Plasma Concentrations of Heroin and Morphine-Related Metabolites after Intranasal and Intramuscular Administration

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Abstract

The disposition of heroin and its metabolites was investigated in four healthy male volunteers following intranasal administration of 6 and 12 mg heroin hydrochloride. In addition, two doses of 6 mg heroin hydrochloride were injected intramuscularly for comparison of pharmacokinetic parameters. Serum samples were analyzed for heroin, 6-acetylmorphine, and morphine by solid-phase extraction–gas chromatography–mass spectrometry. The concentration of morphine glucuronides was determined by high-performance liquid chromatography based on the native fluorescence of the conjugates. Major findings were rapidly rising and declining terminal phases for heroin and 6-acetylmorphine and slowly declining phases of morphine and metabolites after both routes of administration. The area under the curve values of morphine-3-glucuronide depended on dose but not on route of administration. The apparent terminal half-lives of morphine-3-glucuronide ranged from 2.2 to 5.2 h for intranasally administered heroin and were 3.0 and 1.7 h for the intramuscularly applied drug. A mean morphine-3-glucuronide–heroin:area-under-curve ratio of 93 for the intranasal route as compared with 38 for the intramuscular route demonstrated that circulating amounts of heroin were about half the size after intranasal administration of the same dose.

Introduction

The metabolite profile of morphine in humans after different routes of administration has been reported by several groups (1–4). In contrast, there have been few investigations on heroin metabolism, and morphine glucuronides have not been examined (5–11). There is some evidence that production of morphine-3-glucuronide and morphine-6-glucuronide may be profoundly influenced by the route of morphine administration (12). It may be assumed that the pattern of glucuronide plasma levels after heroin dosing will resemble that of morphine.

The intranasal route of heroin administration was reported to be making a comeback in the United States (13). In addition to being an effective route of administration, intranasal use avoids the risk of infection posed by intravenous use.

In 1993, Cone et al. (14) performed a comprehensive clinical study to determine pharmacokinetic and pharmacodynamic parameters of intranasal heroin. Blood samples were collected before and after given time intervals after application of 6 or 12 mg heroin hydrochloride and after intramuscular administration of 6 mg heroin hydrochloride. The concentrations of heroin, 6-acetylmorphine, and morphine were measured by gas chromatography–mass spectrometry (GC–MS) (15).

We report plasma concentrations of morphine-3-glucuronide and morphine-6-glucuronide after administration of single doses of heroin by the intranasal and the intramuscular routes. The morphine glucuronides were determined by reversed-phase high-performance liquid chromatography (HPLC) based on the native fluorescence of the analytes. Frozen plasma samples of four subjects were obtained from the Addiction Research Center (Baltimore, MD); the analytical data of a single person concerning the concentration of the free bases were previously published by Cone et al. (14).

Experimental

Subject dosing and sampling

Four healthy male volunteers who resided for 4–6 weeks on the closed research ward of the Addiction Research Center were treated as described previously (14). Subject ages (years) and weights (kg) were as follows: subject RR, 30, 70.6; subject PP, 39, 60.4; subject QQ, 41, 80.0; subject SS, 29, 68.2. Before participating in the study, subjects were required to have a minimum of 3 days of negative urine tests for opiates.

At weekly intervals, single doses of 6 or 12 mg heroin hydrochloride or lactose as placebo were administered by the intranasal or intramuscular route under double-blind, double-dummy conditions. Intranasal doses were prepared by mixing heroin with lactose to provide a total weight of 100 mg. The powder was divided into equal doses, which were subsequently

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inhaled in each nostril through a short soda straw. Before beginning the study, each subject received a training session inhaling lactose powder.

Blood samples were collected before and periodically after heroin administration and centrifuged; the plasma was frozen. Samples were thawed just before extraction and analysis.

