The bioavailability of intramuscularly administered nicomorphine (Vilan) with its metabolites and their glucuronide conjugates in surgical patients

P.M. Koopman-Kimenai, T.B. Vree, L.H.D.J. Booij and R. Dirksen

1Department of Clinical Pharmacy, 2Institute of Anaesthesiology, Academic Hospital Nijmegen Sint Radboud, Nijmegen, The Netherlands

Abstract. The kinetics of 20 mg nicomorphine intramuscularly were described in 8 patients under combined general and epidural anesthesia. The half-life of nicomorphine was 0.32 ± 0.20 h (mean ± SD) and is governed by the absorption- rather than the elimination rate. The half-life of 6-mononicotinoylmorphine (0.39 ± 0.09 h) was identical to that of the parent compound (p = 0.29), suggesting it is directly related to the absorption rate of nicomorphine. Morphine had a half-life of 1.38 ± 0.31 h. Morphine is subsequently metabolized into morphine-3-glucuronide and morphine-6-glucuronide. The half-life of these 2 glucuronide conjugates was about 2.6 h (p = 0.07). A glucuronide conjugate of 6-mononicotinoylmorphine was not detected. In urine only morphine and its glucuronides are found, with renal clearance values of 214 ml.min⁻¹ for morphine and 132 ml.min⁻¹ for the glucuronides. The bioavailability of this pharmaceutical formulation after intramuscular administration equals that of intravenous administration in surgical patients (at the same dose).

Key words: pharmacokinetics: nicomorphine - 6-mononicotinoylmorphine - morphine - glucuronides - bioavailability

Introduction

Nicomorphine (3,6-dinicotinoylmorphine, DNM) has been introduced as an opioid analgesic both for systemic and perispinal use. Nicomorphine is considered to be a "prodrug" which exerts its analgesic effects through 1 or several of its metabolites [Dirksen et al. 1987, Pinckaers et al. 1982]. The 2 nicotinoyl ester groups increase the lipidsolubility and permit chemical and enzymatic hydrolysis into 3- or 6-mononicotinoylmorphine and then into morphine. Morphine is subsequently glucuronidated at the C3- and C6-position, yielding morphine-3-glucuronide and morphine-6-glucuronide.

In order to measure nicomorphine and its metabolites we developed a sensitive method of analysis by means of HPLC with electrochemical and UV detection [Koopman-Kimenai et al. 1987] and described the pharmacokinetic behavior of nicomorphine and its unconjugated metabolites 6-mononicotinoylmorphine (6MNM) and morphine (M) [Koopman-Kimenai et al. 1991a]. The serum concentration-time course of nicomorphine and its metabolites depend on the route of administration as shown earlier for the unconjugated compounds [Koopman-Kimenai et al. 1991a, 1991b, 1993].

In this study we investigated the pharmacokinetics of nicomorphine with its metabolites and their glucuronide conjugates in patients after intramuscular administration of 20 mg Vilan. The results were compared to those obtained with 20 mg intravenously administered Vilan [Koopman-Kimenai et al. 1993] to assess the bioavailability of Vilan in a comparable group of surgical patients.

Patients and methods

Patients

The study was carried out in n = 8 ASA I-II patients (healthy patients, according to the classification of the Association of American Anesthesiologists), aged 25 - 50 years, mean 37 ± 9 y (± SD), with normal body weights: 62 ± 6 kg and with normal body lengths: 166 ± 6 cm. All patients were scheduled to undergo gynecological elective abdominal surgery. Approval was given by the local Ethics Committee and informed consent obtained from each patient. The patients studied and the method of anesthesia are...
extensively described in our previous article [Koopman-Kimenai 1991a]. Excluded were patients with liver or kidney dysfunction, known allergic reactions, use of opiates or opiate antagonists, or an expected blood loss greater than 500 ml during the surgical procedure.

The patients received 20 mg nicomorphine (Vilan) intramuscularly in the deltoid muscle (1.5 cm deep). The Vilan injections were given during maintenance of anesthesia after the start of surgery when the patient’s condition was stable.

**Drugs**

Nicomorphine (DNM), 3-mononicotinoylmorphine (3MNM), 6-mononicotinoylmorphine (6MNM), morphine (M), and Vilan (nicomorphine hydrochloride) were obtained from Nourypharma (Oss, the Netherlands). Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were obtained from Sigma (St. Louis, MO, USA).

