bupivacaine, ropivacaine is an effective vasoconstrictor (Kopacz 1988).

The vasoconstrictor effects have also been demonstrated in epidural blood flow. Epidural blood flow decreased significantly after epidural administration of ropivacaine (37%), compared with an increased blood flow after epidural administration with bupivacaine (17%) (Dahl 1990). In an animal study, drug concentrations of both ropivacaine and bupivacaine were measured after epidural administration. The peak bupivacaine concentrations occurred earlier than those of ropivacaine (Feldman 1989).

The increase in heart rate in the ropivacaine group was more pronounced compared to the bupivacaine group. This can be related to the electrophysiological depressant effects of bupivacaine. In an isolated rabbit purkinje fiberventricular muscle preparation, ropivacaine was less potent than bupivacaine in terms of its depressant effect on cardiac excitation and conduction (Moller 1990).

Stroke volume and cardiac output increased significantly from control values in both groups. The changes are caused by the absorption of the epinephrine. This was demonstrated in a previous study (Kerkkamp 1990[b], chapter 6). There were no significant changes in stroke volume and cardiac output between the two groups.

In a randomized, double blind study in human volunteers, the effects of intravenous administration of ropivacaine and bupivacaine on the left ventricular function were measured (Bowler 1989). The authors found significant differences in ejection fraction and stroke volume after the end of infusion (mean dose of ropivacaine 150 mg and of bupivacaine 99 mg). The ejection fraction decreased 8% in the ropivacaine group and 10% in the bupivacaine group. In our study the patients received either 150 mg ropivacaine or 150 mg bupivacaine both with epinephrine. Ejection fraction increased significantly in the bupivacaine group two minutes after epidural administration. There were no significant changes in ejection fraction within the ropivacaine group. The hemodynamic effects of adding epinephrine to local anesthetics have been shown by several authors (Bonica 1971, Stanton-Hicks 1973, Otteson 1978, Kerkkamp 1989). In all those studies the cardiodepressive effects of the epidurally injected local anesthetics were reduced or counteracted when a small amount of epinephrine was added to the local anesthetic drug. The differences in ejection fraction between the two groups can be caused by the absorbed epinephrine. Because of the vasoactive properties of ropivacaine, the plasma epinephrine concentration is less in the ropivacaine group compared to the bupivacaine group.

The results suggest that further investigations of ropivacaine and bupivacaine without epinephrine are necessary to determine more accurately the cardiovascular effects after their epidural administration.

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Effects of epidurally and intrathecally administered ropivacaine and bupivacaine in rats

H.E.M. Kerkkamp and R. Dirksen

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Introduction

Local anesthetics reduce the propagation of action potentials in excitable membranes. Since local anesthetics are injected near their sites of action (for instance the peripheral nerves), the effect will be a reversible blockade in transmission of impulses in that nerve.

The potency, onset of action and duration are primarily determined by the physicochemical properties of the various drugs (Concepcion 1984). In addition to this, one other clinically important consideration is the ability of local anesthetic agents to cause a differential blockade of sensory, autonomic sympathetic and motor fibres (Rosenberg 1983).

The investigation of the pharmacology of local anesthetics is performed with isolated nerve preparations, in intact animals and in man. Animal studies with drugs affecting nerve impulses have been performed in dogs, cats, guinea pigs, mice and rats. The technique to evaluate sensory blockade consists in evaluation of an attempt to withdraw the hind-legs in response to pinching of the foot-pads with an Allis tissue forceps. Complete motor blockade is defined as the inability to support the body weight with the hind legs (Åkerman 1985).

These techniques were used to determine the effects of ropivacaine and bupivacaine (Åkerman 1988, Feldman 1988). After intrathecal or epidural injection, the time that the animals were unable to stand on the hind-legs or responded to pinching of the food-pads was shorter after ropivacaine administration compared to bupivacaine administration. In this study a recently developed animal model (Dirksen 1990) was used to quantify and analyse the graded effects as a function of time after epidural or intrathecal administration of ropivacaine and bupivacaine.

Experiments reported herein were approved by the committee on ethical aspects of laboratory animal care and use.

Methods

Male Wistar rats of the outbred strain Cpb:WU(CPB-TNO, Zeist, The Netherlands) weighing 150-300g were used for all the experiments. Pre-experimental conditions were standardized including manufactured food and tap water, housing conditions 12 h. day/night cyclus and an environmental temperature of 21 °C.

Epidural preparation

The animals (n=12) were anesthetized with enflurane vapour. The skin of the back was depilated, and the animal was mounted in a stereotomy instrument. A midline incision was made over the spinous processes of the lower three lumbar vertebrae and extended over the upper part of the sacrum bone. Identification of the lumbar vertebrae was performed by palpation of the iliaca crests. The fascia covering the super-

ficial muscles of the back was opened. The long superficial muscles were dissected from the vertebrae and bluntly retracted to expose the lamina of the vertebrae. After removing the spinous process of the fifth lumbar vertebrae a small hole was drilled into the lamina, which provided access to the lumbar epidural space. A Poly-ethylene catheter was introduced to a length of 1 cm. The tip of the catheter was located at the lumbar enlargement. A drop of Histoacryl tissue adhesive (Braun Melsungen, W-Germany) sealed the space between the drilled hole and the catheter to prevent drug leakage.

A loosely light knot in the catheter filled with dental cement was fixed into the wound to prevent catheter dislocation. The catheter was externalised subcutaneously on the top of the skull. A small piece of stainless-steel was inserted in the proximal end to close the Poly-ethylene catheter.

Intrathecal preparation

In rats under enflurane anesthesia a polyethylene catheter (PE-10) was inserted into the lumbar subarachnoid space through an opening made into the atlanto-occipital membrane according to the procedure described by Yaksh and Rudy (1976).

The catheter was externalised subcutaneously on the top of the skull. The PE-10 catheter, prepared prior to surgery, had a loose knot tied at the point of exit from the cisterna and this was covered with a drop of dental cement. A small piece of tight-fitting stainless-steel wire was inserted into the proximal end of the PE-10 catheter to prevent backflow of cerebrospinal fluid.

After cannulation of the subarachnoid or epidural space the animals were housed separately in a macrolon cage with sawdust bedding. Animals showing motor disturbances were discarded from the study.

Animal model

After a recovery period of 7 days, a rat was anesthetized with intraperitoneal injection of urethrane (1.2 $gr.kg^{-1}$) to allow cannulation of the trachea (Abbocath 14G), the internal jugular vein and the carotid artery. Anesthesia was maintained by subcutaneous administration of urethrane 0.2 $mg.kg^{-1}$.

The rat was then positioned on the experimentation table and artificially normo ventilated with a semi-open electrical valve controlled small animal ventilator. The fresh gas flow was 0.5 $ml.min^{-1}.gr^{-1}$ bodyweight, and was kept constant throughout the experimental procedure in each animal. The body temperature was maintained between 36 and 37 °C.

A noxious electrical transcutaneous stimulus was given to the left hindpaw mounted in a shoe connected to the force transducer (grass FT 03C) that measured the force of withdrawal. The stimulus parameters were set to 4 ms pulse duration, 7.5 mA stimulus strength, 100 Hz pulse frequency, in a train of 500 ms duration, and a repetition rate of 12.5 mHz (0.75 min^{-1}) for the trains (Grass stimulator S88 with stimulus isolation unit SIU 5, and constant current unit CCU 1A).

Determination of effects of the local anesthetic drugs started 1 hour after fixating the animals on the table.

Drug administration

Ropivacaine and bupivacaine were obtained from Astra Alab AB, Sweden. The following doses of the respective drugs were given epidurally: 50 µl 0.75% ropivacaine with 5 $\mu g.ml^{-1}$ epinephrine and 50 µl 0.75% bupivacaine with 5 $\mu g.ml^{-1}$ epinephrine. For intrathecally admistration 10 µl of the same solutions was used. After each injection the catheter was flushed with 10 µl NaCl 0.9%.

The drugs were injected consecutively. The first drug to be injected was either bupivacaine or ropivacaine in a randomized order. Once the force of withdrawal had returned to the pre-injection magnitude (100% recovery), the second injection of a drug was given. The second drug was either ropivacaine or bupivacaine. Thus four groups can be distinguished (table 8.1).

Table 8.1: Epidurally and intrathecally injected rats devided in four different groups.

Group	Number	E/I	First drug*	Second drug**
1	6	E	6xbupivacaine	4xropivacaine
2	6	E	6xropivacaine	4xbupivacaine
3	6	I	6xbupivacaine	6xropivacaine
4	6	I	6xropivacaine	6xbupivacaine

E/I. epidural or intrathecal injection
* number of rats injected with the first local anesthetic drug
** number of rats injected with the second drug

Data sampling and statistical analysis

After one hour stabilisation of the animal, the individual baseline withdrawal force (expressed in g) was measured during 30 min.

The average of the baseline responses was calculated and served to determine the individual relative responses expressed as percentage of the baseline response (100%):

$$\text{Response (\%)} = \frac{\text{withdrawal force}}{\text{mean baseline withdrawal force}} \times 100$$

Each animal served as its own control. Three parameters were used to quantify the inhibition of responses: The onset time (t_o), defined as the time from the end of injection and the occurrence of 0% response. The time of complete blockade (t_c), defined as the duration with 0% response. The duration of 50% recovery (t_{50}), defined as the time were the response returned to 50% of the baseline response.

The results were analysed using a t-test for paired or unpaired observations. All re-

sults are presented as means ± SEM. A p value less than 0.05 was considered statistically significant.

