Rectal administration of nicomorphine in patients improves biological availability of morphine and its glucuronide conjugates

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

Introduction

Nicomorphine (3,6-dinicotinoylmorphine) has been introduced as an opioid analgesic both for systemic and perispinal use. Although the effectiveness of nicomorphine has been established, its action is considered not to relate to the compound itself. Nicomorphine is considered to be a 'prodrug', which exerts its analgesic effects through one or several of its metabolites [1 2]. The two nicotinoyl ester groups increase the lipid solubility and permit chemical and enzymatic hydrolysis into 3- or 6-mononicotinoylmorphine and further into morphine. Morphine is subsequently glucuronidated at the C^3- and C^6-positions, 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 high pressure liquid chromatography (HPLC) with electrochemical and UV detection [3], and described the pharmacokinetic behaviour of nicomorphine and its unconjugated metabolites 6-mononicotinoylmorphine (6MNM) and morphine [4-6]. Considering the fate of nicomorphine in the biological system and the apparent lack of intrinsic activities, the conclusion is justified that not the parent drug but rather the metabolites cause the drug to take effect in man. The serum concentration–time course of nicomorphine and its metabolites depends on the route of administration, as shown earlier for the unconjugated compounds [4-6].

In this study we investigated the pharmacokinetics of nicomorphine and its metabolites with their glucuronide conjugates in patients after rectal administration. The results of this rectal administration were compared to those obtained after intravenous administration in order to establish the absolute bioavailability of nicomorphine and morphine.

Methods

Patients

The study was carried out in 8 healthy patients [class I-II, classification of the Association of American Anesthesiologists (ASA)], aged 25-50 years, with normal body weights. All patients were scheduled to undergo gynaecological elective abdominal surgery. Approval was given by the local Ethics Committee, and informed consent was obtained from each patient. 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.

Anaesthesia

All patients were premedicated orally with diazepam 10 mg 1 h before the induction of anaesthesia. An intravenous drip cannula (18G) was inserted into a suitable arm vein, non-invasive blood pressure moni-

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Abstract
The pharmacokinetics of 30 mg nicomorphine after rectal administration with a suppository are described in 8 patients under combined general and epidural anaesthesia. No nicomorphine or 6-mononicotinoylmorphine could be detected in the serum. Morphine appeared almost instantaneously with a lag-time of 8 min and had a final elimination half-life of 1.48 ± 0.48 h. Morphine was metabolized to morphine-3-glucuronide and morphine-6-glucuronide. These glucuronide conjugates appeared after a lag-time of 12 min and the half-life of these two glucuronide conjugates was similar: about 2.8 h ($P > 0.8$). The glucuronide conjugate of 6-mononicotinoylmorphine was not detected. In the urine only morphine and its glucuronides were found. The renal clearance value for morphine was 162 ml•min^{-1} and for the glucuronides 81 ml•min^{-1}. This study shows that administration of a suppository with 30 mg nicomorphine gives an excellent absolute bioavailability of morphine and its metabolites of 88%. The lipid-soluble prodrug nicomorphine is quickly absorbed and immediately hydrolysed to morphine.

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toring consisted of finger plethysmography, and electrocardiography was commenced. After epidural puncture at the L2-L3 level, a catheter for injection of bupivacaine was introduced. Subsequently, an intra-arterial catheter (20G) was inserted into a radial artery. A urine catheter was introduced and connected to a reservoir.

Epidural anaesthesia was effected by 0.5% bupivacaine with epinephrine including a test dose of 3 ml and a full dose of 11 ml times the body length in metres. The level and intensity of the block was tested 5 and 10 min after the injection of the full dose. Epidural analgesia was maintained by infusion of 0.25% bupivacaine, 4-6 $ml \cdot h^{-1}$ epidurally. Induction of general anaesthesia with thiopentone (3-4 $mg \cdot kg^{-1}$) was followed by relaxation with vecuronium bromide (0.1 $mg \cdot kg^{-1}$) and placement of an orotracheal tube (xylocain 2% ointment). Maintenance of anaesthesia was obtained with an inhalation gas mixture of 67% nitrous oxide in oxygen. Relaxation was maintained with vecuronium bromide 1-2 mg intravenous. Respiration was controlled at an end tidal CO_2 between 4 and 4.5% (vol/vol). Concomitant therapy was noted on the medication form. Care was taken to observe that, according to the protocol of the study, no opioid analgesic except nicomorphine was used.