**Sampling**

Blood samples of 5 ml were taken just before and at regular time intervals during and after anesthesia: 1, 2, 3, 4, 5, 6, 7, 8, 10, 15, 20, 30, 45, 60, 90, 120, 240, 360, 480 min, 12 h, and 24 h after the administration of nicomorphine. The samples were centrifuged at 3,000 rpm and the serum was stored at -20° C until analysis.

Urine samples were taken from the urine catheter in the intervals: 0 - 0.5 h, 0.5 - 1.0 h, 1 - 2 h, 2 - 4 h, 4 - 6 h, 6 - 8 h, 8 - 12 h, 12 - 18 h, 18 - 24 h, 24 - 36 h, and 36 - 48 h. The total volume was measured and a sample (in duplo) was stored at -20° C until analysis.

**Sample preparation**

DNM, 6MNM and M were extracted as previously published [Koopman-Kimenai et al. 1987]. Both morphine glucuronides were quantified simultaneously with morphine under slightly modified conditions. The solid phase was washed with 2 ml of 50 mM diammoniumsulphate (pH 9.3) and eluted with 0.5 ml 0.01 M KH$_2$PO$_4$ buffer pH = 2.1 containing 11% acetonitrile. This is a modification of the method described by Svensson et al. [1986].

Urine samples were treated in the same way because only morphine and its glucuronides could be detected. Because of the higher concentrations 100 µl urine were extracted and the column rinsed with 5 column volumes ammoniumsulphate buffer (50 mM) before the elution with 1 ml 0.01 M KH$_2$PO$_4$ buffer pH = 2.1 containing 11% acetonitrile could be carried out.

**HPLC conditions**

Nicomorphine and its unconjugated metabolites 3MNM, 6MNM, and M were determined by means of HPLC as previously described [Koopman-Kimenai et al. 1987].

Morphine and its glucuronides were separated on a C$_8$-Sper C8 column (Chrompack, Bergen op Zoom, the Netherlands). The mobile phase was a 0.01 M KH$_2$PO$_4$ buffer pH = 2.1 containing 11% acetonitrile and 0.4 g l$^{-1}$ heptane sulfonic acid (Janssen Chimica, Beerse, Belgium). At a flowrate of 2 ml min$^{-1}$, M3G was detected with a UV-detector at wavelength 210 nm (Spectroflow 773, Separations, HI-Ambacht, the Netherlands) at a retention time of 2.3 min. Both M6G and M are electrochemically active and were quantified using an ESA electrochemical detector (ESA, Kratos, Rotterdam, the Netherlands) equipped with an analytical cell (Model 5010). The detector 1 potential was 0.3 V in order to minimize interfering peaks and the detector 2 potential was set at 0.4 V. The retention times were 2.8 min and 3.5 min for M6G and M, respectively.

**Recovery and reproducibility**

**Calibration curve:** The calibration curves were prepared by adding a variable quantity of stock solution to blank serum or urine. The calibration samples for electrochemical detection and UV detection were prepared separately. The calibration graphs were linear for M in concentrations ranging from 5 - 300 ng ml$^{-1}$ ($r = 0.9975$), for 6MNM in concentrations ranging from 2 - 300 ng ml$^{-1}$ ($r = 0.9915$), for 3MNM in concentrations ranging from 10 - 300 ng ml$^{-1}$ ($r = 0.9810$) and for DNM concentrations ranging from 9 - 800 ng ml$^{-1}$ ($r = 0.9965$). After extraction of patient samples, the sample has a volume of 200 µl. This enables injection of the same sample simultaneously on both HPLC systems: 20 µl for electrochemical detection and 100 µl for UV detection. The quantitation limit in serum for M is 5 ng ml$^{-1}$ and 6MNM is 2 ng ml$^{-1}$, for 3MNM 10 ng ml$^{-1}$, and 9 ng ml$^{-1}$ for DNM.

For the measurement of M3G, M6G, and M, the calibration samples contained all 3 compounds. In serum: all calibration graphs were linear. For M3G the concentrations ranged from 25 - 580 ng ml$^{-1}$ ($r = 0.9992$). For M6G the concentrations ranged from 5 - 100 ng ml$^{-1}$ ($r = 0.9982$) and for M this range was from 5 - 90 ng ml$^{-1}$ ($r = 0.9963$) The quantitation limit is 25 ng ml$^{-1}$ for M3G and 5 ng ml$^{-1}$ for M6G and M. The limit of quantitation was defined as 3 times the noise level, but dealing with patient samples, the nature and amount of comedication and endogenous compounds present, sometimes strongly influence the minimum quantity that can be measured.

