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Case Report

Ropivacaine Plasma Concentrations after 192-Hour High Dose Epidural Ropivacaine Infusion in a Pediatric Patient without Side Effects

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Received 23 January 2018; Accepted 1 July 2018; Published 11 July 2018

1. Introduction

Since cocaine was introduced in the 19th century by Carl Koller and Sigmund Freud, the use of local anesthetics (LA) has evolved enormously. Local anesthetics can be used to produce local, locoregional, and neuraxial nerve blockade. Binding of LA to various subtypes of sodium channels (Na\textsubscript{v}) in the nervous system produces nerve blockade. Currently 7 subtypes of Na\textsubscript{v} are known in the nervous system. Blocking on these receptors can potentially cause minor side effects such as a metallic taste or tingling, but also severe side effects such as seizures and cardiac arrest. All these symptoms and adverse effects are referred to as local anesthetic systemic toxicity (LAST) [1]. In pediatrics little is known about the absolute maximum dosages for epidural infusion of ropivacaine. Only two studies [2, 3] have been performed in pediatrics assessing the safe use of ropivacaine given via continuous epidural infusion for maximum dose of 0.4 mg kg\textsuperscript{-1} h\textsuperscript{-1}. In this case report we present and discuss a case of continuous administration of ropivacaine 0.56 mg kg\textsuperscript{-1} h\textsuperscript{-1} in the epidural space for over 8 days to control severe pain after bilateral amputation and reveal its concentration in venous and arterial plasma after 8 days. Written informed consent was obtained from the patient’s parent for publication of this report.

2. Clinical Presentation

A previously healthy 7-year-old male presented to a community hospital with severe lower extremity trauma due to accident with a truck. The patient was instantly brought to the OR and the surgeon performed a lower right and upper left leg guillotine amputation. During surgery the patient received one litre of crystalloids, two units of packed cells, and one unit plasma and remained hemodynamically stable with low noradrenaline dosage. For postoperative analgesia a n. ischiadicus and a n. popliteal catheter were placed during surgery in the left and right lower extremity, respectively. Since much postoperative pain was expected ropivacaine infusion of 0.2 mg kg\textsuperscript{-1} h\textsuperscript{-1} was started over each catheters (0.4 mg kg\textsuperscript{-1} h\textsuperscript{-1} in total), postoperatively. Intravenous infusion of esketamin 0.2 mg kg\textsuperscript{-1} h\textsuperscript{-1} and morphine 20 mcg kg\textsuperscript{-1} h\textsuperscript{-1} was started additionally. Initially peripheral catheters were preferred since less hemodynamic
CONCLUSIONS OF ROPIVACaine AFTER 8 DAYS. THE UNBOUND AND BOUND

Pain was tolerated well. No long-term side effects such as
sensations of ropivacaine after 8 days. The unbound and bound
toxic consequences were expected. Postoperative analgesia was
not sufficient anymore, most probably due to peripheral
catheter manipulation after several debridements and stump
clousure on OR. Therefore, the peripheral catheters were
removed and since the patient was hemodynamically stable
and had no fever anymore a tunneled epidural catheter (L4-
L5) was placed and ropivacaine 0.4 mg kg⁻¹ h⁻¹ infusion
was started epidurally. This resulted in adequate pain man-
gement during rest and additional morphine was stopped
since it caused itching. However, during wound treatment the
next day the patient experienced again nonacceptable pain. A
bolus of esketamin did not reduce pain to acceptable levels.
Moreover, infusion of esketamin is controversial since it may
induce liver enzyme disorder and it was stopped [4]. One
day after epidural placement a bolus of 10 ml ropivacaine
0.375% with 5 mcg of sufentanil resulted in adequate pain
relief, and we increased continuous epidural infusion to 0.48
mg kg⁻¹ h⁻¹ of ropivacaine. Initially a bilateral sensory
block was present at T12/L1 without a motor block. We
observed the patient in a medium care unit with continuously
pulse oximetry, 3-lead ECG (no qualitative 12-lead ECG
analysis) and blood pressure monitoring. Furthermore, our
nurses are trained to recognize symptoms of LAST and
the patient was monitored on a daily basis by the acute
care service. Since we did not observe symptoms of LAST
whatesoever, no side effects of epidural bupivacaine 0.5 mg
kg⁻¹ h⁻¹ were described in literature [5], the department of
pediatric anesthesiology approved these high concentrations,
and adequate pain relief was obtained and these high dosages
were accepted. After taking into account the weight loss due
to amputation we were actually infusing at 0.56 mg kg⁻¹ h⁻¹.