Materials and Methods

HPLC analysis (16)

Chemicals and reagents. All reagents were of HPLC or analytical grade. Morphine hydrochloride trihydrate (formula weight, 375.8) was purchased from Merck (Darmstadt, Germany); morphine-3-β-D-glucuronide (formula weight, 461.5) and morphine-6-β-D-glucuronide dihydrate (formula weight, 497.5) were obtained from Sigma (München, Germany); and acetonitrile and methanol were obtained from Roth (Karlsruhe, Germany). Triethylammonium phosphate buffer (TEAP, 1M) was obtained from Fluka (Buchs, Switzerland) and diluted in a ratio of 1:40 with double distilled water before use.

Solid-phase extraction columns (C_8, 50 mg) were obtained from Varian (Harbor City, CA). Ammonium bicarbonate buffer (500 µL, 1mM, pH 9.2) was added to 250 µL plasma before extraction. The residue was reconstituted with 100 µL methanol, and 80 µL was injected into the HPLC system.

Instrumentation. HPLC analysis was performed with a Hewlett Packard (Waldbronn, Germany) 1050 series LC pump, a Shimadzu (Duisburg, Germany) fluorescence detector, and a Spectra Physics (Darmstadt, Germany) SP 4290 integrator. Samples were eluted from an Et 250/4 Nucleosil 100 5 C_{18} AB reversed-phase column (250 mm × 4 mm, 5 µm, Macherey & Nagel, Düren, Germany) with diluted TEAP as the mobile phase. For detection, the excitation wavelength was 220 nm, and emission was recorded at 340 nm.

Linearity, reproducibility, and recovery. Calibration curves were prepared by adding known concentrations of drug solution to drug-free plasma. The calibration curves were linear for morphine-3-glucuronide from 5 to 500 ng/mL ($r = 0.996$), and for morphine and morphine-6-glucuronide from 15 to 500 ng/mL ($r = 0.996$, $r = 0.998$). The detection limits were 3 ng/mL for morphine-3-glucuronide and 10 ng/mL for both morphine and morphine-6-glucuronide as determined from a blank value ($n = 5$, mean plus 3 standard deviations) (17). With patient samples, the nature and amount of endogenous compounds present sometimes strongly influenced the minimum quantity that could be measured. Intra-assay and interassay coefficients of variation ranged from 4.4 to 6.1% for morphine-3-glucuronide, from 2.9 to 5.7% for morphine, and from 3.7 to 7.2% for morphine-6-glucuronide ($n = 5$, 100 ng/mL for each analyte). The recoveries from spiked plasma samples ($n = 5$, 100 ng/mL) were determined to be 71, 62, and 71% for morphine, morphine-6-glucuronide, and morphine-3-glucuronide, respectively, by comparison with the pure drug substances.

GC–MS analysis (heroin, morphine, 6-acetylmorphine)

All GC–MS analyses, with the exception of a single series (subject SS), were performed by the Addiction Research Center according to a procedure published by Goldberger et al. (15). Blood samples were assayed for heroin, 6-acetylmorphine, and morphine after solid-phase extraction, and the drug substances were identified and measured using their deuterated analogues as internal standards.

The remaining samples were tested for 6-acetylmorphine and morphine by a GC–MS assay according to a modified procedure published by Schmitt et al. (18). The detection limits were comparable with those obtained by Goldberger et al. (15). Chromabond drug solid-phase extraction columns (Macherey & Nagel) were used for sample preparation, and deuterated internal standard substances (Radian, Austin, TX) were used for quantitation.

Pharmacokinetic calculations

Peak plasma concentrations (c_{max}) and time of peak concentrations (t_{max}) were determined for all analytes by visual inspection of the individual plasma concentration profiles. The area under the drug concentration versus time plot (AUC) up to the final observed value was calculated by the trapezoidal rule (19). Morphine and morphine-3-glucuronide declined in a biphasic manner (2). The mean elimination rate constant (β) was determined from a semilogarithmic plot of the terminal phase using linear regression. The apparent half life was calculated according to the equation $t_{1/2} = 0.693/\beta$. When the mean value is given, ± denotes one standard deviation.