In urine also all calibration curves were linear. The ranges and correlation coefficients are as follows: For
M3G: 1 - 20 µg.ml\(^{-1}\) (\(r = 0.9988\)), for M6G: 0.2 - 10 µg.ml\(^{-1}\) (\(r = 0.9997\)) and for M 0.2 - 10 µg.ml\(^{-1}\) (\(r = 0.9996\)). The quantitation limit is 1 µg.ml\(^{-1}\) for M3G and 0.2 µg.ml\(^{-1}\) for M6G and M.

The reproducibility was approximately 5% for the concentration ranges of all the above mentioned compounds.

The recoveries for the cyanopropyl extraction procedure for DNM, 6MNM, and 3MNM, and M were 69%, 96%, 91%, and 87%, respectively. The percentages of recovery for the cyclohexyl extraction procedure for M3G, M6G, and M were 96%, 97%, and 97%, respectively.

Procedure for the detection of glucuronides

Deglucuronidation was carried out with \(\beta\)-glucuronidase type H-2 from Helix pomatia (G-0876, Sigma, St Louis, USA). A sample of 100 µl was mixed with 25 µl \(\beta\)-glucuronidase type H-2 and 125 µl buffer (0.2 M sodiumacetate pH = 5.0). The reaction was carried out overnight and was stopped by addition of 800 µl 500 mM diammoniumsulphate buffer pH = 9.3, followed immediately by the extraction procedure. Both morphine glucuronides are commercially available, and calibration samples, with a known amount of glucuronides, were subjected to this reaction. Under these conditions the glucuronides completely disappeared from the chromatogram while there was an equal molar increase in morphine concentration.

Pharmacokinetics

All pharmacokinetic calculations were carried out using the computer package MW/Pharm obtained from Mediware (Groningen, the Netherlands) [Proost and Meijer 1992]. This is a nonlinear curvefitting program based on the least-square method. All data were fitted in a model implying an extravascular administration with a lag time and a 1-compartment elimination profile. The coefficient of determination (\(r^2\)) shows the fit between calculated curve and the serum-time data. The area under the serum concentration-time curve (AUC\(_{0-\infty}\)) was calculated from the data of the fitted curve and extrapolated to infinite time (all rest areas were below 25%). Total body clearance (CL\(_{BM}\)) was calculated as Dose/AUC\(_{0-\infty}\). The maximum serum concentration C\(_{\text{max}}\) (ng.ml\(^{-1}\)) occurs at t\(_{\text{max}}\) (h) in the fitted curve.

The renal clearance (CL\(_{R}\)) of all metabolites present in the urine was calculated as excretion rate (µg.min\(^{-1}\)) divided by the serum concentration (µg.ml\(^{-1}\)) at the midpoint of the urine collection interval.

Bioavailability is defined in 3 levels as the percentage of the AUC\(_{0-\infty}\) of:

- the parent compound,
- the active metabolites (6MNM + M + M6G),
- all measured compounds (DNM + 6MNM + M + M3G + M6G) after intramuscular administration in comparison to the intravenous administration (of the same dose nicomorphine).

Statistics

P values were calculated using analysis of variance according to standard procedures. Statistical difference is defined at \(p < 0.05\).

Results

Figure 1 shows representative serum concentration-time curves of nicomorphine and its metabolites in a patient (No. 6) after an i.m. dose of 20 mg nicomorphine. Nicomorphine (DNM) was detectable in serum during 1 hour and was eliminated with a half-life of 0.29 h. Its apparent half-life is governed by its rate of absorption and in the different patients it varied between 0.11 and 0.71 h (Table 1). 6-Nicotinoylmorphine (6MNM) was almost instantaneously formed, at t\(_{\text{max}}\) (0.16 h) it reached a C\(_{\text{max}}\) of 55 ng.ml\(^{-1}\) and it was eliminated with a t\(_{1/2}\) of 0.30 h. Mor-

![serum conc. ug/ml](image-url)