The patients received 30 mg nicomorphine (Vilan®) as a suppository. Nicomorphine was given during maintenance of anaesthesia after the start of surgery when the patient's condition was stable.

The demographic data of the patients are listed in Table 1.

Table 1 *Demographic data of the patients*

Patient	*Gender*	*Age (year)*	*Body length (cm)*	*Body weight (kg)*	*ASA class**
A	F	45	160	88	I
B	F	42	165	70	I
C	F	63	175	75	II
D	F	30	165	60	I
E	F	29	165	63	I
F	F	42	161	55	I
G	F	35	176	58	I
H	F	49	175	78	I
Mean (±SD)		42 ± 11	168 ± 6	68 ± 11	

*Association of American Anaesthesiologists classification.

Drugs

Nicomorphine, 3-mononicotinoylmorphine (3MNM), 6-mononicotinoylmorphine (6MNM), morphine, and 30 mg Vilan® suppositories were obtained from Nourypharma (Oss, the Netherlands). Morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were obtained from Sigma (St. Louis, USA).

Sampling

Blood samples of 5 ml were taken just before and at regular time intervals during and after anaesthesia: 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

To quantify nicomorphine, 6-MNM, and morphine, serum was extracted with the Baker-10 extraction system (Baker Chemicals, cat.nr. 70180, Deventer, the Netherlands) fitted with 1 ml disposable extraction columns as a cleaning-up procedure. The extraction columns, packed with cyanopropylsilane bonded to silica gel (CN, Baker, cat.nr. 7021-01), were conditioned with two column volumes of methanol, two column volumes of water, and 1 ml 500 mmol/l diammoniumsulfate (pH 9.3). Serum (0.5 ml), diluted with an additional 0.5 ml of 500 mmol/l diammoniumsulfate buffer (pH 9.3), was brought onto the top of the column. The column was washed with 2 ml of 50 mmol/l diammoniumsulfate (pH 9.3). The sample was eluted with 2 ml chloroform + isopropanol (90 + 10, vol/vol). The organic phase was evaporated to dryness under a mild stream of nitrogen at 37°C, and the residue dissolved in 200 µl water. This enabled the simultaneous injection of the same sample on two different HPLC systems: a 20 µl injection volume for electrochemical detection (to quantify 6MNM, 3MNM and morphine) and 50 µl for UV detection (to quantify nicomorphine). As 3MNM was never detected in patients' samples, it was after some time omitted from the calibration samples.

Slightly modified conditions were used to quantify both morphine glucuronides (M3G and M6G). Under these conditions morphine could be quantified simultaneously. The solid phase extraction of 0.6 ml serum was carried out on 1 ml cyclohexyl cartridges (C_6H_6, Baker, cat.nr. 7212-01). It was washed with 2 ml of 50 mmol/l diammoniumsulfate (pH 9.3) and eluted with 0.5 ml 0.01 mol/l KH_2PO_4 buffer (pH = 2.1) containing 11% acetonitrile.

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 was extracted and the cyclohexyl column rinsed with 5 column volumes ammoniumsulfate buffer (50 mmol/l) before the elution with 1 ml 0.01 mol/l KH_2PO_4 buffer (pH = 2.1) containing 11% acetonitrile could be carried out.

HPLC conditions

Nicomorphine and its unconjugated metabolites 3MNM, 6MNM and morphine were determined by means of HPLC as previously described [3].

Morphine and its glucuronides were separated on

a Cp-Sper C8 column (Chrompack, Bergen op Zoom, the Netherlands). The mobile phase was a 0.01 mol/l KH_2PO_4 buffer (pH = 2.1) containing 11% acetonitrile and 0.4 g•l^{-1} heptanesulfonic acid. At a flow rate of 2 ml•min^{-1}, M3G was detected with a UV detector at 210 nm (Spectroflow 773, Separations, Hendrik-Ido-Ambacht, the Netherlands) at a retention time of 2.3 min. Both M6G and morphine are electrochemically active and were quantified using an 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 morphine, respectively.

Recovery and reproducibility

The calibration curves were prepared by adding a variable quantity of stock solution to blank serum or urine. The calibration samples for the determination of nicomorphine, 6MNM, 3MNM and morphine were prepared separately for electrochemical and UV detection. The calibration graphs were linear for morphine in concentrations ranging from 2 to 300 ng•ml^{-1} (r = 0.9875), for 6MNM and 3MNM in concentrations ranging from 15 to 300 ng•ml^{-1} (r = 0.9915 and 0.9810, respectively) and for nicomorphine concentrations ranging from 70 to 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 50 µl for UV detection. The quantitation limit in serum for morphine is 2 ng•ml^{-1}, for 6MNM 10 ng•ml^{-1}, for 3MNM 30 ng•ml^{-1}, and for nicomorphine 40 ng•ml^{-1}.