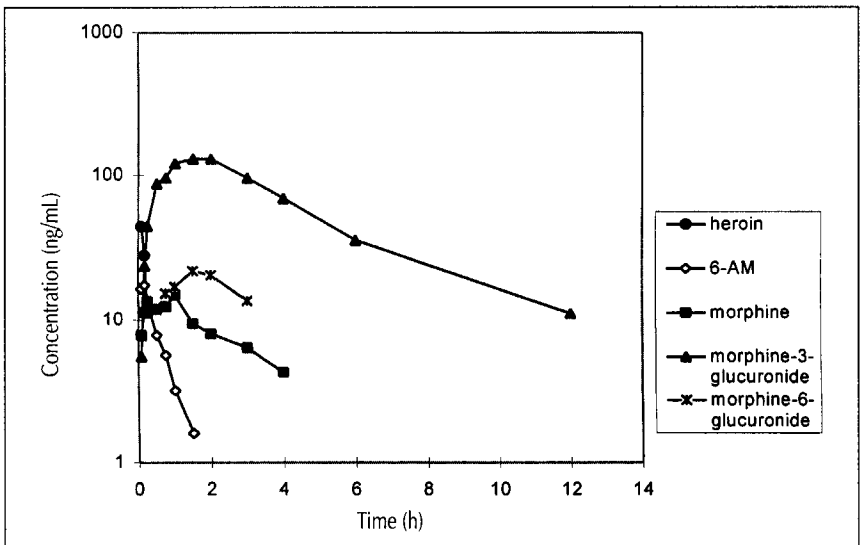

Figure 1. Semilogarithmic plot of plasma concentration of heroin and its metabolites after the administration of 12 mg heroin hydrochloride by the intranasal route to subject QQ.

Results

Figure 1 illustrates plasma concentrations of heroin and its metabolites following intranasal administration of 12 mg heroin

Table I. Heroin and Metabolite Plasma Concentrations

Time (h)	Heroin (ng/mL)	6-Acetyl-morphine (ng/mL)	Morphine (ng/mL)	Morphine-3-glucuronide (ng/mL)	Morphine-6-glucuronide (ng/mL)
Subject RR, 6.0 mg IN*					
–0.50	0.0	0.0	0.0	0.0	–
0.08	9.8	9.7	2.4	0.0	–
0.17	7.1	10.6	2.9	7.6	–
0.25	3.1	9.2	4.5	18.9	–
0.50	0.0	5.2	6.2	32.4	–
0.75	0.0	5.2	3.2	–	–
1.00	0.0	2.5	4.4	18.5	–
1.50	0.0	1.3	3.7	32.1	–
2.00	0.0	0.0	0.0	28.5	–
3.00	0.0	0.0	0.0	22.8	–
4.00	0.0	0.0	0.0	–	–
6.00	0.0	0.0	0.0	26.2	–
12.00	0.0	0.0	0.0	7.2	–
24.00	0.0	0.0	0.0	0.0	–
Subject RR, 12.0 mg IN					
–0.50	0.0	0.0	0.0	0.0	–
0.08	24.5	11.6	3.7	6.4	–
0.17	15.8	13.6	4.7	23.3	–
0.25	8.1	12.9	7.4	36.9	–
0.50	0.0	6.7	7.7	17.5	–
0.75	0.0	3.5	7.2	49.7	–
1.00	0.0	2.7	6.7	88.2	11.3
1.50	0.0	2.3	10.0	46.4	18.7
2.00	0.0	0.0	4.1	44.8	23.9
3.00	0.0	0.0	0.0	52.9	–
4.00	0.0	0.0	0.0	26.9	–
6.00	0.0	0.0	0.0	39.0	–
12.00	0.0	0.0	0.0	5.6	–
24.00	0.0	0.0	0.0	0.0	–
Subject RR, 6.0 mg IM†					
–0.50	0.0	0.0	0.0	0.0	–
0.08	45.7	22.6	6.8	42.9	–
0.17	19.2	19.5	7.9	58.9	–
0.25	14.2	15.2	7.1	66.5	–
0.50	0.0	7.2	7.7	92.9	–
0.75	0.0	4.4	7.5	86.5	–
1.00	0.0	2.4	6.1	89.1	–
1.50	0.0	1.2	5.4	72.3	–
2.00	0.0	0.0	3.9	77.4	–
3.00	0.0	0.0	4.8	51.4	–
4.00	0.0	0.0	0.0	–	–
6.00	0.0	0.0	0.0	27.9	–
12.00	0.0	0.0	0.0	0.0	–
24.00	0.0	0.0	0.0	0.0	–
Subject SS, 6.0 mg IN					
–0.50	–	0.0	0.0	0.0	–
0.08	–	3.1	1.4	0.0	–
0.17	–	3.8	6.6	0.0	–
0.25	–	1.8	4.9	6.8	–
0.50	–	0.0	2.7	26.7	–
0.75	–	0.0	2.8	28.7	–
1.00	–	0.0	2.0	33.4	–
1.50	–	0.0	2.2	32.7	–
2.00	–	0.0	1.6	33.5	–
3.00	–	0.0	1.4	39.1	–
4.00	–	0.0	1.0	33.2	–
6.00	–	0.0	0.0	–	–
12.00	–	0.0	0.0	21.4	–
24.00	–	0.0	0.0	0.0	–