Results

Effects after epidural administration

After epidural administration of ropivacaine or bupivacaine, the withdrawal responses to noxious electrical transcutaneous stimulation were completely inhibited (0% response). In four rats (two in each group) the second administration of a drug did not result in an inhibition of the withdrawal response. Postmortem examination of epidural injection with methylene blue revealed that leakage of the injected volume from the bore hole had occurred. The responses after epidural drug injections of the groups 1 and 2 are summarized in tables 8.2, 8.3 and 8.4. The figures 8.1 and 8.2 show the withdrawal responses as percentage of their controls (response %) as a function of time.

There were no statistically significant differences in t_0 values assessed in group 1 and group 2 after injection of the two drugs. The mean t_c time after bupivacaine injection (65.8 min) was significantly longer than that of ropivacaine (26.5min) in group 1 (table 8.2).

Although the mean times of complete blockade of the second injection of either bupivacaine or ropivacaine were shorter compared to the first injection, it was not statistically different (table 8.3). The t_{50} values after epidural injection of either ropivacaine and bupivacaine are shown in table 8.4. The t_{50} values of group 1 and 2 were significant different in both group 1 and 2 in regard to the mean times for bupivacaine and ropivacaine. No statistically significant differences were found for t_{50} between group 1 and 2 in regard to the same local anesthetic agent.

Table 8 2: Mean onset time (t_0) and duration of complete blockade (t_c) in min after epidural administrations of 50 µl ropivacaine and bupivacaine

Group		Drug	t_0	p	t_c	p
	1^0	bupivacaine	2 0(0 7)		65 8(6 4)	
1				0 278		0 003
	2^0	ropivacaine	3 2(1 7)		26 5(6 3)	
	1^0	ropivacaine	3 8(0 5)		33 2(4 3)	
2				0 121		0 135
	2^0	bupivacaine	4 7(0 4)		42 8(8 3)	

1^0= first injection
2^0= second injection (in consecutive to 1^0)
SEM in brackets

Table 8 3· Mean onset time (t_0) and duration of complete blockade (t_c) in min after epidurally injection for the same local anesthetic agent in group 1 and 2

Group		Drug	t_o	*p*	t_c	*p*
1	1^0	bupivacaine	2 0(0 7)	0 126	65 8(6 4)	0 082
	2^0	bupivacaine	4 7(0 4)		42 8(8 3)	
2	1^0	ropivacaine	3 8(0 5)	0 745	33 2(4 3)	0 432
	2^0	ropivacaine	3 2(1 7)		26 5(6 3)	

1^0=first injection
2^0=second injection (in consecutive to 1^0)
SEM in brackets

Table 8 4· T_{50} values in min after consecutive epidural injections of 50 µl bupivacaine and ropivacaine.

Group		Drug	t_{50}	*p*
1	1^0	bupivacaine	84 6(6 7)	0 005
	2^0	ropivacaine	44 5(4 8)	
2	1^0	ropivacaine	53 6(4 9)	0 014
	2^0	bupivacaine	80 5(5 1)	

1^0= first injection
2^0= second injection (in consecutive to 1^0)
SEM in brackets

Table 8.5 Mean onset time (t_0) and duration of complete blockade (t_c) in min after intrathecally injection for the same local anesthetic agent in group 3 and 4

Group		Drug	t_0	*p*	t_c	*p*
3	1^0	bupivacaine	1 0(0 6)	0 175	23 0(6 4)	0 005
	2^0	ropivacaine	1 6(0 6)		12 5(2 9)	
4	1^0	ropivacaine	4 2(0 5)	0 158	10 2(3 6)	0 186
	2^0	bupivacaine	2 8(0 7)		15 5(6 4)	

1^0= first injection
2^0= second injection (in consecutive to 1^0)
SEM in brackets

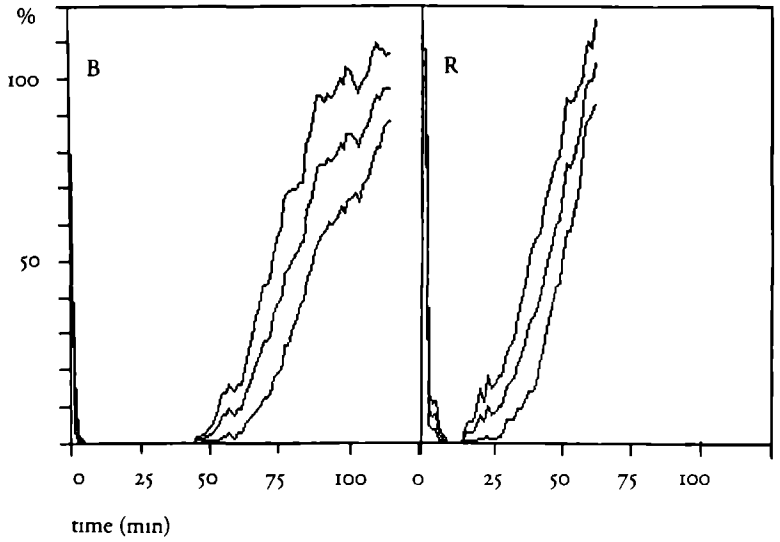

Figure 8 1 Withdrawal responses as percentage of their controls (response %) as a function of time after consecutive epidural injections of 50 µl bupivacaine and ropivacaine (group 1) The middle curve represents the response, the upper and lower curve the SEM (bupivacaine B, ropivacaine R)

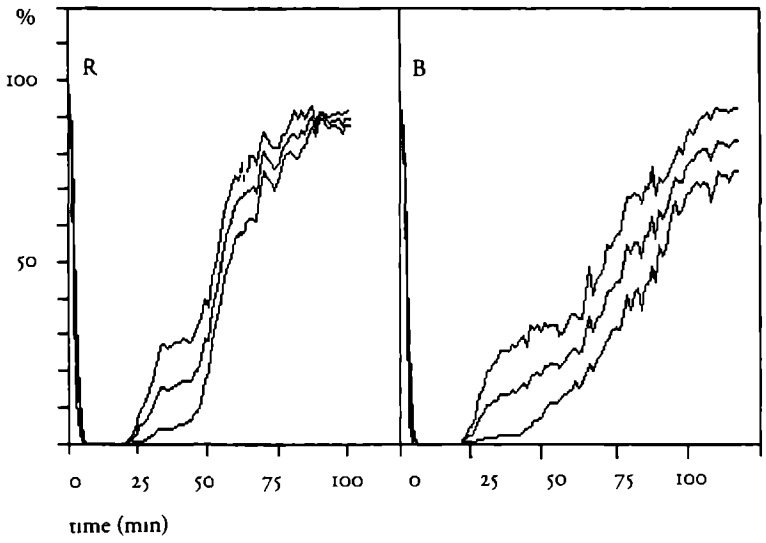

Figure 8 2 Withdrawal responses as percentage of their controls (response %) as a function of time after consecutive epidural injections of 50 µl ropivacaine and bupivacaine (group 2) The middle curve represents the response, the upper and lower curve the SEM (ropivacaine R, bupivacaine B)

Effects after intrathecal administration

The responses for t_o, t_c and t_{50} after intrathecal injection of ropivacaine and bupivacaine are summarized in the tables 8.5, 8.6, 8.7 and figures 8.3 and 8.4.

The t_o values (min) after injection of ropivacaine and bupivacaine were not different (table 8.5). The t_c values in group 3 were significant longer for bupivacaine (23.0 min) compared to ropivacaine (12.5 min) (table 8.5). The t_c values in group 4 were not statistically different.

No significantly differences were found in duration of complete blockade between bupivacaine in group 3 and 4, however the mean time tended to be longer in group 3 (first injection). The t_{50} values after intrathecal injection of bupivacaine and ropivacaine are shown in table 8.7. The t_{50} values are significant different in group 3.

Table 8.6: Mean onset time (t_0) and duration of complete blockade (t_c) in min after intrathecally injection for the same local anesthetic agent in group 3 and 4.

Group		Drug	t_o	*p*	t_c	*p*
3	1^0	bupivacaine	1 0(0.6)	0.101	230(2.4)	0.338
	2^0	bupivacaine	2 8(0.7)		15.5(6.4)	
4	1^0	ropivacaine	4 2(0.5)	0.102	10.2(3.6)	0.660
	2^0	ropivacaine	1.6(0 6)		12.5(2.9)	

1^0= first injection
2^0= second injection (in consecutive to 1^0)
SEM in brackets

Table 8.7:T_{50} values in min after consecutive intrathecal injections of 10 µl bupivacaine and ropivacaine.

Group		Drug	t_{50}	*p*
3	1^0	bupivacaine	39 8(3.5)	0.007
	2^0	ropivacaine	26 0(4.9)	
4	1^0	ropivacaine	27.5(4.3)	0.393
	2^0	bupivacaine	36.0(7.2)	

1^0= first injection
2^0= second injection (in consecutive to 1^0)
SEM in brackets

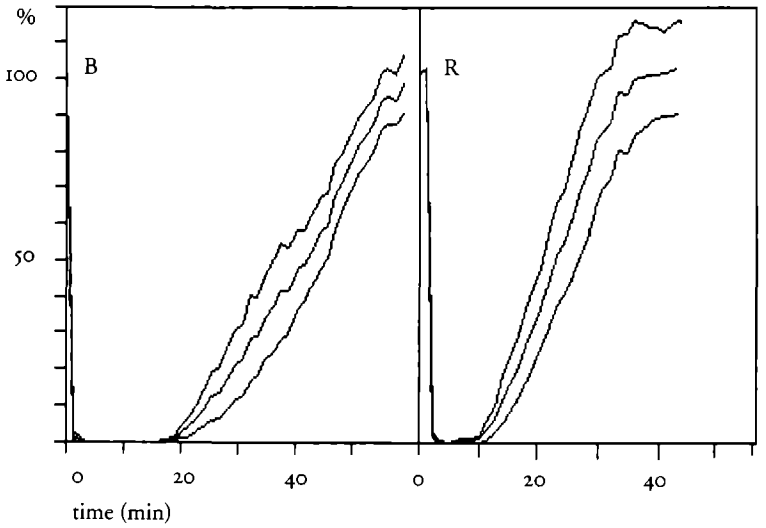

Figure 8.3: Withdrawal responses as percentage of their controls (response %) as a function of time after consecutive intrathecal injections of 10 µl bupivacaine and ropivacaine (group 3). The middle curve represents the response, the upper and lower curve the SEM (bupivacaine: B, ropivacaine:R).

