Oral diacetylmorphine (heroin) yields greater morphine bioavailability than oral morphine: bioavailability related to dosage and prior opioid exposure

Ulrike Halbsguth, Katharina M. Rentsch,¹ Dominique Eich-Höchli,² Isabel Diterich³ & Karin Fattinger⁴

Blood Transfusion Service SRC Ltd Bern, Bern, ¹Institute of Clinical Chemistry, University Hospital Zürich, ²Psychiatric University Hospital Zürich and ³Division of Clinical Pharmacology and Toxicology, University Hospital Zürich, Zürich, and ⁴Department of General Internal Medicine, Inselspital–University Hospital Bern and University of Bern, Bern, Switzerland

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Venosclerosis prevents many opioid addicts in heroin substitution programmes from injecting intravenously, which makes consideration of other routes of administration necessary.
- Even high doses of oral diacetylmorphine are completely converted to morphine presystemically.
- Morphine bioavailability in heroin addicts after high-dose oral diacetylmorphine administration is considerably higher than expected based on prior data obtained with relatively low oral diacetylmorphine or morphine doses in healthy subjects or patients receiving treatment for pain (64–72% vs. 20–25%).

WHAT THIS STUDY ADDS

- Morphine influx into systemic circulation is more rapid after oral diacetylmorphine than after oral morphine, resulting in earlier and more than double maximal concentrations.
- In opioid-dependent people, bioavailability of morphine from oral doses of diacetylmorphine is also 37% higher than that of oral morphine.
- Morphine bioavailability is two and 1.5 times higher in chronic users than in opioid-naïve subjects after low oral doses of diacetylmorphine or morphine, respectively.
- Oral absorption of morphine from diacetylmorphine is dose dependent, i.e. bioavailability increases with diacetylmorphine dose.

Correspondence

Dr Karin Fattinger, Department of General Internal Medicine, Inselspital–University Hospital Bern and University of Bern, CH–3010 Bern, Switzerland.
Tel: + 41 31 632 2111, ask for 181 8009
Fax: + 41 31 632 8885
E-mail: karin.fattinger@insel.ch

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AIMS

In the Swiss heroin substitution trials, patients are treated with self-administered diacetylmorphine (heroin). Intravenous administration is not possible in patients that have venosclerosis. Earlier studies have demonstrated that oral diacetylmorphine may be used, although it is completely converted to morphine presystemically. Morphine bioavailability after high-dose oral diacetylmorphine is considerably higher than would be predicted from low-dose trials. The aim was to investigate whether the unexpectedly high bioavailability is due to a difference in the drug examined, and whether it depends on previous exposure or on dose.

METHODS

Opioid-naïve healthy volunteers and dependent patients from the Swiss heroin trials ($n = 8$ per group) received low doses of intravenous and oral deuterium-labelled morphine and diacetylmorphine, respectively. Patients also received a high oral diacetylmorphine dose.

RESULTS

The maximum plasma concentration (C_{max}) of morphine was twofold higher after oral diacetylmorphine than after morphine administration in both groups. However, morphine bioavailability was considerably higher in chronic users [diacetylmorphine 45.6% (95% confidence interval 40.0, 51.3), morphine 37.2% (30.1, 44.3)] than in naïve subjects [diacetylmorphine 22.9% (16.4, 29.4), morphine 23.9% (16.5, 31.2)] after low oral doses (48.5 μ mol) of either diacetylmorphine or morphine. Morphine clearance was similar in both groups. Moreover, oral absorption of morphine from diacetylmorphine was found to be dose dependent, with bioavailability reaching 64.2% (55.3, 73.1) for high diacetylmorphine doses (1601 μ mol).

CONCLUSIONS

Oral absorption of opioids is substance-, dose- and patient collective-dependent, suggesting that there may be a saturation of first-pass processes, the exact mechanism of which is not yet understood.