* Intranasal
† Intramuscular

hydrochloride in a single subject (subject QQ). Complete tabulations of plasma concentrations of heroin, 6-acetylmorphine, morphine, morphine-3-glucuronide, and morphine-6-glucuronide for all subjects are listed in Table I. A summary of the individual pharmacokinetic parameters is given in Table II.

Heroin was rapidly absorbed independently of the route of administration; the terminal phase showed a steep decline except for subject PP. Heroin concentrations peaked in blood within 5 min of both routes of administration. The c_{max} and the AUC after intramuscular application were significantly higher when compared with 6 mg intranasal heroin. The terminal phase $t_{1/2}$ was estimated to be 5.4 ± 0.6 min for intranasal and intramuscular administration.

6-Acetylmorphine was formed almost instantaneously and reached the peak concentration almost at the same time as heroin. Similiar to heroin, c_{max} and AUC were higher for intramuscular heroin compared with 6 mg intranasal heroin. For 6-acetylmorphine, the mean terminal phase $t_{1/2}$ was calculated to be 22.8 ± 4.2 min.

As for morphine, t_{max} showed a marked dependence on the dose but not on the route of administration. After administration of 6 mg heroin, the peak of morphine concentrations was within the range of 10.2 to 30 min whereas after administration of 12 mg heroin, time of peak was within 43.8 to 90 min. Except for intramuscular injection, morphine concentration profiles exhibited a nonlinear decline at the semilogarithmic plot. A second peak concentration could be observed for some subjects after the intranasal administration of heroin. The apparent half-life of morphine varied from 90 to 180 min and tended to higher values with a dose of 12 mg of heroin.

As can be seen from Figure 1, the shapes of the morphine-3-glucuronide curves parallel those of the morphine curves. The mean values of t_{max} for morphine-3-glucuronide decreased in the following order: 12 mg intranasal heroin (120 ± 42 min) > 6 mg intranasal heroin (70.8 ± 63 min) > 6 mg intramuscular heroin (19.8 ± 9.6 min). The mean peak concentration for 6 mg intranasal heroin was lower when compared with 6 mg intramuscular heroin, although a difference between the two routes of administration with respect to the AUC was not observed.

Morphine-6-glucuronide is a minor metabolite of morphine and also of heroin.