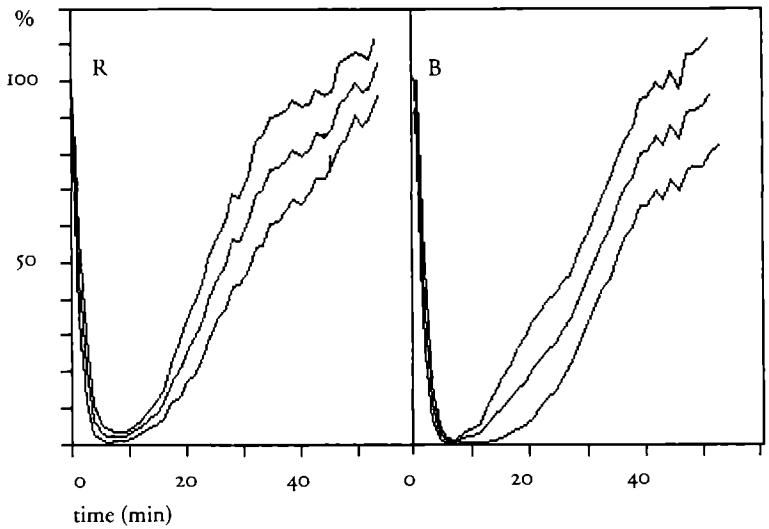

Figure 8.4: Withdrawal responses as percentage of their controls (response %) as a function of time after consecutive intrathecal injections of 10 µl ropivacaine and bupivacaine (group 2). The middle curve represents the response, the upper and lower curve the SEM (ropivacaine: R, bupivacaine: B).

Our study shows that both ropivacaine and bupivacaine inhibit the withdrawal responses elicited with noxious transcutaneous electric stimulation after epidural and intrathecal injection.

Experimental models have been described in various animals to evaluate the efficacy of new local anesthetic agents. After the originally described technique for intrathecal injection in the rat and mouse by Yaksh and Rudy (1976), many authors used the model for the evaluation of intrathecally injected drugs. The catheter technique has the advantage that comparative studies can be performed in one and the same animal. In all the studies complete sensory blockade is considered present if the animal does not vocalize or attempt to withdraw the hind legs in response to painful stimuli. Complete motor blockade is defined as inability to stand on the hind-limbs. Although such methods may provide information on the presence of sensory and motor blockade, it is obvious that a change of motor performance modifies the ability to respond to noxious stimuli for determination of sensory blockade. This means that the evaluation of sensory blockade is dependent on the regression of motor blockade. Besides this, graded responses after intrathecal or epidural injections of local anesthetics can not be detected.

The model used in our study allows the measurement of graded responses to noxious stimuli. The model used in this study provides a useful method to evaluate the potencies of local anesthetics after epidural or intrathecal administration. The period of complete blockade (t_c) after epidural administration was significant longer for bupivacaine compared to ropivacaine in group 1. This difference was not found in group 2. The t_c values of each second drug tended to be shorter compared to the same drug when given as first drug. Consecutive injections of local anesthetics are known to exhibit a shorter lasting effect, a phenomenon referred to as tachyphylaxis. Tachyphylaxis of an effector response is known to develop when the intervals between administrations of local anesthetics are long enough to allow blockade to wear off completely. Due to this, one has to enhance the dose above that of its first in order to maintain the same effect of blockade (Bromage 1969).

Comparison of the t_{50} values after epidural injection shows more reproducible results compared to the t_c values. Statistical analysis between group 1 and 2 for bupivacaine and ropivacaine respectively, indicates a faster return to 50% response for ropivacaine than for bupivacaine.

The t_c values after epidural administration are longer compared to the t_c values after intrathecal administration, possibly due to the difference in injected doses (50 µl versus 10 µl for epidural and spinal injections respectively).

Previous studies in dogs and guinea pigs suggest that intrathecally or epidurally injected ropivacaine is less potent than bupivacaine in blocking neurons (Åkerman 1988, Feldman 1988). In these studies the anesthetic potency, defined as the amount of local anesthetic required to block to the same degree, after intrathecal injection is 1:1.5

for bupivacaine and ropivacaine (Åkerman 1988, Feldman 1988). When a similar comparison of potency is applied to our study, the potencies after intrathecally administration at 50% recovery (t_{50}) are for group 3 and 4, 1:1.5 and 1:1.3 respectively.

An in vitro study in isolated rabbit vagus nerves, indicated that ropivacaine appears to produce relatively less blockade of motor fibers than does bupivacaine but with similar sensory blockade (Bader 1989). Differences in pharmacology of local anesthetics such as onset of action, duration of action and potency can be explained by physical and chemical properties (Concepcion 1984). Bupivacaine is more lipid soluble than ropivacaine in sciatic nerve and subcutaneous fat (Rosenberg 1983). The shorter duration of blockade after epidural and intrathecal injection and the difference in recovery with ropivacaine compared to bupivacaine may be due to a more rapid dissociation from nervous tissue due to its lesser affinity to lipids (Rosenberg 1986).

In conclusion the animal model used in our study to evaluate local anesthetic potency, provides more reliable information compared to "old" techniques. After epidural and intrathecal administration in rats, ropivacaine is less potent than bupivacaine in terms of inhibition of withdrawal responses after noxious stimulation.

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An open study comparison of 0.5%, 0.75% and 1.0% ropivacaine, with epinephrine, in epidural anesthesia in patients undergoing urologic surgery

H.E.M. Kerkkamp[1], M.J.M. Gielen[1], M. WattwiL[2], K.H. Axelsson[2], W. Dirkes[3], H. Kehlet[3], H.H. Edström[4]

1 Institute for Anesthesiology, University of Nijmegen, Nijmegen, The Netherlands.
2 Örebro Medical Center Hospital, Örebro, Sweden.
3 Department of Gastroenterology and Anesthesiology, Hvidovre University Hospital, Hvidovre, Denmark.
4 Astra Pain Control, Södertälje, Sweden.

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Abstract

Ropivacaine 0.5%, 0.75% and 1.0% with epinephrine 5 $\mu g.ml^{-1}$ was investigated in an open, multi-center study for lumbar epidural anesthesia in 46 patients undergoing urologic surgery. The onset time for analgesia to T12 was 5-7 minutes after the end of the ropivacaine injection. Maximum segmental levels of analgesia (T4-6) were not different between the groups. Complete motor blockade was obtained in 3/15, 7/15 and 10/15 patients in the 0.5%, 0.75% and 1.0% groups, respectively. Duration of analgesia at the T10 level was 2.5 hours in the 0.5% group, and increased to 4 hours in the 1.0% group. Analgesia was satisfactory for surgery in all patients except for 2/15 in each of the 0.5% and 0.75% groups and 1/15 in the 1.0% group. Hypotension was experienced by three, six and three patients in the 0.5%, 0.75% and 1.0% groups respectively. Bradycardia was seen in two patients in the 0.5% group and in one patient in the 1.0% group. Backache was experienced by seven patients (four in the 0.5%, two in the 0.75% and one in the 1.0% group). No late occurring adverse experiences were observed. In conclusion 0.5%, 0.75% and 1.0% ropivacaine with epinephrine provide adequate analgesia and motor blockade for urological surgery.

Introduction

Ropivacaine is the (S)-enantiomer of 1-propyl-2′,6′-pipecoloxylidide, a new amide-type local anesthetic agent with a chemical formula similar to that of bupivacaine and mepivacaine. If animal data can be used to extrapolate local anesthetic potency to man, ropivacaine seems to provide a greater margin of safety than bupivacaine (Reiz 1989).

When used for epidural anesthesia in the dog, 1.0% ropivacaine seems comparable to 0.75% bupivacaine (Åkerman 1988). There is also evidence both from in vitro and in vivo studies that the cardiotoxic potential is lower with ropivacaine as compared to bupivacaine (Moller 1986). Consequently, ropivacaine might provide advantages over bupivacaine when used for epidural anesthesia in man.

The present study was initiated to evaluate the clinical efficacy of ropivacaine in different concentrations with epinephrine added when used for epidural anesthesia.

Methods

This nonrandomized, open multi-center study was approved by the ethics committees of each of the three institutions that took part in the study. Informed consent (according to the Helsinki declaration) was obtained from 46 ASA I-II patients, scheduled to undergo urologic surgery under epidural anesthesia.

The series began at each institution, with five patients being given 0.5% ropivacaine, after which 5 patients were given 0.75% ropivacaine, and finally 1.0% ropivacaine was administered to five patients. All ropivacaine solutions contained epinephrine 5 $\mu g.ml^{-1}$.The solutions were manufactured by Astra Pain Control (Södertälje, Sweden).