**Fig. 1** The serum concentration-time curves of nicomorphine (DNM) and its metabolites 6-mononicotinoylmorphine (6MNM), morphine (M), morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in a patient after an i.m. dose of 20 mg nicomorphine.
Table 1  Pharmacokinetic parameters of nicomorphine and its metabolites after an intramuscular dose of 20 mg Vilan

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>mean (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nemicomorphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng.mL$^{-1}$)</td>
<td>74</td>
<td>73</td>
<td>39</td>
<td>104</td>
<td>179</td>
<td>100</td>
<td>102</td>
<td>50</td>
<td>90 ± 43</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>0.18</td>
<td>0.06</td>
<td>0.26</td>
<td>0.07</td>
<td>0.06</td>
<td>0.16</td>
<td>0.15</td>
<td>0.20</td>
<td>0.15 ± 0.09</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (µg.h.L$^{-1}$)</td>
<td>90</td>
<td>58</td>
<td>31</td>
<td>31</td>
<td>39</td>
<td>61</td>
<td>54</td>
<td>42</td>
<td>50 ± 20</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (µM.h.L$^{-1}$)</td>
<td>0.18</td>
<td>0.12</td>
<td>0.06</td>
<td>0.06</td>
<td>0.08</td>
<td>0.12</td>
<td>0.11</td>
<td>0.08</td>
<td>0.10 ± 0.04</td>
</tr>
<tr>
<td>CL$_{\text{im}}$ (L/h)</td>
<td>223</td>
<td>346</td>
<td>636</td>
<td>638</td>
<td>509</td>
<td>328</td>
<td>370</td>
<td>520</td>
<td>446 ± 152</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>0.71</td>
<td>0.51</td>
<td>0.32</td>
<td>0.16</td>
<td>0.11</td>
<td>0.29</td>
<td>0.24</td>
<td>0.41</td>
<td>0.32 ± 0.20</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.926</td>
<td>0.892</td>
<td>0.972</td>
<td>0.916</td>
<td>0.988</td>
<td>0.981</td>
<td>0.985</td>
<td>0.834</td>
<td></td>
</tr>
</tbody>
</table>

6-mononicotinoylmorphine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>mean (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng.mL$^{-1}$)</td>
<td>34</td>
<td>38</td>
<td>46</td>
<td>60</td>
<td>95</td>
<td>55</td>
<td>53</td>
<td>33</td>
<td>52 ± 20</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>0.22</td>
<td>0.15</td>
<td>0.35</td>
<td>0.11</td>
<td>0.09</td>
<td>0.29</td>
<td>0.17</td>
<td>0.17</td>
<td>0.19 ± 0.09</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (µg.h.L$^{-1}$)</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>45</td>
<td>40</td>
<td>47</td>
<td>44</td>
<td>48</td>
<td>41 ± 7</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (µM.h.L$^{-1}$)</td>
<td>0.08</td>
<td>0.08</td>
<td>0.13</td>
<td>0.12</td>
<td>0.10</td>
<td>0.12</td>
<td>0.11</td>
<td>0.12</td>
<td>0.11 ± 0.02</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>0.42</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td>0.23</td>
<td>0.30</td>
<td>0.45</td>
<td>0.89</td>
<td>0.39 ± 0.09</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.933</td>
<td>0.976</td>
<td>0.966</td>
<td>0.968</td>
<td>0.983</td>
<td>0.984</td>
<td>0.979</td>
<td>0.802</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters of nicomorphine and its metabolites after an intramuscular dose of 20 mg Vilan

Figure 2 shows renal excretion rate-time profiles of nicomorphine and its metabolites in the same patient of Figure 1. Morphine-3-glucuronide was the main metabolite in urine. Of the dose administered 63.3% appeared in the urine as M3G, 11.1% as M and 7.6% as M6G.