Table I (continued). Heroin and Metabolite Plasma Concentrations

Time (h)	Heroin (ng/mL)	6-Acetyl-morphine (ng/mL)	Morphine (ng/mL)	Morphine-3-glucuronide (ng/mL)	Morphine-6-glucuronide (ng/mL)
Subject SS, 12.0 mg IN*					
-0.42	–	0.0	0.0	0.0	–
0.12	–	4.9	2.1	0.0	–
0.22	–	3.2	2.4	7.5	–
0.28	–	1.6	3.5	16.2	–
0.50	–	1.2	4.1	47.3	–
0.73	–	1.7	5.3	38.7	–
0.97	–	0.0	4.6	36.9	–
1.42	–	0.0	4.4	45.5	–
1.97	–	0.0	3.6	63.7	–
3.00	–	0.0	2.2	92.5	–
3.75	–	0.0	1.7	–	–
5.75	–	0.0	1.4	43.9	–
11.75	–	0.0	0.0	7.4	–
23.75	–	0.0	0.0	0.0	–
Subject SS, 6.0 mg IM†					
-0.50	–	–	–	0.0	–
0.08	–	–	–	27.9	–
0.17	–	–	–	92.1	–
0.25	–	–	–	85.6	–
0.50	–	–	–	85.5	–
0.75	–	–	–	69.2	–
1.00	–	–	3.5	–	–
1.50	–	–	3.1	68.6	–
2.00	–	–	1.9	49.2	–
3.00	–	–	1.3	36.3	–
4.00	–	–	1.3	23.5	–
6.00	–	–	0.0	8.7	–
12.00	–	–	0.0	0.0	–
24.00	–	–	0.0	0.0	–
Subject PP, 6.0 mg IN					
-0.50	0.0	0.0	0.0	0.0	–
0.08	13.0	4.3	0.0	0.0	–
0.17	8.8	3.5	5.2	5.7	–
0.25	13.3	2.8	6.3	12.6	–
0.50	0.0	3.9	2.1	82.3	–
0.75	0.0	1.0	5.7	61.4	–
1.00	0.0	0.0	5.0	39.1	–
1.50	0.0	0.0	5.0	55.6	–
2.00	0.0	0.0	3.5	36.9	–
3.00	0.0	0.0	2.6	25.6	–
4.00	0.0	0.0	0.0	18.9	–
6.00	0.0	0.0	0.0	12.9	–
12.00	0.0	0.0	0.0	7.5	–
24.00	0.0	0.0	0.0	0.0	–
Subject PP, 12.0 mg IN					
-0.50	0.0	0.0	0.0	0.0	–
0.08	39.3	4.4	3.2	4.9	–
0.17	19.7	3.4	5.7	22.5	–
0.25	6.9	3.7	8.5	31.7	–
0.50	0.0	2.3	7.6	43.8	–
0.75	0.0	2.4	7.9	38.6	–
1.00	0.0	0.0	9.8	68.3	–
1.50	0.0	0.0	13.2	121.2	–
2.00	0.0	0.0	8.2	137.4	–
3.00	0.0	0.0	6.4	129.8	–
4.00	0.0	0.0	5.4	95.1	–
6.00	0.0	0.0	4.1	53.0	–
12.00	0.0	0.0	0.0	16.7	–
24.00	0.0	0.0	0.0	8.9	–

* Intranasal
† Intramuscular

The determination of morphine-6-glucuronide was difficult because of low concentrations and matrix interferences. After 12 mg snorted heroin, morphine-6-glucuronide peak concentrations ranged from 90 to 120 min with c_{max} values of 21.9 and 23.9 ng/mL.

Discussion

The disposition of heroin and its metabolites was investigated in four healthy male volunteers following intranasal administration of 6 and 12 mg heroin hydrochloride and intramuscular injection of 6 mg heroin hydrochloride.

Administration of heroin by both routes resulted in a rapid appearance of heroin, 6-acetylmorphine, and morphine in blood. Equal doses of heroin showed somewhat higher peak concentrations of the parent drug and 6-acetylmorphine when given by the intramuscular route, indicating that absorption and metabolism occured more rapidly.

The precise delivery of drugs is more associated with intravenous than with intramuscular administration. Besides the vascularity of the injection site, the absorption rate is assumed to be influenced by lipid solubility and the degree of ionization of the drug. The fraction of heroin as a solute existing in the ionized form is given by the Henderson–Hasselbalch equation. At the physiological pH value, the extent of ionization of heroin (pK_a, 7.6 [20]) was calculated to be 55%. Heroin is well-absorbed even though the drug is largely ionized, which suggests that absorption is governed by the high lipid solubility of the base.