Premedication consisting of 10-20 mg diazepam was given orally 90 minutes prior to anesthesia. A balanced electrolyte solution (500 ml) was given before the administration of ropivacaine. At each institution the epidural blockade was performed by one investigator and the efficacy assessments were performed, after injection, by another investigator during the entire study period.

With the patient in the lateral decubitus position and after infiltrating the skin with local anesthesia, a 16 or 18 gauge Tuohy needle was introduced in the L2-3 or L3-4 interspace using the midline approach and the loss-of-resistance technique with air. An epidural catheter was inserted approximately 3 cm cephalad and the patient was turned to the supine position. A test dose of 3 ml of lidocaine 1.0% with epinephrine (5 $\mu g.ml^{-1}$) was injected. Approximately 4 minutes after the test dose, 5 ml of one of the ropivacaine solutions was injected every minute to a total of 20 ml. The level of analgesia was tested segmentally with a blunt needle every 2-5 minutes for approximately 30 minutes and then every 15-30 minutes after the end of the injection of the main ropivacaine dose. The degree of motor blockade was evaluated using the Bromage scale (Bromage 1965).

Heart rate and blood pressure were monitored prior to and during the anesthesia. Cardiovascular effects, which included any episode of hypotension (as defined by a>30% drop in pre-block systolic blood pressure, or a systolic blood pressure < 90 mm Hg) or bradycardia (defined as a heart rate of less than 50 beats per minute), were recorded and treated according to standard anesthetic practice.

Statistical analysis was performed using analysis of variance and if $p < 0.05$, it was followed by Wilcoxon's rank sum test, and the difference between proportions was determined by Chi-square test; $p < 0.05$ was considered statistically significant.

Results

Forty-six patients, 45 male and one female, took part in the study. One patient was excluded from the efficacy evaluations because of technical failure. For demographic data see table 9.1. The groups were comparable in age, height and weight. All the times given are from the end of the ropivacaine injection.

Onset of analgesia and motor blockade

The mean onset time for analgesia to the T12 level was 5-7 minutes after the end of injection of all ropivacaine concentrations. There is a low power to detect differences between onset times at any segmental level. At the T12 level, the standard deviation of onset is about 3 minutes. The mean difference between onset times would have to have been larger than approximately 4 minutes to have a power of 90% to achieve significant differences.

In this study, onset time was measured with a precision of about 5 minutes. Hence, differences between onset times of a few minutes are difficult to detect. No significant differences in onset times were found between the three groups at any segmental level (figure 9.1). No significant differences were found between the groups in the mean maximum level of analgesia (T4-6) or the time to reach it (30-45 minutes).

Table 9.1: Demographic data (mean ± SEM).

Ropivacaine concentration with epinephrine	0.5% (n=15)	0.75% (n=15)	1.0% (n=15)
Age (years)	60(13)	57(14)	57(14)
Sex	0f/15m	1f/14m	0f/15m
Height (cm)	178(7)	176(9)	176(8)
Weight (kg)	80(7)	80(12)	80(17)

n=number of patients
f=female
m=male

Complete motor blockade (of both legs) was obtained in three out of 15 patients in the 0.5% group, in seven of 15 patients in the 0.75% group and ten of 15 patients in the 1.0% group, and the difference between the 0.5% and the 1.0% groups was significant. Onset to complete blockade (i.e. degree 3 on the Bromage scale) was 53 minutes in the 1.0% group (median value).

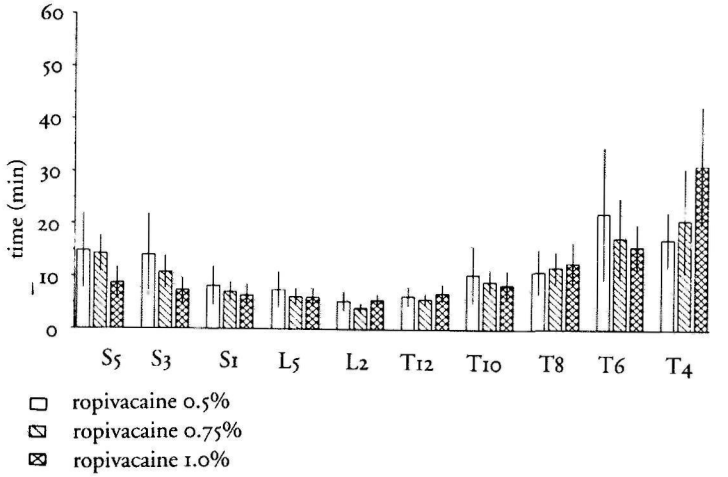

Figure 9.1: Onset of analgesia, mean ±1.96x SEM, approximate 95% confidence interval.

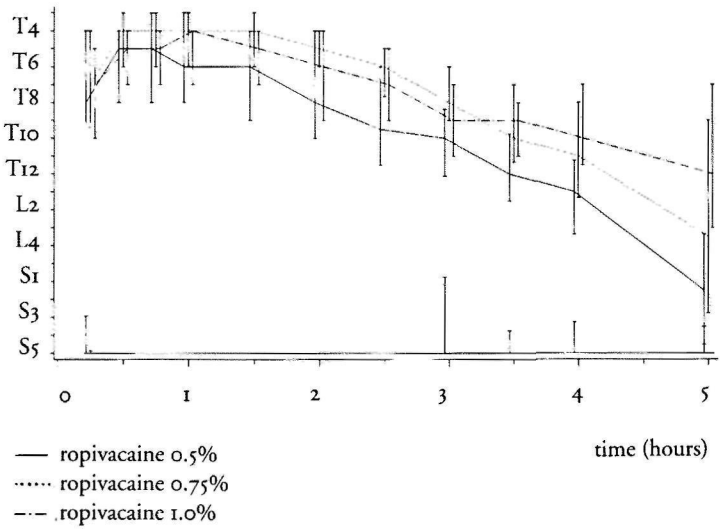

Figure 9.2: Segmental level of analgesia, median values. The upper level of analgesia is significant higher 3-5 hours in the 1.0% group and 2.5-3.5 hours in the 0.75% group after the epidural injection, compared to the 05% group.

Cephalad and caudal level of analgesia

The cephalad level of analgesia was significantly higher in the 1.0% group from 3 to 5 hours after the end of the injection, and in the 0.75% group 2.5, to 3.5 hours after injection, both compared to the 0.5% group. No differences were found at any time between the 0.75% and the 1.0% groups (see figure 9.2). The S5 segment was blocked in 43/45 patients.

Duration of analgesia and motor blockade

Duration of analgesia increased with increasing ropivacaine concentration: at T10, analgesia lasted from 2.5 hours (0.5% ropivacaine) to 4 hours (1.0% ropivacaine); at L2 for 3.5-4.5 hours; at L5, 3.5-5 hours, and at S5, 3.5-5.5 hours (figure 9.3).

The duration in the S1-3 segments, in the lumbar segments and the lower thoracic segments (T10-12) was significantly longer for 0.75% and 1.0% ropivacaine compared to 0.5% ropivacaine. The 1.0% solution also produced a significantly longer duration of analgesia than 0.5% ropivacaine at S5.

Duration of motor blockade also increased with increasing ropivacaine concentration: duration of degree 2 motor blockde increased from 2 hours in the 0.5% group to 3 and 3.5 hours in the 0.75% and 1.0% groups, respectively (figure 9.4). Ropivacaine 1.0% produced a significantly longer duration of all degrees of motor blockade compared to the 0.5% solution, and significant differences were also found between the 0.75% and 0.5% groups for the degrees 2 and 3. No significant differences were found between the 1.0% and the 0.75 groups.

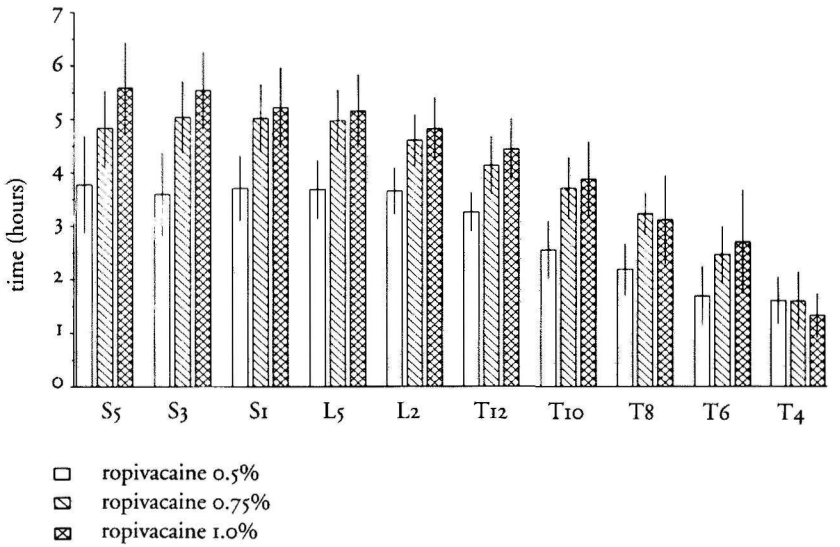

Figure 9.3: Duration of analgesia at different segmental levels: mean ± 1.96 x SEM, approximate 95% confidence interval. At the S1-3, lumbar and low thoracic segments the duration of analgesia is significant longer for the 0.75% and 1.0% group compared to the 0.5% group.