For the measurement of M3G, M6G and morphine, the calibration samples contained all three compounds. In serum all calibration graphs were linear. For M3G the concentrations ranged from 25 to 580 ng•ml^{-1} (r = 0.9882), for M6G from 5 to 100 ng•ml^{-1} (r = 0.9892) and for morphine this range was from 2 to 90 ng•ml^{-1} (r = 0.9753). The quantitation limit is 25 ng•ml^{-1} for M3G, 5 ng•ml^{-1} for M6G and 2 ng•ml^{-1} for morphine. In urine also all calibration curves were linear. The ranges and correlation coefficients are 4-20 µg•ml^{-1} for M3G (r = 0.9988), 1-7 µg•ml^{-1} for M6G (r = 0.9997) and 1-6 µg•ml^{-1} for morphine (r = 0.9996). The quantitation limit is 1 µg•ml^{-1} for M3G and 0.2 µg•ml^{-1} for M6G and morphine.

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

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

Procedure for the detection of glucuronides

Deglucuronidation was carried out with β-glucuronidase type H-2 from *Helix pomatia* (G-0876, Sigma, St. Louis, USA). A sample of 100 µl was mixed with 25 µl β-glucuronidase type H-2 and 125 µl buffer (0.2 mol/l sodium acetate pH = 5.0). The reaction was carried out overnight and was stopped by the addition of 800 µl 500 mmol/l diammonium sulfate 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. This deglucuronidation was carried out if the amount of M6G was not sufficient to be weighed accurately. In patient samples this procedure was used to determine the presence of morphine-3,6-diglucuronide. If this diglucuronide was present, an unknown peak had to disappear from the chromatogram and the increase in morphine concentration had to be more than that accounted for by the former presence of M3G and M6G.

Pharmacokinetics

All pharmacokinetic calculations were carried out using the computer package MW/Pharm® obtained from Mediware (Groningen, the Netherlands) [4]. This is a non-linear curve-fitting program, based on the least-square method. Morphine was fitted as an extravascular administration with a lag time and a two-compartment elimination model. M3G and M6G were fitted as an extravascular administration with a lag time and a one-compartment elimination. The coefficient of determination (r^2) shows what the fit to the serum data looks like. 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. This could be done because the AUC of the observed data and the AUC of the fitted curve correlated well: r(M3G) = 0.9971, r(M6G) = 0.9907 and r(morphine) = 0.9987. The maximum serum concentration C_{max} (ng•ml^{-1}) occurs at t_{max} (h). The renal clearance CL_r was calculated as µg excreted/$AUC_{0-\infty}$. As the parent compound was not detected in serum, pharmacokinetic parameters such as CL and V_{ss} could not be calculated.