Intranasal administration will not ensure the delivery of exact quantities of heroin, thus explaining the intersubject variability of the pharmacokinetic parameters (Table II). Lactose, which is a common diluent and carrier in pharmaceutical formulations, was used to make up the heroin powder. The dry formulation avoided local toxicity of undiluted drug substance and hydrolysis of heroin and was reported to have comparable activity to an equivalent dose administered as a nebulized solution (21). When heroin was given intranasally, the rate of absorption was controlled by how fast the drug dissolved in the stagnant aqueous layer of the mucosal cells. Absorption of a drug from a solid dosage form is assumed to proceed more slowly than absorption from

solution. The nasal mucous represents a biological barrier; the physicochemical properties of a drug for good absorption were similiar to those required for the gastrointestinal tract. However, the nasal mucous was reported to be more permeable than those of the gut. This may be due to numerous fenestrated capillaries acting more like filters than lipid membranes in terms of permeability and readily picking up drugs. Nasal absorption seems not to be restricted to the un-ionized form of a compound (22). McMartin (23) proposed two mechanisms of drug transport: a fast rate dependent on lipophilicity and a slow rate dependent on molecular weight. As the molecular weight cutoff for mean nasal absorption was reported to be about 1000 daltons, lipophilicity of heroin was responsible for absorption rate. The nasal cilia move the overlying mucous, hence adhesing drug molecules along the nasal cavity towards the throat, thus distributing the heroin powder. Heroin may also be deposited in the throat and in the upper gastrointestinal tract. Although local metabolism of drugs in the nasal mucous has not been reported (24), heroin molecules could be subject to hydrolysis as soon as they reach the blood stream.

Table I (continued). Heroin and Metabolite Plasma Concentrations

Time (h)	Heroin (ng/mL)	6-Acetyl-morphine (ng/mL)	Morphine (ng/mL)	Morphine-3-glucuronide (ng/mL)	Morphine-6-glucuronide (ng/mL)
Subject QQ, 6.0 mg IN*					
–0.50	0.0	0.0	0.0	0.0	–
0.08	23.3	7.7	3.3	5.7	–
0.17	10.5	6.6	6.1	12.2	–
0.25	19.6	5.7	5.8	27.6	–
0.50	0.0	2.7	5.5	43.0	–
0.75	0.0	1.6	4.1	44.0	–
1.00	0.0	0.0	5.5	43.5	–
1.50	0.0	0.0	3.2	34.3	–
2.00	0.0	0.0	0.0	23.8	–
3.00	0.0	0.0	0.0	26.7	–
4.00	0.0	0.0	0.0	16.5	–
6.00	0.0	0.0	0.0	15.3	–
12.00	0.0	0.0	0.0	0.0	–
24.00	0.0	0.0	0.0	0.0	–
Subject QQ, 12.0 mg IN					
–0.50	0.0	0.0	0.0	0.0	–
0.08	44.3	16.4	7.8	5.6	–
0.17	28.0	17.4	11.3	23.8	–
0.25	11.2	13.2	13.5	44.5	–
0.50	0.0	7.8	11.9	87.6	–
0.75	0.0	5.7	12.4	96.4	15.2
1.00	0.0	3.2	15.0	121.6	17.0
1.50	0.0	1.6	9.4	130.5	21.9
2.00	0.0	0.0	8.0	131.0	20.5
3.00	0.0	0.0	6.4	96.0	13.6
4.00	0.0	0.0	4.3	69.5	–
6.00	0.0	0.0	0.0	35.6	–
12.00	0.0	0.0	0.0	11.0	–
24.00	0.0	0.0	0.0	0.0	–