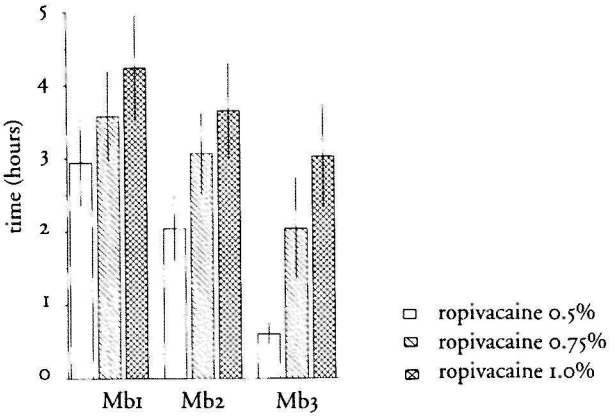

Figure 9.4: Duration of different degrees of motor blockade of the lower limbs: mean ± 1.96x SEM, approximate 95% confidence interval. There is a significant difference in duration of all degrees motor blockade for the 1.0% group, compared to the 0.5% group. There is a significant difference between the 0.75% and 0.5% groups for the degrees 2 and 3 motor blockade.

Cardiovascular effects

No clinically relevant differences were found between the groups in regard to the changes in heart rate or mean arterial blood pressure (figures 9.5 and 9.6). Hypotension requiring intravenous ephedrine was experienced by three patients in each of the 0.5% and 1.0% groups and by six patients in the 0.75% group. Bradycardia requiring atropine was seen in two patients in the 0.5% group and in one patient in the 1.0% group. Nausea and ventricular ectopic beats each were experienced by one patient in the 1.0% group.

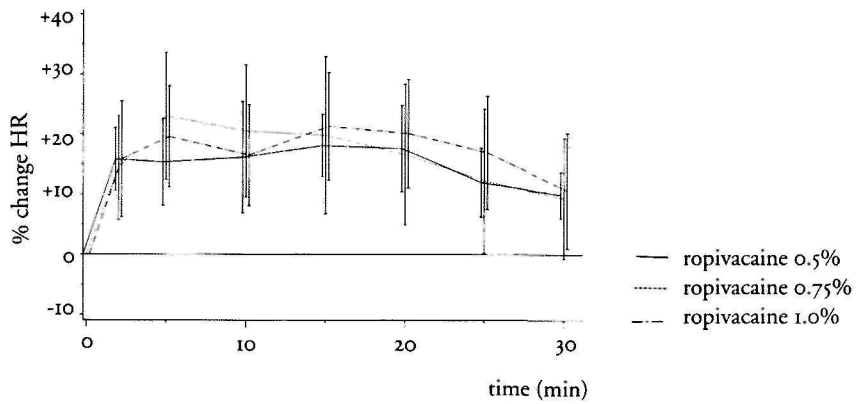

Figure 9.5: Relative changes in heart rate during the first 30 minutes after injection, mean ± 1.96 x SEM, approximate 95% confidence interval.

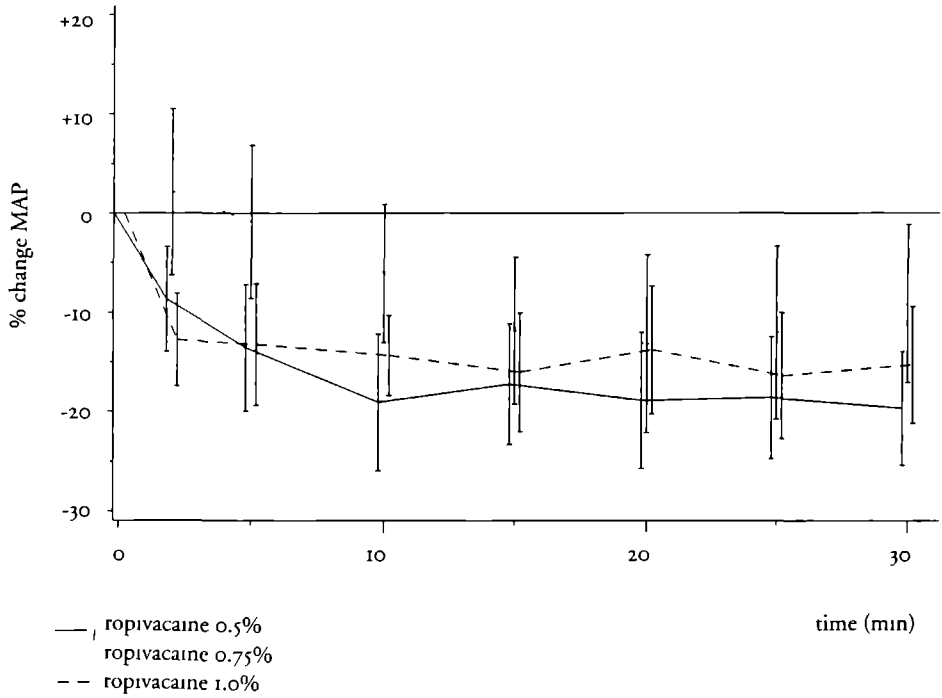

Figure 9 6 Relative changes in mean arterial blood pressure (MAP) during the first 30 minutes after injection, mean ± 1 96 x SEM, approximate 95% confidence interval.

Quality of surgical anesthesia

Surgery was undertaken after 11-138 minutes (mean, 47) and surgical time was 12-120 minutes (mean, 44). Analgesia was satisfactory in all patients except 2/15 in each of the 0.5% and 0.75% groups and 1 of the 1.0% group. Two of these were given either fentanyl or nothing for the pain; one, N_2O/O_2, and two, N_2O/O_2 with isoflurane at the end of surgery.

Adverse events

Backache (or back pain) was experienced by seven patients (four in the 0.5% group, two in the 0.75% group and one in the 1.0% group). One patient (given 0.75% ropivacaine) suffered from headache. Breathing difficulties, due to the high block, were reported from one patient in the 0.5% group and shivering was seen in six patients (three in the 0.5% group, one in the 0.75% group and two in the 1.0% group).

All adverse experiences were mild or moderate, and all patients recovered completely. All patients were questioned on the sixth day (or later) after surgery for possible neurologic disturbances or other late complications that may have been related to the blockade. In no case was any late complication reported.

When a fixed volume of a local anesthetic is injected epidurally, an increase in concentration of the drug normally results in a more profound block, with a more rapid onset and increased duration of analgesia (Littlewood 1977). However, increasing the concentration (and dosage) may also lead to systemic toxicity. Consequently, an optimal concentration exists. Increasing the concentration above this optimal concentration produces little or no further degree of conduction blockade (Scott 1980).

For onset of analgesia or motor blockade, maximum cephaled spread or frequency of S_5 dermatome blockade no difference could be verified in any of these three drug concentrations. On the other hand, a higher frequency of complete motor blockade was obtained in the 1.0% group as compared to the 0.5% group. After epidural administration of any local anesthetic, duration of analgesia (and motor blockade) should be expected to be dose dependent, as has been shown with bupivacaine, etidocaine and prilocaine (Littlewood 1977). In the present study, significant differences in duration of analgesia were found between 0.5% ropivacaine and 0.75% or 1.0% ropivacaine but not between 0.75% and 1.0% ropivacaine. Wether this is due to low statistical power or to the vasoactive properties of ropivacaine and whether these are dose (or concentration) dependent remains to be shown in future studies (Åkerman 1987, Kopacz 1988, Forsberg 1988).

Cardiovascular changes as observed in this study were not different from what has been seen in other epidural studies, with other agents, and in none of the patients were unusual electrocardiographic effects recorded. The present study demonstrates ropivacaine to be a useful local anesthetic for epidural anaesthesia: the blocks produced adequate surgical anesthesia in 40 out of 45 patients, and the failures were equally distributed between the groups.

To conclude, in this open study, 20 ml of 0.5%, 0.75% and 1.0% ropivacaine with 5 $\mu g.ml^{-1}$ epinephrine has been shown to produce adequate surgical anesthesia and motor block for urologic surgery.

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Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia

H.E.M. Kerkkamp[1], M.J.M. Gielen[1], H.H. Edström[2]

1 Institute for Anesthesiology, University of Nijmegen,Nijmegen, The Netherlands.
2 Astra Pain Control AB, Södertälje, Sweden.

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Abstract

Forty-three ASA physical status I and II patients, scheduled for elective urologic surgery, were randomly entered into a randomized double-blind study using 20 ml bupivacaine 0.75% or 20 ml ropivacaine 0.75%, both with 5 $\mu g.ml^{-1}$ epinephrine. Two patients were excluded from evaluation of efficacy due to technical failure. After a test dose of 3 ml bupivacaine 0.75% with epinephrine or ropivacaine 0.75% with epinephrine, 17 ml of either solution was given in incremental doses over 4 minutes (4, 4, 4 and 5ml). Analgesia was satisfactory for surgery in all patients except for one in each group. The onset time of analgesia was short: after administration of ropivacaine and bupivacaine, the T12 dermatome was blocked within 6-8 minutes. Mean maximum upper level of analgesia was similar in the groups -T8±0.6 and T7±0.6 (mean ± SEM)- for ropivacaine and bupivacaine, respectively. Duration of analgesia at the T10 level was 190±12 minutes in the ropivacaine group and 234±20 minutes in the bupivacaine group and was significantly shorter for ropivacaine at T10, L2 and S5 segments. Frequency of complete motor block was significantly lower in the ropivacaine group (7/21) than in the bupivacaine group (16/20). No differences were found in onset to various degrees of motor block, however, the duration of degree 1 motor block was significantly shorter in the ropivacaine group. Hypotension and bradycardia requiring treatment were experienced by seven and three patients, respectively, in the bupivacaine group, and by two and one patient, respectively, in the ropivacaine group. No postoperative adverse events related to anesthesia were observed. Ropivacaine 0.75% with epinephrine is an effective long-acting local anesthetic. Duration of sensory block is similar to that of bupivacaine 0.75% with epinephrine; however, the motor block is less profound and of shorter duration.