Introduction

Opioid addiction is a serious public health concern. As it became apparent towards the end of the last century that many heavily dependent opioid addicts could not be retained in the available detoxification and methadone programmes, medical prescription of pharmaceutically pure diacetylmorphine (heroin) was established in Switzerland and other European countries as a treatment option for heavily dependent opioid addicts [1–4]. The Swiss Cohort Study on Medical Prescription of Heroin demonstrated reductions in mortality and morbidity, as well as improvement of patients' social situations, including reduced involvement in illegal activities and enhanced ability for employment. Hence the practice has been shown to reduce the overall socioeconomic impact of opioid addiction [5, 6]. Furthermore, the medicalization of heroin dependency was associated with a reduction of the population of problematic heroin users in Switzerland [7].

Diacetylmorphine was evaluated as an analgesic in the 1980s. When the systemic bioavailability of single 52-mg doses of diacetylmorphine and morphine was compared in three chronic pain patients using a crossover design [8], no diacetylmorphine and no monoacetylmorphine could be detected in the systemic circulation, and relative morphine bioavailability was 21% lower for diacetylmorphine than for morphine. Hence, oral diacetylmorphine failed to show advantages over morphine and its kinetic properties were not further investigated.

With the aim of elucidating the pharmacokinetic basis of diacetylmorphine substitution treatments, we characterized diacetylmorphine disposition after intravenous (i.v.) administration in opioid-dependent patients [9]. However, many patients must receive prescribed diacetylmorphine orally rather than intravenously due to venosclerosis [10]. We therefore studied the kinetics of diacetylmorphine and its metabolites such as morphine after oral diacetylmorphine in opioid-dependent patients [11] and found that oral diacetylmorphine, up to doses of 600 mg, led to only negligible systemic diacetylmorphine and monoacetylmorphine concentrations. However, our study in opioid-dependent patients showed for the first time that high doses of oral diacetylmorphine, considered as a morphine prodrug, lead to unexpectedly high morphine bioavailabilities of 64, 66 and 72% for average doses of 206, 413 and 619 mg, respectively. Furthermore, a test dose of 66 mg morphine-d3 given concomitantly with the high diacetylmorphine doses exhibited a bioavailability of 58%, which is lower than for diacetylmorphine, but still unexpectedly high compared with the morphine bioavailability of 20–25% reported in the literature for healthy volunteers [12]. Absorption of the morphine metabolite after administration of the high oral diacetylmorphine dose was faster than that of the concomitant morphine-d3 dose, leading to higher (dose-corrected) maximal concentrations occurring at earlier times. Thus, the absorption char-

acteristics of diacetylmorphine obtained with very high doses of diacetylmorphine in opioid-dependent patients [11] differ markedly from those obtained in patients with chronic pain who received a four to 10 times lower single dose of diacetylmorphine [8]. Unfortunately, Inturissi *et al.* [8] did not report whether their subjects were opioid-naïve or had been receiving chronic treatment with opioids. These seemingly incongruent findings may be due to differences in the subject population, such as opioid-dependent vs. non-opioid-exposed patients, or to oral diacetylmorphine exhibiting dose-dependent absorption kinetics.

The aim of the current study was to investigate whether the unexpectedly high bioavailability of morphine after oral diacetylmorphine in addicted subjects is due to a difference in administered medication (morphine vs. its precursor diacetylmorphine) and whether oral absorption of morphine depends on previous exposure and dose. For this purpose, the kinetics of morphine and morphine glucuronides were studied in opioid-naïve healthy subjects and opioid-dependent patients from the Swiss heroin substitution trial. Opioid-naïve and opioid-dependent subjects were given a low dose of i.v. and oral deuterium-labelled morphine and an equimolar dose of oral deuterium-labelled diacetylmorphine. Kinetics was also studied in the opioid-dependent patients after administration of a high oral diacetylmorphine dose.