* Intranasal
† Intramuscular

Blood is supposed to be the major site of 6-acetylmorphine production, although the site of heroin hydrolysis by cholinesterase includes tissues other than blood (25,26). The apparent elimination half-life ($t_{1/2}$) of heroin was shorter when compared with the $t_{1/2}$ = 19 ± 12 min of the prodrug nicomorphine (3,6-dinicotinoylmorphine), which may be attributed to steric hindrance, the latter compound being a more bulky substrate (27). With respect to the limit of detection, heroin and 6-acetylmorphine could be determined after drug administration for periods of 30 and 90 min at most. The $t_{1/2}$ of 6-acetylmorphine was slightly longer than that of heroin, indicating that its rate of elimination was slower than its rate of formation. Heroin is considered to be a prodrug, and it exerts its effects through its active metabolites, 6-acetylmorphine, morphine, and morphine-6-glucuronide. Findings in animals indicated that morphine-3-glucuronide may antagonize the analgesic action of morphine and morphine-6-glucuronide (28), and morphine-3-glucuronide was suggested that morphine-3-glucuronide may be responsible for the paradoxical pain observed in patient-given morphine (29).

Hydrolysis of 6-acetylmorphine to morphine is accomplished by a hydrolase enzyme bound to the surface of the red blood cells (30). As for morphine, the time of peak concentrations and apparent elimination half-life seemed to depend on dose regardless of the route of administration. There was no marked decline in plasma morphine concentrations up to 45-min postdose, indicating that morphine was being formed from its precursors during this phase while being metabolized at the same time. In addition, enterohepatic cycling may have occurred, similiar to that which has been reported to occur in rats and dogs (31,32). The morphine plasma concentration versus hour plots decreased more slowly compared with the parent drug or 6-acetylmorphine (Table I); the mean $t_{1/2}$ for a dose of 6 mg heroin was in the same range when compared with intravenously administered heroin (10). A second, more slowly declining phase of the plasma curves seemed to follow the first slope. For example, a second elimination half-life of about 15 h that was based on urinary excretion curves was presented by Hasselström et al. (2) after both oral and intravenous administration. The morphine/heroin–AUC ratio after intramuscular administration was similiar to the mean morphine/nicomorphine–AUC ratio (27), suggesting that morphine was formed in the same proportion from both prodrugs.

The major pathway for the biotransformation of morphine is hepatic glucuronidation at the 3- and 6-hydroxyl positions to form morphine-6-glucuronide and morphine-3-glucuronide. Morphine is mainly metabolized to morphine-3-glucuronide and, to a lesser extent, to the important, pharmaco-

logically active morphine-6-glucuronide. Peak concentration of morphine-3-glucuronide seemed to depend on dose and on route of application. After intranasal administration, a second peak was observed for some of the volunteers. Possible explanations include transient storage of the parent drug or a product formed by hydrolysis in the nasal cavity, and a minor part of the dose was subject to presystemic metabolism. The formation of a plateau was still more marked, and the morphine-3-glucuronide plasma concentration versus hour plot declined more slowly. Taking intersubject variability into account, a distinctive difference in morphine-3-glucuronide apparent elimination half-lives could not be established because of the amount of drug given.

Whereas morphine is cleared via the cation transport system, the glucuronides are cleared by glomerular filtration and tubular reabsorption. Tubular reabsorption of larger hydrophilic molecules such as glucuronides is an unusual phenomenon but may be explained by Carrupt's (33) conclusion from forcefield and quantum mechanical calculations that morphine glucuronides can exist in two conformational forms, the folded conformer being similiar to morphine in lipophilicity. Another reason may be deconjugation by the colonic flora and reabsorption of morphine because morphine, morphine-3-glucuronide, and morphine-6-glucuronide have all been demonstrated in bile (34).

When the amount of intranasally applied heroin was doubled, the AUC was doubled, as is generally the case for intravenously administered drug. Morphine-3-glucuronide–heroin ratios of AUC were 93 for the intranasal route and 38 for the intramuscular route. This difference could be attributed solely to differences after the two methods of administration and especially to differences in circulating amounts of heroin, morphine, and 6-acetylmorphine. The latter ratio was similiar to a morphine-3-glucuronide–nicomorphine-AUC ratio of 32 derived from the data presented by Koopman-Kimenai (27). With morphine-6-glucuronide, the metabolic situation may be generally estimated from the fate of morphine-3-glucuronide and appropriate data in the literature according to the administration of nicomorphine.