Introduction

Ropivacaine, a new amino amide local anesthetic agent, is the pure (S)-enantiomer of a chain shortened analog of bupivacaine (propyl instead of butyl side chain). Animal experiments have suggested that ropivacaine is less cardiotoxic than bupivacaine and may also possess a greater safety margin between the convulsant and lethal doses (Reiz 1989, Morishima 1985, Pederson 1988).

Additional animals studies have indicated that ropivacaine has an anesthetic profile similar to that of bupivacaine, although ropivacaine 0.75% has a shorter duration of motor block than bupivacaine 0.75% (Arthur 1988, Feldman 1988, Morishima 1985).

In a number of open clinical studies, epidural administration of ropivacaine 0.75%, without and with epinephrine, has resulted in satisfactory surgical analgesia, although the degree of motor block has been less marked (Conception 1989, Katz 1989, Kerkkamp 1990, Thomson 1989) than with bupivacaine. No comparative studies in humans have yet been reported. This randomized, double-blind study examined the neural block characteristics of 20 ml of 0.75% solutions of ropivacaine and bupivacaine, both with epinephrine, after epidural administration in humans.

Methods

Forty male and three female patients of ASA physical status I and II were entered into a randomized double-blind study of ropivacaine and bupivacaine that had been approved by the institution's Human Ethics Committee. Two male patients (in the bupivacaine group) were excluded from evaluation of efficacy due to technical failures. Informed consent was obtained from all patients prior to admission into the study. All patients were scheduled for elective urologic surgery under epidural anesthesia. Excluded were patients with a history of significant neurologic, cardiopulmonary, and psychiatric disease, patients with a history of drug abuse, and women of childbearing potential.

Premedication consisted of 5-10 mg diazepam given orally about 90 minutes prior to the induction of anesthesia. All patients received at least 500 ml of balanced electrolyte solution intravenously before administration of the epidural block. Lumbar epidural puncture was performed at the L2-L3 or L3-L4 interspace with the patient in the lateral position. The epidural space was identified by a loss-of-resistance technique with air using an 18G Tuohy needle via the midline approach. An epidural catheter was inserted 3 cm cephaled and the patient was turned supine.

A test dose of 3 ml of either ropivacaine 0.75% or bupivacaine 0.75% (Astra Pain Control, Södertälje, Sweden), both with 5 $\mu g.ml^{-1}$ of epinephrine, was given. After 3-4 minutes, a total dose of 17 ml of the same solution as was used for the test dose was injected in incremental doses over approximately 4 minutes. The total dose given was

150 mg ropivacaine and bupivacaine, respectively. The epidural block was performed by one investigator (MJMG) and the assessments of efficacy by another investigator (HEMK).

The upper and lower levels of analgesia were determined bilaterally with the blunt end of a Sherwood B400 27G short bevel needle at 2 minutes, and then every 5-minutes after the end of the injection of the last dose for 30 minutes, and every 15-30 minutes thereafter until normal sensation had completely returned.

Motor block was assessed by use of a modified Bromage scale after each determination of analgesia (3= unable to flex hip, knee or ankle; 2= able to dorsiflex ankle only; 1= able to flex knee and ankle; 0= able to raise extended leg off bed).

Heart rate was obtained from continuous ECG monitoring and blood pressure from an automatic cycling blood pressure recording device (Dinamap, Criticon, Tampa, USA) immediately prior to block, at 2, 5, 10, 15, 25 and 30 minutes after initiation of the block, and then every 30 minutes for 3 hours. Cardiovascular effects, which included any episode of hypotension (>30% decrease from pre-block systolic blood pressure) or bradycardia (heart rate < 50 bpm) were recorded and treated according to standard anesthetic practice.

The intensity and outcome of any adverse event during hospitalization was recorded. All patients were contacted between the sixth and 14th day after surgery to see wether any late complications had occurred. Interval data are expressed as mean (onset and duration of analgesia, onset and duration of motor block, changes in heart rate and arterial pressure) and ordinal data as median (segmental levels of analgesia).

Statistical analysis for differences between distributions were analyzed by Wilcoxon's rank sum test, and differences between frequencies by chi-square or Fisher's exact test. A p value less than 0.05 was considered significant.

Results

Twenty-one patients received 20 ml ropivacaine 0.75% with epinephrine and 20 patients were given 20 ml bupivacaine 0.75% with epinephrine. Demographic data are summarized in table 1. The groups were comparable in age, height and weight. All times given are from the end of the epidural injection.

Quality of surgical anesthesia

Duration of surgery was 55 ± 6 (mean ± SEM) minutes in the ropivacaine group and 70 ± 9 minutes in the bupivacaine group. Analgesia was satisfactory for surgery in all patients but two, one in each group who required general anesthesia due to pain from surgery. They were given fentanyl, pentothal, and a combination of oxygen, nitrous oxide and isoflurane.

Onset of analgesia and motor block

Mean time to reach the maximum upper level of analgesia was 20.1 ± 1.2 minutes for ropivacaine and 21.8 ± 1.8 for bupivacaine. The mean onset to T12 was 7.9 ± 0.7 minutes for ropivacaine and 6.8 ± 0.6 minutes for bupivacaine. The mean onset time to block S1 was 4.6 ± 0.7 minutes for ropivacaine and 4.7 ± 0.6 minutes for bupivacaine. No differences were found between the groups in onset either to maximum upper segmental spread or to any segment. Nor were any significant differences found between the groups with regard to onset to various grades of motor block of the lower limbs. However, the frequency of degrees 2 and 3 (complete) motor block was significantly lower in the ropivacaine group (table 2).

Table 10.1: Demografic data (mean ± SEM).

	Ropivacaine 0.75% (n=21)	Bupivacaine 0.75% (n=20)
Age (years)	42.6 (3 0)	52 9 (3 3)
Sex	2f/19m	1f/19m
Height (cm)	179.6 (1.5)	177 0 (1 5)
Weight (kg)	79.2 (2.2)	76.6 (1 7)

n= number of patients
f= female
m= male

Table 10.2: Frequency of different degrees of motor block of the lower limbs.

Degree of motor blockade	Ropivacaine 0.75% (n=21)	Bupivacaine 0.75% (n=20)	Level of significance
1	20/21(95.2%)	20/20(100%)	NS
2	15/21(71.4%)	20/20(100%)	$p<0.05$
3	7/21(33.3%)	16/20(80%)	$p<0.01$

NS= not significant
n= number of patients

Spread of analgesia

Median upper and lower segmental levels of analgesia at various time intervals after injection are summarized in figure 10.1. Mean maximum upper level of analgesia was T8 ± 0.6 for ropivacaine and T7 ± 0.6 for bupivacaine. The range was T3-T10 and T3-T9, respectively. The level of analgesia was higher for bupivacaine, but only at 5 hours after injection. All patients but one (in the ropivacaine group) had block of the S5 dermatome.

Duration of analgesia and motor block

Mean duration for T10, L2 and S5 was 190 ± 12, 289 ± 11 and 430 ± 18 minutes for

ropivacaine, respectively, and 234 ± 20, 331 ± 18 and 496 ± 26 minutes for bupivacaine, respectively. However, at these levels the duration was shorter in the ropivacaine group compared to the bupivacaine group (figure 10.2). Ropivacaine produced a significantly shorter duration of degree 1 motor blockade (252 ± 19 minutes) than bupivacaine (320 ± 23 minutes). In no patient did the motor block last longer than the sensory blockade.

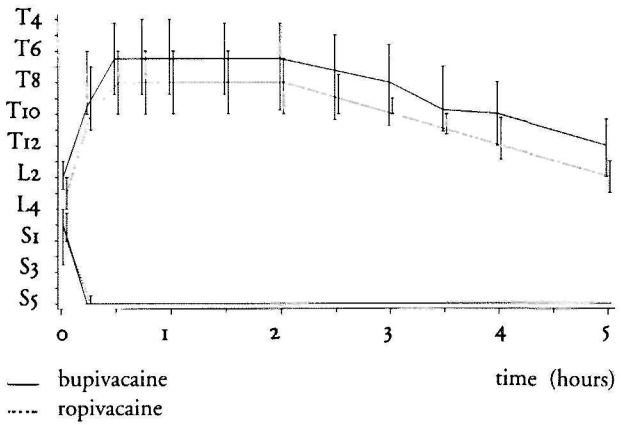

Figure 10.1: Segmental levels of analgesia at different time intervals after the end of the epidural injection (median, upper and lower level). There is a significant difference between the groups 5 hours after injection.

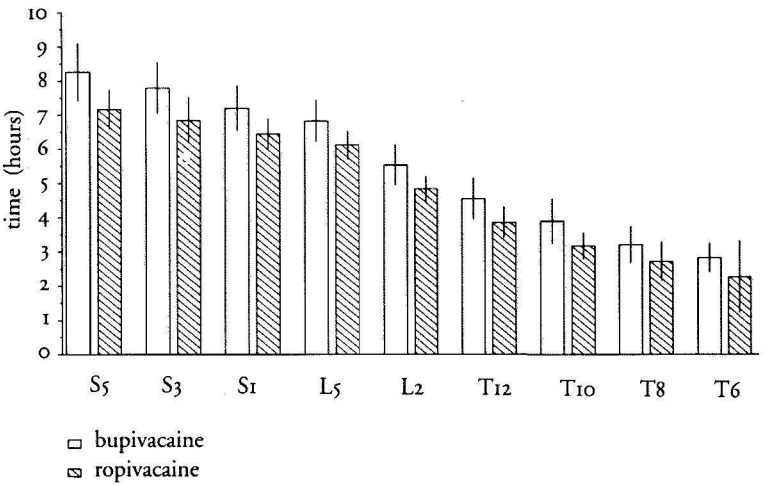

Figure 10.2: Duration of analgesia at different time intervals after the end of injection (mean ±1.96 x SEM, approximate 95% confidence interval). There is a significant difference between the groups at the T10, L2 and 5 segments.