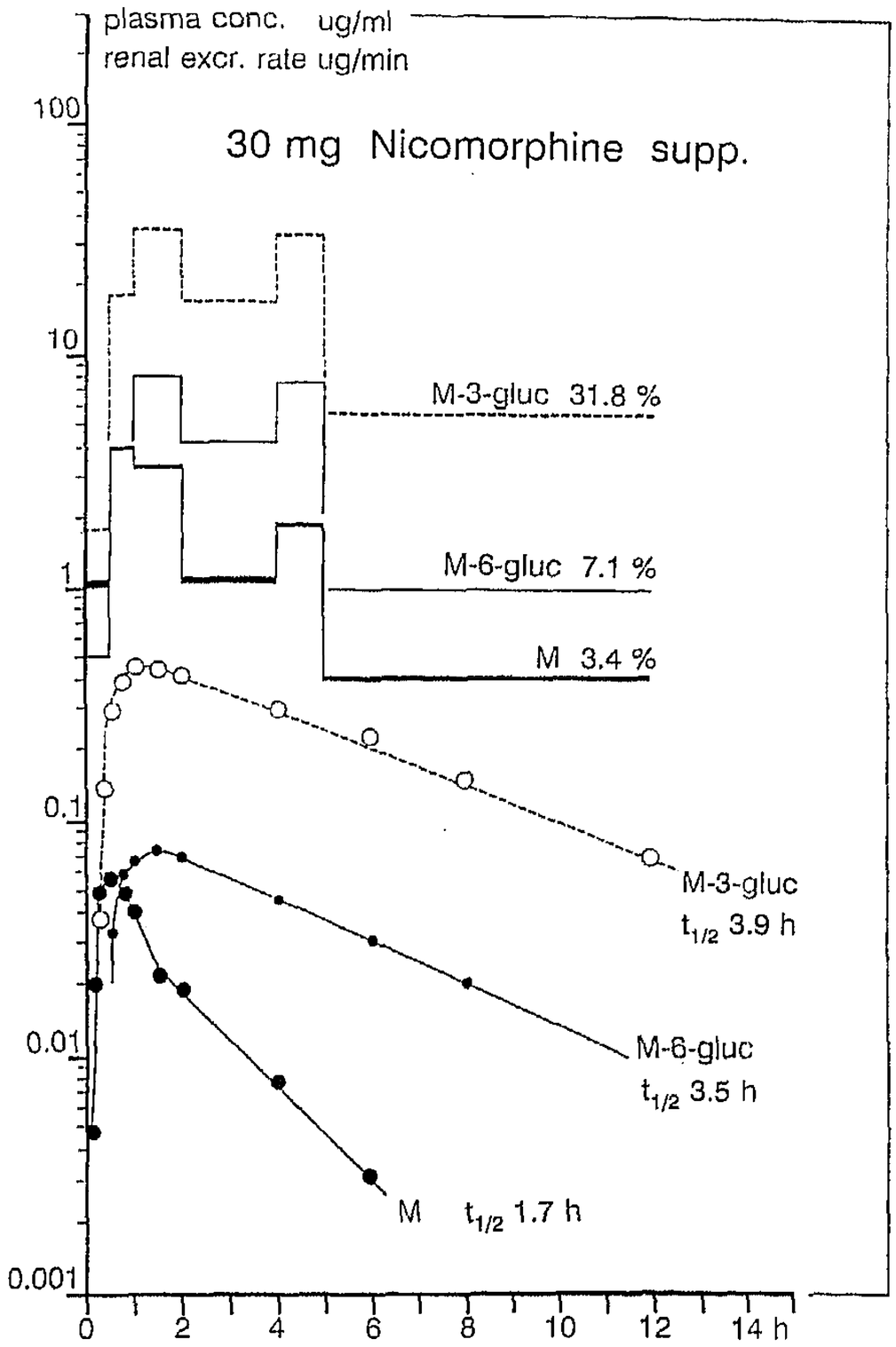
Statistics

P values were calculated using analysis of variance according to standard procedures. Statistically significant differences are assumed at $P < 0.05$.

Results

Figure 1 shows representative serum concentration–time curves of all metabolites in a patient after a rectal dose of 30 mg nicomorphine. The parent compound nicomorphine nor the metabolite 6MNM or 3MNM were detectable in the serum. Morphine appeared after a lag time of 10 min, reached a C_{max} of 52 ng•ml^{-1} at t_{max} of 34 min and was eliminated with a final half-life ($t_{1/2\beta}$) of 1.7 h. M3G and M6G appeared in the serum about 17 min after administration and reached their maximum concentration after 1.3 h. They were eliminated with almost identical half-lives of 3.89 h (M3G) and 3.47 h (M6G).

The renal excretion rate–time profiles of this patient are also shown. M3G was the main metabolite in the urine. Of the dose administered, 31.8%



▲ Figure 1

The serum concentration–time curves and the renal excretion–time curves for a patient after a rectal dose of 30 mg nicomorphine as a suppository

appeared in the urine as M3G, 7.1% as M6G and 3.4% as morphine.

Table 2 summarizes the pharmacokinetic parameters of nicomorphine and its metabolites in the 8 patients. The $t_{1/2\beta}$ of morphine (1.48 ± 0.48 h) differed significantly from those of M3G and M6G ($P < 0.015$). The $t_{1/2\beta}$ of M3G (2.80 ± 1.08 h) and M6G (2.71 ± 1.05 h) were similar ($P > 0.8$). The renal clearance of morphine (162 ± 70 ml•min^{-1}) differed significantly from that of M3G (71 ± 19 ml•min^{-1}) and M6G (91 ± 41 ml•min^{-1}) ($P < 0.0035$). The renal clearance values of both glucuronides were similar ($P = 0.23$).

Discussion

Metabolism

When given intravenously or intramuscularly, nicomorphine is quickly metabolized to the metabolites 6MNM and morphine with a half-life of 1 min [5-7]. No 3MNM was detected. This study shows that after rectal administration, nicomorphine was not present in serum, nor could the metabolites 6MNM and 3MNM be detected in the serum. Apparently the rate of hydrolysis in the alkaline colon was high. Morphine was found in the serum 8 min after administration. Its terminal elimination half-life was 1.48 ± 0.48 h. The rate of the morphine formation must be due to enzymatic reactions in the rectum.