Materials and methods

Drugs

Diacetylmorphine tablets were obtained from DiaMo Narcotics Ltd (Thun, Switzerland). 3,6-diacetylmorphine-(N-methyl-d3) HCl and morphine-(N-methyl-d3) HCl (purity 99.57%) were purchased from Lipomed (Arlesheim, Switzerland). The doses of deuterium-labelled diacetylmorphine and morphine for oral administration were prepared by DiaMo Narcotics Ltd, whereas the doses of deuterium-labelled morphine for i.v. administration were prepared by the canton Zurich pharmacy (Kantonsspital Zürich, Switzerland). Diacetylmorphine, monoacetylmorphine, morphine, morphine-d3, morphine-3-glucuronide, morphine-d3-3-glucuronide, morphine-6-glucuronide, morphine-d3-6-glucuronide and codeine-d3 used as assay standards were purchased from Lipomed.

Clinical study

The study protocol was approved by the Ethics Committee of the Canton of Zürich, Switzerland. Opioid-naïve volunteers and opioid-dependent patients were recruited by notice board announcements at local universities and the clinics providing medical heroin prescription programmes conducted by the Swiss Federal Office of Public Health, respectively. Opioid-naïve volunteers were asked to

contact the study centre directly, whereas opioid-dependent patients were asked to first contact their treating physicians for a referral. Potential participants in the age range 20–55 years were interviewed and examined to exclude renal and hepatic impairment, anaemia, HIV infection, pregnancy, treatment with medications known to induce or inhibit drug-metabolizing enzymes and hypersensitivity to any of the study medications. Opioid-naïve volunteers were included only if they reported no history of opioid abuse, and they were evaluated by a psychiatrist to exclude an unstable personality. Meanwhile, opioid-dependent patients had to be treated with a consistent daily parenteral diacetylmorphine dose of ≥ 300 mg or a daily oral diacetylmorphine dose of ≥ 900 mg. Subjects were required to be free of skin infections on the forearms and were required to abstain from other illegal drugs.

One opioid-naïve volunteer was excluded because of anaemia. Among the 12 opioid-dependent patients referred to the study, one was excluded as a result of testing positive for cocaine, two because of concomitant diseases and one because he had withdrawn from the heroin substitution programme. Three female and five male opioid-naïve volunteers and five female and three male opioid-dependent patients were ultimately included and provided written informed consent. Mean (range) age, weight and body mass index (BMI) of the opioid-naïve subjects were 30 years (21–42), 76 kg (54–106) and 25 kg m^{-2} (21–36). Mean (range) age, weight and BMI of the opioid-dependent patients were 35 years (26–46), 73 kg (60–88) and 25 kg m^{-2} (22–29).

Among the opioid-naïve volunteers, four were tobacco smokers and two occasionally smoked cannabis. All opioid-dependent patients were tobacco smokers. They had been opioid-dependent for ≥ 5 years before entering the heroin substitution programme and had participated in programmes on medical prescription of heroin for a mean of 2.9 years (range 0.3–10 years). One patient had a chronic hepatitis C infection, one had a hepatitis B and C co-infection, and two had a hepatitis C serological scar. No other concurrent disease conditions were present in the study population. All study participants had normal renal function and no signs of liver

damage (transaminases less than double the upper limit, normal International Normalized Ratio and normal abdominal ultrasound examination). Occasional use of illegal drugs other than heroin was reported by all opioid-dependent patients, and urinary drug screening at the prestudy visit was positive for cannabis in three and for methaqualone in one of the opioid-dependent patients. One patient was taking mirtazapine.

After an overnight fast, the study participants arrived at the Clinical Research Unit at 07.30 h. Opioid-naïve subjects stayed for 3 days and opioid-dependent subjects stayed for 4 days. Urine drug screening at admission was negative in all subjects for ethanol, cocaine, methadone, barbiturates, amphetamines, lysergic acid diethylamide and benzodiazepines. Morphine, morphine-3-glucuronide and morphine-6-glucuronide concentrations before test drug administration were measured in opioid-dependent subjects on day 4 and amounted to 293 ± 186 , 3476 ± 2638 and $676 \pm 428 \text{ nmol l}^{-1}$.