Cardiovascular effects

No differences were found between the groups with regard to relative changes in heart rate or mean arterial pressure during the first 30 minutes after injection (figures 10.3 and 10.4). Hypotension requiring administration of intravenous ephedrine was experienced by 2 out of 21 (9%) patients in the ropivacaine group and by seven out of 20 (35%) patients in the bupivacaine group. Three patients in the bupivacaine group (15%) experienced bradycardia. In one patient given ropivacaine, manipulation within the bladder resulted in a vasovagal reaction with resultant bradycardia.

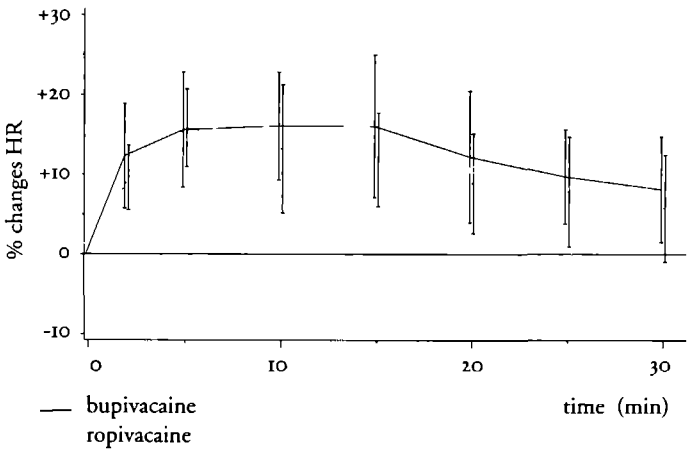

Figure 10.3: Relative changes in heart rate at different time intervals after the end of injection (mean ± 1,96 x SEM, approximate 95% confidence interval).

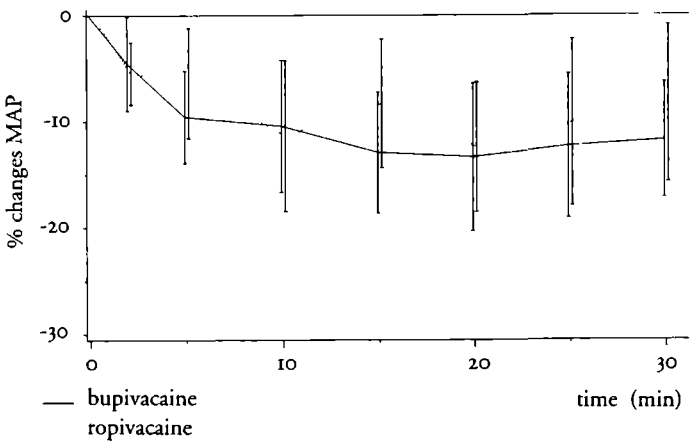

Figure 10.4: Relative changes in mean arterial blood pressure at different time intervals after the end of injection (mean ± 1.96 x SEM, approximate 95% confidence interval).

Adverse events

Shivering after injection of the local anesthetic occurred in one patient and mild backache was experienced by two patients, all in the bupivacaine group and on the first day after surgery. All patients made a complete recovery. No late occuring adverse events were observed in any patient.

Discussion

All currently available local anesthetics have advantages and disadvantages. Bupivacaine provides sensory analgesia at relatively low concentrations without producing profound motor block of the lower limbs, which makes it a very useful agent for obstetric anesthesia and for certain acute postoperative pain and chronic pain states where prolonged sensory analgesia with minimal motor involvement is wanted.

After unintentional intravenous administration of bupivacaine, however, cardiovascular collapse with fatal outcome has been reported (Albright 1979). Previous studies in animals do suggest that the cardiotoxicity of bupivacaine is greater than that of ropivacaine when used in equal doses (Arthur 1986, Moller 1986). Ropivacaine appears to provide a greater margin of safety than does bupivacaine when used in equal dosage (Reiz 1989).

Our investigation has demonstrated that ropivacaine 0.75% is an effective long-acting local anesthetic agent after epidural administration. No differences were found between ropivacaine and bupivacaine in onset of analgesia and motor block, spread of analgesia or quality of surgical anesthesia although duration of analgesia was shorter in the ropivacaine group at T10, L2 and S5 dermatomes.

Significantly fewer patients had degree 2 and 3 motor block after administration of ropivacaine compared to bupivacaine. Duration of degree 1 motor block was shorter in the ropivacaine group compared to the bupivacaine group. This is in accordance with studies in animals that have shown ropivacaine to be a less potent drug than bupivacaine in terms of producing motor block after epidural administration (Feldman 1988).

Comparison of the physicochemical properties of ropivacaine and bupivacaine shows that the pKa values are almost identical (bupivacaine: 8.10, ropivacaine 8.07) and the ratio between the ionized cation and unionized base at physiological pH is similar for the drugs. Ropivacaine, however, is less lipid soluble than bupivacaine (Rosenberg 1986). The greater lipid solubility of bupivacaine should have a major role in penetration of the large myelinated A fibers and may be the explanation of the differences we have seen between ropivacaine and bupivacaine with regard to motor block (Narahashi 1971).

Differential nerve block is of importance for the usefulness of a local anesthetic in the clinical situation. Ropivacaine may be better suited than bupivacaine for obstetric analgesia and for postoperative pain relief than for surgery requiring profound muscle

relaxation. How epinephrine affects the sensory/motor separation of ropivacaine and how it interacts with the vasoactivity of ropivacaine is not yet clear (Åkerman 1987, Kopacz 1988). In the present study, no signs of significant cardiovascular depression, adverse events, or signs of toxicity were experienced. Transient hypotension occurred in 9% of the patients in the ropivacaine group and in 35% in the bupivacaine group and was readily corrected with intravenous administration of ephedrine. The magnitude of mean arterial blood pressure changes after administration of bupivacaine was similar to that reported by other investigators (Whalley 1987).

In conclusion, ropivacaine 0.75% with epinephrine is an effective, long-acting local anesthetic when used for epidural anesthesia for urologic procedures. The duration of analgesia is similar to that of bupivacaine although the motor block is less profound and of shorter duration.

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Summary and conclusions

CHAPTER 1 describes the aims and objectives of this thesis entitled: "Ropivacaine versus bupivacaine, characteristics and clinical aspects in lumbar epidural blockade".

CHAPTER 2 outlines briefly the history, physicochemical properties and mechanisms of action of local anesthetics. Because the physicochemical properties of local anesthetics are responsible for the clinical profile of these drugs, this chapter deals with molecular weight, lipid solubility, pK and protein binding in particular.

CHAPTER 3 deals with the structural differences between ropivacaine and bupivacaine. By means of X-ray diffraction techniques an attempt is made to provide an insight into the 3-dimensional structure of the active forms of both ropivacaine and bupivacaine. After a brief introduction to the basis for this technique, the results of this experimental study are discussed. Although the structure of ropivacaine and bupivacaine differ only by a CH_3 group, the molecular packing arrangements are different.

CHAPTER 4 concerns a study of the literature on the cardiovascular effects of epidural blockade. Cardiovascular alterations following epidural blockade are related to the type and dosage of the administered local anesthetic, the addition of vasoconstrictors, the extent of the sympathetic blockade and the cardiovascular status of the patient.

CHAPTER 5 describes the technique of noninvasive monitoring by electrical bioimpedance. To begin with, basic principles of the circulatory system are shown. Historical features are presented.Then the development of the mathematical formulas used to calculate stroke volume are discussed. The calculations are based on rhythmic variation in thoracic electrical bioimpedance induced by fluctuations in the caliber of the large vessels and the flow of the blood in these vessels.

CHAPTER 6 describes the hemodynamic effects in epidural blockade after administration of bupivacaine with and without epinephrine. Changes in hemodynamic performances occurred within two to four minutes. Cardiac output, stroke volume and end diastolic volume increased in the epinephrine group. The differences are explained by the vasoactive effects of epinephrine.

CHAPTER 7 deals with the hemodynamic effects in lumbar epidural blockade with ropivacaine and bupivacaine, both with epinephrine. The hemodynamic differences found in this study are related to the vasoactive properties of ropivacaine.

CHAPTER 8 reports on an experimental study in rats, which involved the inhibition of withdrawal responses after epidural and intrathecal administration of bupivacaine and ropivacaine. Several experimental models are used to evaluate the efficacy of local anesthetics. The model used in this study allows the measurement of graded responses. After epidural and intrathecal administration, ropivacaine is less potent than

bupivacaine in terms of inhibition withdrawal responses, after noxious stimulation.

CHAPTER 9 describes an open multi-center study to evaluate the clinical efficacy of ropivacaine in different concentrations (0.5%, 0.75% and 1.0%, with epinephrine) when used for epidural anesthesia. No differences in onset times were found between the three concentrations. The degree and duration of motor blockade increased with increasing ropivacaine concentration. Duration of analgesia increased with increasing ropivacaine concentration. This study as demonstrated that ropivacaine is an effective, long-acting local anesthetic agent when administered in the epidural space in man.