Conclusion

The data in this study were limited to the administration of two intranasally and two intramuscularly applied heroin doses; consequently, general conclusions are tenuous. However, the data clearly demonstrate the very rapid decrease in plasma concentrations of heroin and 6-acetylmorphine, a slowly declining terminal phase for morphine, and morphine-3-glucuronide levels that decayed even more slowly. The metabolite profile of heroin was similiar to that of nicomorphine. As for intranasal administration, the time course of the morphine-3-glucuronide–morphine ratio appeared to be dependent more on

Table II. Pharmacokinetic Parameters after Intranasal Application of 12 and 6 mg Heroin Hydrochloride and Intramuscular Administration of 6 mg Heroin Hydrochloride

	12 mg intranasal				6 mg intranasal				6 mg intramuscular	
	RR	SS	PP	QQ	RR	SS	PP	QQ	RR	SS
c_{max} heroin (ng/mL)	24.5	n.d.*	39.3	44.3	9.8	n.d.	13.3	23.3	45.7	n.d.
t_{max} heroin (min)	4.8	n.d.	4.8	4.8	4.8	n.d.	15.0	4.8	4.8	4.8
$t_{1/2}$ heroin (min)	6.0	n.d.	3.6	4.8	6.0	n.d.	n.d.	n.d.	5.4	n.d.
AUC† heroin (nmol/L-h)	10.0	n.d.	14.0	17.5	4.0	n.d.	6.2	9.7	16.2	n.d.
c_{max} 6-acetylmorphine (ng/mL)	13.6	4.9	4.4	17.4	10.6	3.8	4.3	7.7	22.6	n.d.
t_{max} 6-acetylmorphine (min)	10.2	7.2	4.8	10.2	10.2	10.2	4.8	4.8	4.8	n.d.
$t_{1/2}$ 6-acetylmorphine (min)	28.2	n.d.	n.d.	23.4	26.4	n.d.	n.d.	16.8	19.2	n.d.
AUC 6-acetylmorphine (nmol/L-h)	25.6	5.2	6.5	30.5	21.6	2.7	6.7	9.1	30.8	n.d.
c_{max} morphine (ng/mL)	10.0	5.3	13.2	15.0	6.2	6.6	6.3	6.1	7.9	n.d.
t_{max} morphine (min)	90.0	43.8	90.0	60.0	30.0	10.2	15.0	10.2	10.2	n.d.
$t_{1/2}$ morphine (min)	n.d.	144.0	180.0	108.0	n.d.	102.0	n.d.	n.d.	90.0	114.0
AUC morphine (nmol/L-h)	49.4	55.3	143.7	121.9	21.3	28.0	41.0	24.5	57.8	n.d.
c_{max} morphine-3-glucuronide (ng/mL)	88.2	92.5	137.4	131.0	32.4	39.1	82.3	44.0	93.0	92.1
t_{max} morphine-3-glucuronide (min)	60.0	180.0	120.0	120.0	30.0	180.0	30.0	45.0	30.0	10.2
$t_{1/2}$ morphine-3-glucuronide (min)	n.d.	138.0	186.0	168.0	312.0	n.d.	132.0	192.0	180.0	102.0
AUC morphine-3-glucuronide (nmol/L-h)	826.8	1079.3	1964.0	1386.7	892.7	745.1	513.7	243.9	730.4	520.9
c_{max} morphine-6-glucuronide (ng/mL)	23.9	n.d.	n.d.	21.9	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
t_{max} morphine-6-glucuronide (min)	120.0	n.d.	n.d.	90.0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d

* Not detected.
† Area under the curve.

the individual pharmacokinetic parameters than on dosage. The differences seen in the mean AUC ratios of heroin and morphine-3-glucuronide were due to differences in plasma concentrations of the parent drug. The results suggest a dose-response relationship when connected to the observations of Cone (14) that behavioral and physiological effects were approximately equivalent following intranasal administration of 12 mg of heroin hydrochloride and intramuscular administration of 6 mg heroin hydrochloride.

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