Table 1 summarizes the pharmacokinetic parameters of nicomorphine and its metabolites in the 8 patients. The

Phen was present in the first serum sample, reached a $C_{\text{max}}$ of 36 ng.mL$^{-1}$ at $t_{\text{max}}$ of 0.74 h and was eliminated with a $t_{1/2}$ of 1.4 h. Morphine-3-glucuronide and morphine-6-glucuronide appeared simultaneously in the serum and reached their maximum concentration after 1.37 h. They were eliminated with almost identical half-lives of 3.66 h (M3G) and 2.54 h (M6G).
Table 2 Bioavailability and AUCAOC after i.m. and i.v. administration of 20 mg nicomorphine in surgical patients

<table>
<thead>
<tr>
<th>Compound</th>
<th>AUCAOC (μM h L⁻¹) Intravenous*</th>
<th>AUCAOC (μM h L⁻¹) Intramuscular</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNM</td>
<td>0.06 ± 0.02</td>
<td>0.10 ± 0.04</td>
<td>156%</td>
</tr>
<tr>
<td>6MNM</td>
<td>0.07 ± 0.01</td>
<td>0.11 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>0.40 ± 0.11</td>
<td>0.37 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>M3G</td>
<td>3.81 ± 0.79</td>
<td>3.11 ± 0.88</td>
<td></td>
</tr>
<tr>
<td>M6G</td>
<td>0.44 ± 0.13</td>
<td>0.38 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Active compounds:</td>
<td>0.91 ± 0.17</td>
<td>0.86 ± 0.12</td>
<td>95%</td>
</tr>
<tr>
<td>(6MNM + M + M6G)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4.78 ± 0.81</td>
<td>4.07 ± 0.89</td>
<td>85%</td>
</tr>
</tbody>
</table>

*Taken from [Koopman-Kimenai et al. 1994]

Discussion

Metabolism

When given intravenously nicomorphine is quick metabolized into the metabolites 6-mononicotinoylmorphine and morphine with a half-life of 1 min [Koopman-Kimenai et al. 1993]. This study shows that after intramuscular administration, nicomorphine was unexpectedly present in serum for a relatively long period. Its apparent elimination half-life is, therefore, governed by its rate of absorption and varied between 0.11 and 0.71 h.

The metabolite 6MNM is present instantaneously in the serum while 3MNM could not be detected. The latter compound is unstable in solution (stock solution, blood) with rapid hydrolysis to morphine. The compound 6MNM is stable and can be measured. The elimination half-life of 6MNM is similar to that of nicomorphine: 0.39 ± 0.09 h (p = 0.29), indicating that its rate of elimination is higher than the rate of absorption or formation. The whole process is governed by the rate of absorption of the parent drug nicomorphine.

In 6MNM glucuronidation is only possible at the 3-position. However, no peak in the chromatogram is present at a retention time that would fit the compound 6MNM3G. Moreover, treatment of the serum and urine samples with β-glucuronidase did not result in the increase of the concentration of 6MNM, while under these conditions M3G and M6G completely were converted to M.

Morphine was found in the serum 5 min after administration. Its elimination half-life was 1.38 ± 0.31 h. The rate of the morphine formation may not entirely be due to enzymatic reactions, but partly due to hydrolysis of 3MNM in serum.

In 6MNM glucuronidation is only possible at the 3-position. However, no peak in the chromatogram is present at a retention time that would fit the compound 6MNM3G. Moreover, treatment of the serum and urine samples with β-glucuronidase did not result in the increase of the concentration of 6MNM, while under these conditions M3G and M6G completely were converted to M.

Morphine was found in the serum 5 min after administration. Its elimination half-life was 1.38 ± 0.31 h. The rate of the morphine formation may not entirely be due to enzymatic reactions, but partly due to hydrolysis of 3MNM in serum.

Morphine is glucuronidated at the 3 and 6 position. These 2 glucuronide conjugates were present in plasma [Boerner et al. 1975, Garrett and Gürkan 1978, Garrett and Jackson 1979] and urine [Moore et al. 1984, Säwe et al. 1985]. Morphine-3-glucuronide has been shown to be a potent functional antagonist of morphine and morphine-6-...
glucuronide gives antinociception after intracerebro-ventricular administration to rats [Gong et al. 1991, Smith et al. 1990]. The conjugate morphine-6-glucuronide contributes to the analgesic effect [Osborne et al. 1990, 1993, Shimomura et al. 1971]. No diglucuronide of morphine was found.