CHAPTER 10 describes the neural blockade characteristics of 0.75% bupivacaine and 0.75% ropivacaine following epidural administration in forty three patients. No differences were found between the groups, neither in terms of onset time to maximum upper levelof sensory blockade nor in terms of onset time to any segment. Motor blockade is less profound and of shorter duration after ropivacaine administration compared to bupivacaine. The duration of analgesia was shorter in the ropivacaine group at T10. Analgesia was satisfactory for surgery in both groups.

Conclusions

Epidural blockade has achieved wide popularity as a means to provide excellent surgical anesthesia and postoperative analgesia. This popularity is a result of the development of local anesthetics with long duration and good sensory blockade.

Bupivacaine was the first local anesthetic agent that combined the properties of an acceptable onset, long duration of action, profound blockade and separation of sensory and motor blockade. However, there has been considerable concern regarding the untoward cardiovascular effects after accidental intravenous administration of bupivacaine.

Ropivacaine is a new local anesthetic which has been shown to be less toxic compared to bupivacaine. The clinical effects of ropivacaine in epidural anesthesia seems to be comparable to that of bupivacaine for sensory blockade. However, ropivacaine at equal concentrations produces less motor blockade than bupivacaine. These findings are related to the physicochemical properties of these local anesthetics. Moreover, ropivacaine seems to have a greater margin of safety than bupivacaine.

HOOFDSTUK 1 beschrijft het doel van de studies van dit proefschrift met de titel: Ropivacaine versus bupivacaine, karakteristieken en klinische aspecten in lumbale epidurale blockade.

HOOFDSTUK 2 geeft een korte beschrijving van de historie, fysicochemische eigenschappen en werkingsmechanismen van lokale anesthetica. Omdat de fysicochemische eigenschappen van lokaal anesthetica, het moleculair gewicht, de vetoplosbaarheid, de pk en de eiwit binding, verantwoordelijk zijn voor het klinisch profiel van deze farmaca, worden deze uitvoerig beschreven.

HOOFDSTUK 3 beschrijft de strukturele verschillen tussen ropivacaine en bupivacaine. Met behulp van röntgen-diffraktie technieken is getracht de driemensionale struktuur van de aktieve vormen van ropivacaine en bupivacaine inzichtelijk te maken. Na een korte inleiding betreffende deze techniek, worden de resultaten van deze experimentele studie besproken. Hoewel ropivacaine en bupivacaine slechts verschillen in een CH_3 groep, is de molekulaire pakking verschillend.

In HOOFDSTUK 4 worden aan de hand van een literatuur studie, de cardiovasculaire effekten van de epidurale blokkade besproken. Cardiovasculaire veranderingen na epidurale blokkade zijn gerelateerd aan het type en de dosis van het toegediende lokaal anestheticum, de toevoeging van vasoaktieve farmaka, de uitbreiding van het sympatisch blok en de cardiovasculaire status van de patient.

HOOFDSTUK 5 beschrijft de techniek van niet invasieve monitoring met behulp van elektrische bio-impedantie. Basale principes van het circulatoire systeem worden besproken. Historische hoofdpunten en de ontwikkeling van de mathematische formule om het slag volume te bereken op basis van de ritmische variatie in thoracale elektrische weerstand, geinduceerd door fluktuaties in de doorsnee van de grote vaten en de bloedstroom door deze vaten, wordt uiteengezet.

HOOFDSTUK 6 beschrijft de hemodynamische effekten bij epidurale blokkade na toediening van bupivacaine met en zonder adrenaline. Hemodynamische veranderingen traden binnen de 2 tot 4 minuten op. Hartminuut volume, slag volume en eind diastolisch volume namen toe in de adrenaline groep. De verschillen worden verklaard door de vasoaktieve effekten van adrenaline.

HOOFDSTUK 7 geeft een overzicht van de hemodynamische effekten bij lumbale epidurale blokkade met ropivacaine en bupivacaine beide met adrenaline. De gevonden hemodynamische verschillen zijn gerelateerd aan de vasoaktieve eigenschappen van ropivacaine.

HOOFDSTUK 8 behandelt een experimentele studie in ratten, waarbij de inhibitie van de terugtrek respons na epidurale en intrathecale toediening van ropivacaine en bupivacaine gemeten wordt. Verschillende experimentele modellen worden gebruikt om de werkzaamheid van lokaal anesthetica te evalueren. Het model gebruikt in deze studie biedt de mogelijkheid tot weergave van graduele metingen. Na epidurale en intrathecale toediening, is ropivacaine minder potent in de zin van het onderdrukken van de terugtrek respons na het geven van een pijnprikkel.

HOOFDSTUK 9 beschrijft een open multicenter studie waarin de klinische werkzaamheid van drie verschillende concentraties (0.5%, 0.75% en 1.0%) ropivacaine na epidurale toediening geevalueerd wordt. De tijden die het begin van de blokkade aangeven, waren niet verschillend bij de 3 verschillende concentraties. De graad en de duur van de motore blokkade nam toe met oplopende ropivacaine concentratie, alsmede de analgesie duur. De studie toonde aan dat ropivacaine een effektief, lang werkend lokaal anestheticum is, wanneer het bij mensen epiduraal wordt toegediend.

HOOFDSTUK 10 beschrijft de blokkerende werking van bupivacaine 0.75% en ropivacaine 0.75% na epidurale toediening bij 43 patienten. De tijden van het begin van de sensorische blokkade en de maximale hoogte van blokkade zijn niet verschillend in beide groepen. De motore blokkade is minder in de ropivacaine groep ten opzichte van de bupivacaine groep. De analgesie duur ter hoogte van het thoracale segment 10 is korter in de ropivacaine groep. Analgesie voor chirurgie is in beide groepen goed.

Conclusies

Epidurale blokkade heeft een grote populariteit verworven om goede chirurgische anesthesie en postoperatieve analgesie te verschaffen. Dit is het gevolg van de ontwikkeling van lokaal anesthetica met lange werkingsduur en goede sensorische blokkade.

Bupivacaine was het eerste lokaal anestheticum welke de eigenschappen van een acceptabele inwerkingsduur, lange werkingsduur, diepe blokkade en scheiding tussen sensorische en motore blokkade verenigde. Echter, er bestaat een aanzienlijke bezorgdheid met betrekking tot de ongunstige cardiovasculaire effekten na toevallige intraveneuse toediening van bupivacaine.

Ropivacaine is een nieuw lokaal anestheticum, waarvan is aangetoond dat het minder toxisch is vergeleken met bupivacaine. De klinische effekten van ropivacaine bij epidurale toediening, zijn vergelijkbaar met die van bupivacaine voor sensore blokkade. Echter ropivacaine veroorzaakt minder motore blokkade bij gelijkwaardige concentraties in vergelijking met bupivacaine. Deze bevindingen zijn gerelateerd aan de physicochemische eigenschappen van deze lokaal anesthetica. Bovendien blijkt ropivacaine een grotere veiligheidsmarge te hebben dan bupivacaine.

The author was born on the 8th of March 1956 in The Hague. He obtained his sec ondary school certificate in 1975 at the Simon Stevin College in The Hague. Fron 1975 to 1982 he studied at the Medical School of Erasmus University in Rotterdam graduating on 19th March 1982. From March 1982 to October 1982 he was a junio house officer at the Department of Cardiology of the Sint Franciscus Hospital Rotterdam.

He specialized in anesthesiology at the Institute for Anesthesiology of the Sin Radboud Hospital, University of Nijmegen (head: Prof. Dr. J.F. Crul), where on th 15th of January 1987 he became a qualified and registered anesthesiologist.

From January 1987 to November 1989 he worked as a staff member of the same insti tute (head: Prof. Dr. L.H.D.J. Booij). During this time he was given the opportunit to conduct the research for this thesis. Since the 1st of November 1989 he has been as signed to the Canisius-Wilhelmina Hospital in Nijmegen as a consultant anesthesi ologist.

STELLINGEN

behorende bij het proefschrift

Ropivacaine versus bupivacaine

characteristics and clinical aspects in lumbar epidural blockade

H E M. KERKKAMP

Nijmegen 21 november 1990

1

De fysicochemische eigenschappen van een lokaal anestheticum, bepalen mede de klinische werkzaamheid.

2

Hemodynamische metingen kunnen op een veilige, betrouwbare en niet invasieve wijze verricht worden met behulp van thoracale bioimpedantie monitoring.

3

Adrenaline toegevoegd aan epiduraal toegediende langwerkende lokaal anesthetica, is meer van invloed op de hemodynamiek van de patiënt dan op de werkingsduur van het anestheticum.

4

Door de uitgesproken differentiële zenuwblokkade, is epiduraal toegediend ropivacaine geschikt voor obstetrische en postoperatieve epidurale pijnbestrijding.

5

Voor snelle en accurate hemoglobine bepalingen is de hemocue zeer geschikt.

6

De dextraan dilutietechniek is een betrouwbare methode voor het bepalen van het circulerend plasmavolume.

7

Ook voor huisartsen dient een stage anesthesiologie in het curriculum opgenomen te worden.

8

Gezien het feit dat absoluut en verhoudingsgewijs de sterfte van mensen tijdens anesthesie geringer is dan de sterfte in het algemeen, zou het interessant zijn te onderzoeken of een toestand van anesthesie een positieve invloed heeft op de levensduur.

9

Het gezegde: schoenmaker houd je bij je leest, geldt ook ten aanzien van de keuze van de anesthesie techniek.

10

Anesthesiologie is een kind van de tijd, de budgetering maakt het een kind van de rekening.

11

Een consensus betekent dat iedereen afspreekt iets collectief te zeggen, wat niemand individueel gelooft. *Abba Eban. Uit: From Beirut to Jerusalem, Thomas Friedman.*

12

Automobiliteit is belangrijker dan een automobiel voor iedereen.

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