Morphine is glucuronidated at the C3 and C6 positions. The two glucuronide conjugates were present in plasma [8-10] and urine [11]. M3G has been shown to be a potent functional antagonist of morphine and M6G antinociception after intracerebroventricular administration to rats [12 13]. The conjugate M6G contributes to the analgesic effect [14 15]. The final serum half-life of morphine varied between 1.03 and 2.34 h (mean 1.48 h). In one patient (H) a one-compartment model fitted best as can be seen from the fact that both elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$) were identical. The apparent terminal elimination half-life of morphine is shorter than the half-life of both glucuronides: mean 2.80 h for M3G and 2.71 h for M6G. Hanna *et al.* [16] found that M6G declined in parallel with morphine in the terminal phase after administration of morphine. As no attention was paid to M3G, no conclusions can be drawn about the competing pathways. It is important to measure M3G, because if present in larger concentrations it can be a source of morphine in the terminal phase, due to the enterohepatic circulation and deglucuronidation in the intestine [17-19]. Unfortunately, our quantitation limit is not low enough to visualize the fact that after administration of nicomorphine (30 mg), morphine, M3G and M6G are running parallel in the terminal phase. Long-lasting steady-state levels of morphine and its glucuronides are reported in patients with kidney failure [20 21]. The terminal phase of morphine is formed out of the glucuronides and runs parallel to both glucuronides, as excellently shown by D'Honneur *et al.* [22]. Deglucuronidation of the morphine glucuronides in the intestine, and the enterohepatic recirculation govern the terminal half-life of morphine [23-25], which is clearly visible after an oral dose of 30 mg morphine sulphate [22; Guelen PJM, personal communication].

Biological availability

After intravenous administration of 30 mg nicomorphine the mean total sum of the areas under the serum concentration–time curves is 7.8 µmol•h•l^{-1} ($AUC_{0-\infty}$ of nicomorphine + 6MNM + morphine + M3G + M6G) [26], which is in the same order of magnitude as after rectal administration of 30 mg nicomorphine: 6.9 µmol•h•l^{-1} ($AUC_{0-\infty}$ of morphine + M3G + M6G). Thus the biological availability of nicomorphine from a suppository is 0%; the biological availability of this pharmaceutical formulation, expressed as the morphine bioavailability ($AUC_{0-\infty}$ of morphine + M3G + M6G) after administration of the suppository is 88% compared to the intravenous administration. The rectal administration of morphine in a suppository results in a large variation in bioavailability (31-72%) relative to an extravascular administration. The absolute biological availability of morphine alone was 53.3 ± 17.8% as reported by Jonsson *et al.* [27].

Reported variation in bioavailability is in part due to the analytical methodology and the analytes measured. Morphine biological availability in the literature is expressed relative to an intramuscular administration [28 29], oral administration (30%) [30 33], rectal administration of a tablet (30-70%) [32] or other rectal formulations [33].

The present study shows that administration of a suppository with 30 mg nicomorphine gives an excellent absolute biological availability of morphine

Table 2 *Pharmacokinetic parameters of the metabolites of nicomorphine after a 30 mg suppository*