Since few studies are performed to assess intravenous
ropivacaine concentration after subsequent epidural infusion
for days in pediatrics, we obtained venous and arterial
samples after 8 days of epidural ropivacaine infusion and
continued epidural infusion. Venous sampling resulted in
1.1 mg/l and 0.06 mg/l bound and unbound ropivacaine
concentration, respectively. Arterial sampling resulted in
1.2 mg/l and 0.05 mg/l bound and unbound ropivacaine
concentration, respectively. To our knowledge there were no
other laboratory tests which we could perform to monitor for
ropivacaine toxicity, other than more frequent testing which
we did not find ethical to do in a child.

After 11 days, our patient was transferred, with the epidu-
ral in situ, to another hospital closer to his hometown. In
follow-up, we learned that the epidural catheter was luxated
during transport and thus removed. At this moment, the
pain was tolerated well. No long-term side effects such as
paresthesia were observed.

3. Discussion

As far as we know, this case report is the first report on admin-
istering 0.56 mg kg⁻¹ h⁻¹ ropivacaine epidurally for 8 consec-
tutive days in a pediatric case with severe trauma and hence
pain. Therefore, we sampled venous and arterial concentra-
tions of ropivacaine after 8 days. The unbound and bound
ropivacaine concentrations fractions showed an equal dis-
tribution in the arterial and venous compartment. However,
Knudsen et al. [6] showed a 2-fold and 4-fold higher arterial
than venous ropivacaine concentration after IV-infusion for
bound and unbound fraction, respectively. Different concen-
trations of local anesthetics in the venous and arterial com-
partment were observed in other studies after extravascular
administration as well and they show that an equilibrium was
reached after 2h of extravascular administration [7, 8]. This
effect is known as the so-called flip-flop effect and is caused
by slow distribution of local anesthetics and is also identified
in epidural infusion. This helps us understand why we found
an equal distribution of plasma ropivacaine concentrations in
the venous and arterial compartment in our patient.

Furthermore, Knudsen et al. showed first adverse effects
for unbound ropivacaine at 0.15 mg/l in adults; the concen-
trations measured in our case were well below this con-
centration. The question what concentrations of ropivacaine
are necessary to cause LAST symptoms in pediatrics cannot
be directly answered with this comparison because of the
different pharmacology between children and adults such
as bigger volume of distribution in children (not important
in this case since steady-state was attained) and a higher
susceptibility for LA in peripheral blocks [9]. However, the
higher concentrations measured in this case report are not
causing LAST symptoms in this patient. Evidence is available
that toxic concentration for bupivacaine is reached at 3.7 mg
l⁻¹ in children [10]. Unfortunately no study revealed thus far
the toxic concentration of ropivacaine for children.

Concentrations we measured in this case report are in
line with other studies by Bösenberg et al. [2] and Berde
et al. [3]. Since they only assessed infusion for 24-72h, we
showed what concentration of ropivacaine after 192h is not
accumulating. This was also shown by Berde et al., who
showed stable and decreased concentrations of unbound
ropivacaine throughout epidural infusion. Because we only
report one case one should be prudent with generalization,
especially since we only sampled at day 8.

Gustorff et al. [11] described a case report where they
performed ropivacaine continuous epidural infusion at 1.14
mg kg⁻¹ h⁻¹ with an optional bolus of 1.36 mg kg⁻¹. After
70 hours they measured a total concentration of 1.54 ml l⁻¹
in plasma. Unfortunately they did not mention the bound
and unbound concentration, so it is difficult to compare our
measurement with their data other than stating that their total
concentration was higher than we found. This can be easily
explained by the fact that they were infusing at higher rates
and in addition had a bolus function.

Based on this case report we cannot advise to allow higher
concentrations of epidural ropivacaine as advised in current
literature in infants than 0.4 mg kg⁻¹ h⁻¹, since we only
took one measurement and thus cannot describe the typical
pharmacological profile of 0.56 mg kg⁻¹ h⁻¹. Further studies
are needed to explore safety of these concentrations in larger
populations of children. However, we can conclude that we
did not observe any side effect nor symptoms of LAST. More-
over, the unbound ropivacaine plasma concentrations we
measured did not reach toxic levels if compared to current lit-
erature. So we advise clinicians to consider titrate ropivacaine
infiltration to higher concentrations when pain treatment is difficult to manage. Of course, it is mandatory to monitor regularly for symptoms of LAST when higher concentrations of ropivacaine are infused epidurally. Moreover, clinical symptoms are most important to observe since it is known that large variability exists in serum free/total local anesthetic concentration and sensitivity to local anesthetics [7]. Unfortunately, only few laboratories offer the possibility of assessing the concentration of ropivacaine in plasma, so clinicians must take into account the fact that it might take some time (weeks) before ropivacaine concentrations are measured.

Consent

Parent of patient provided written informed consent for publication.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Glenn van de Vossenberg was responsible for care taking of patient, interpretation of data, and drafting and writing the case report. Selina van de Wal was responsible for care taking of patient, drafting, and revising. Andrea Muller and Edward Tan were responsible for care taking of patient and revising. Kris Vissers performed revision.

References