Bioavailability

After intravenous administration of 20 mg nicomorphine to a comparable group of surgical patients the mean AUC\(_{0-\infty}\) of the parent compound is 32 ± 10 \(\mu\)g.h.l\(^{-1}\) (0.06 ± 0.02 \(\mu\)M.h.l\(^{-1}\)) [Koopman-Kimenai et al. 1994]. After intramuscular administration of the same dose the mean AUC\(_{0-\infty}\) of the parent compound is higher: 50 ± 20 \(\mu\)g.h.l\(^{-1}\) (0.10 ± 0.04 \(\mu\)M.h.l\(^{-1}\)) (Table 1). This results in a bioavailability of the parent compound of 156% (Table 2). This result can be explained by the fact that the apparent elimination half-life is governed by the absorption- rather than the elimination rate.

The bioavailability of this pharmaceutical formulation can be expressed as AUC\(_{0-\infty}\) (\(\mu\)M.h.l\(^{-1}\)) of the parent compound and all metabolites after i.m. administration in comparison to that after i.v. administration (at the same dose). After intravenous administration of 20 mg nicomorphine the total sum of the area under the serum concentration time curve (AUC\(_{0-\infty}\) of DNM + 6MN M + M3G + M6G) is 4.78 \(\mu\)M.h.l\(^{-1}\) [Koopman-Kimenai et al. 1994] which is in the same order of magnitude as after intramuscular administration of 20 mg nicomorphine: 4.07 \(\mu\)M.h.l\(^{-1}\), indicating a bioavailability of 85% (Table 2). If only the active compounds are taken into account, the AUC\(_{0-\infty}\) of 6MN M + M + M6G after i.v. and i.m. after the same dose have to be compared. The AUC\(_{0-\infty}\) (6MN M + M + M6G) are identical: 0.91 \(\mu\)M.h.l\(^{-1}\) (i.v.) and 0.86 \(\mu\)M.h.l\(^{-1}\) (i.m.), resulting in an i.m. bioavailability of the active compounds of 95%. After i.v. administration the parent compound and 6MN M comprised only 2.9% of the total AUC. Because of the slower absorption of nicomorphine from the muscular mass it is longer present in the blood and, therefore, nicomorphine and 6MN M comprised a larger part of the total AUC\(_{0-\infty}\) after i.m. administration: 5.5% (as was also indicated by the bioavailability of the parent compound of 156%) [Koopman-Kimenai et al. 1994]. The assessment of bioavailability in surgical patients is only feasible using a parallel study design, approximating the absolute bioavailability obtained from a cross-over design.

Renal clearance

In urine only morphine and its conjugates were present. The renal clearance (CLR\(_{\text{r}}\)) of all metabolites is listed in Table 1. There are large inter-individual differences, but it is remarkable that the renal clearance of morphine (mean 214 \(\text{ml.min}^{-1}\)) is higher than that of both glucuronides (mean 132 \(\text{ml.min}^{-1}\)). This is explained by the different excretion mechanisms: morphine is cleared via the organic cation transport system, while the glucuronides are cleared by glomerular filtration and tubular reabsorption [Greven 1981]. These results are in perfect accordance with our results after i.v. administration: 200 (M) and 115 \(\text{ml.min}^{-1}\) (M3G, M6G), respectively. As van Crugten et al. [1991] described, it is an unusual phenomenon that glucuronide metabolites, which are larger and less lipophilic than morphine, undergo net tubular reabsorption. However, Carrupt et al. [1991] described that M6G and to a lesser extent M3G are far more lipophilic than predicted and, in fact, are not much less lipophilic than morphine.

Clinical implications

The prodrug nicomorphine is biotransformed into 3 (active) metabolites: 6-mononicotinoylmorphine, morphine and morphine-6-glucuronide. Because of the relatively slow absorption of nicomorphine from the muscle mass after i.m. injection the active metabolites 6-mononicotinoylmorphine, morphine and morphine-6-glucuronide are longer present in the body than after i.v. administration.

The bioavailability of intramuscular nicomorphine is 156% of that after i.v. administration. The bioavailability of the pharmaceutical formulation and that of the active compounds are equal after i.m. and i.v. administration (85% and 95% resp.).

REFERENCES

Koopman-Kimenai, Vree, Booij and Dirksen


Osborne R, Joel S, Trew D, Slevin M 1990 Morphine and metabolite behavior after different routes of morphine administration: Demonstration of the importance of the active metabolite morphine-6-glucuronide. Clin Pharmacol Ther 47: 12-19


Pinckaers JWM, Nijhuis GMM, Dirksen R 1982 Postoperative nicomorphine analgesia by spinal or epidural application. Anästh Intensivmed 152: 16-24