*Parameter**	*Patient*								
	A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*Mean (±SD)*
Morphine									
C_{max} (ng•ml^{-1})	37	49	52	48	45	32	66	27	45 ± 12
t_{max} (h)	0.72	0.52	0.56	0.47	0.28	0.62	0.48	0.55	0.53 ± 0.13
$AUC_{0-\infty}$ (µg•h•l^{-1})	77	71	103	83	55	47	114	31	73 ± 28
Lag time (h)	0.16	0.23	0.16	0.08	0.08	0.12	0.09	0.12	0.13 ± 0.05
$t_{1/2abs}$ (h)	0.37	0.15	0.22	0.20	0.12	0.32	0.23	0.30	0.24 ± 0.09
$t_{1/2\alpha}$ (h)	0.35	0.15	0.22	0.20	0.12	0.35	0.23	0.30	0.24 ± 0.09
$t_{1/2\beta}$ (h)	2.34	1.04	1.71	1.08	1.57	1.03	1.61	0.30	1.48 ± 0.48
r^2	0.9699	0.9700	0.9816	0.9825	0.9721	0.8645	0.9657	0.9230	
CL_r (ml•min^{-1})	82	135	95	122	129	240	229	261	162 ± 70
% in urine	2.2	3.3	3.4	3.5	2.5	3.7	7.3	2.8	3.6 ± 1.6
Morphine-3-glucuronide									
C_{max} (ng•ml^{-1})	502	371	455	520	757	379	608	514	513 ± 125
t_{max} (h)	1.37	1.45	1.28	0.79	0.73	1.21	1.02	1.64	1.19 ± 0.32
$AUC_{0-\infty}$ (µg•h•l^{-1})	4,147	2,096	3,078	2,285	2,431	1,733	2,836	2,303	2,614 ± 746
Lag time (h)	0.21	0.16	0.22	0.11	0.11	0.14	0.15	0.14	0.16 ± 0.04
$t_{1/2abs}$ (h)	0.26	0.39	0.25	0.16	0.17	0.33	0.23	0.69	0.31 ± 0.17
$t_{1/2}$ (h)	4.84	2.87	3.89	2.53	1.74	2.29	2.55	1.67	2.80 ± 1.08
r^2	0.9898	0.9912	0.9984	0.9617	0.9721	0.9888	0.9923	0.9100	
CL (ml•min^{-1})	40	77	48	64	78	91	78	91	71 ± 19
% in urine	36.1	35.0	31.8	31.5	40.8	34.2	47.5	45.1	37.8 ± 6.0
Morphine-6-glucuronide									
C_{max} (ng•ml^{-1})	79	58	73	99	151	53	73	89	84 ± 31
t_{max} (h)	1.20	1.77	1.40	0.71	0.80	1.38	1.25	0.83	1.17 ± 0.36
$AUC_{0-\infty}$ (µg•h•l^{-1})	481	446	455	468	490	184	415	305	406 ± 107
Lag time (h)	0.42	0.04	0.32	0.24	0.17	0.09	0.16	0.44	0.24 ± 0.15
$t_{1/2abs}$ (h)	0.17	0.51	0.27	0.09	0.17	0.89	0.29	0.08	0.31 ± 0.27
$t_{1/2}$ (h)	3.65	3.90	3.47	2.91	1.74	0.89	3.07	2.08	2.71 ± 1.05
r^2	0.9830	0.9757	0.9973	0.9883	0.9743	0.9791	0.9622	0.9991	
CL_r (ml•min^{-1})	67	76	72	69	63	176	74	130	91 ± 41
% in urine	7.0	7.3	7.1	7.0	6.6	7.0	6.6	8.6	7.2 ± 0.6

*C_{max}: maximum serum concentration; t_{max}: time at which C_{max} occurs; $AUC_{0-\infty}$: area under the serum concentration–time curve; lag time: time after which the compound appears in the serum; $t_{1/2abs}$: absorption half-life; $t_{1/2\alpha,\beta}$: half-life of elimination of the different phases; r^2: coefficient of determination of the fitted curve; CL_r: µg excreted/$AUC_{0-\infty}$; % in urine: total amount (% molar) recovered in the urine as percentage of the dose of the administered compound.

and its metabolites of 88%. The lipid-soluble prodrug nicomorphine is rapidly absorbed and immediately hydrolysed to morphine.

Renal clearance

In the urine only morphine and its conjugates were present. The renal clearance (CL_r) of the metabolites is listed in Table 2. There are large inter-individual differences, but it is remarkable that the renal clearance of morphine (mean 162 ml•min^{-1}) is higher than that of both glucuronides (mean 81 ml•min^{-1}). This can be 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 [34 35]. These results are comparable with our results after intravenous administration: 200 ml•min^{-1} (morphine) and 115 ml•min^{-1} (M3G and M6G), respectively [25]. As van Crugten *et al.* [36] 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.* [37] 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 itself. It has been reported that the clearance of morphine, apart from enterohepatic cycling, is influenced by several factors, *e.g.* age, race and also variation in hepatic blood flow during peri- and postoperative situations [38]. There is no evidence or indication about the existence of a morphine-3,6-diglucuronide [39].

Conclusion

This study shows that administration of a suppository with 30 mg nicomorphine gives an excellent absolute biological availability of 88% of morphine and its

metabolites. The lipid-soluble prodrug nicomorphine is rapidly absorbed and immediately hydrolysed to morphine. The action of rectally administered nicomorphine must be explained by the formation of two (active) metabolites: morphine and morphine-6-glucuronide. The kinetics of these metabolites after the rectal administration of nicomorphine finally resemble those after morphine administration.

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