Each morning, all study participants received 10 mg of metoclopramide intravenously. On the first day, a peripheral venous line was inserted in the radial or cubital vein (all opioid-naïve volunteers, one opioid-dependent patient for all 4 days and another for the last study day) or an arterial catheter (all other opioid-dependent patients, because of venosclerosis) was inserted in the radial artery for blood sampling. Since arteriovenous concentration differences are only predominant during the first few minutes after drug administration of i.v. diacetylmorphine [9], such differences are not expected to be of relevance in the current study on drug absorption after oral intake, as drug absorption through the gastrointestinal tract is relatively slow. The first postdose blood samples were thus collected 5 min after drug administration. Similar plasma concentration profiles in the one opioid-dependent patient with venous sampling compared with the other opioid-dependents with arterial sampling confirmed no relevant effects of the sampling site.

An overview of the study schedule is provided in Table 1. Morphine disposition on day 1 was characterized for each study participant by i.v. administration of $24.3 \mu\text{mol}$ (7 mg morphine-d3 base) of morphine-d3 dissolved in 30 ml of NaCl (0.9%) over 5 min. Blood samples

Table 1

Sequence of study sessions and doses

Study day	Dose	Opioid-naïve volunteers	Opioid-dependent patients
1	Low dose of morphine-d3 ($24.3 \mu\text{mol}$, 7 mg) intravenously over 5'	X	X
2	Low dose ($48.5 \mu\text{mol}$) of morphine-d3 (14 mg) or diacetylmorphine-d3 (19.7 mg) orally in randomized order	X	X
3	Low dose ($48.5 \mu\text{mol}$) of morphine-d3 (14 mg) or diacetylmorphine-d3 (19.7 mg) orally in randomized order	X	X
4	High dose of diacetylmorphine (usual parenteral daily diacetylmorphine dose, average of $1601 \mu\text{mol}$) and low dose of morphine-d3 ($48.5 \mu\text{mol}$) orally		X

(2 ml) were collected before and 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 45, 50 and 55 min and 1, 1.25, 1.5, 2, 3, 5 and 8 h after drug administration. Blood samples were centrifuged and the plasma was stored at -20°C . In order to maintain their substitution treatment, all opioid-dependent patients also received their usual diacetylmorphine doses (on average 232 mg, range 100–370 mg parenteral dose equivalents of diacetylmorphine) starting 30 min after i.v. morphine-d3 administration. On each of the study days, the remaining diacetylmorphine doses (on average 293 mg, range 200–430 mg of parenteral dose equivalents) were administered in the late afternoon, after the 8 h study session.

On days 2 and 3, the participants received a low dose (48.5 μmol) of morphine-d3 (14.0 mg morphine-d3 base) or diacetylmorphine-d3 (18.1 mg diacetylmorphine-d3 base) orally with 200 ml of water. Blood samples were collected at the same time points as on day 1 except that no samples were collected at 2.5 and 7.5 min. Of course, substitution treatments could not be withheld in the opioid-dependent patients on these study days. To minimize any potential influences, supplemental doses of diacetylmorphine (on average 278 mg, range 150–370 mg) were delayed for 2 h after we had administered the low oral study doses and were given not by oral, but by the i.v. or intramuscular route. It is known from a study comparing different diacetylmorphine preparations with nonparametric deconvolution (unpublished observation) that absorption of oral immediate-release diacetylmorphine preparations is rapid and that >70% of the dose is absorbed within the first 2 h. Therefore, the observed differences, which were most prominent early after drug administration (see below), should not have been affected by supplement doses administered after 2 h, or later, on the study days.

On day 4, the opioid-dependent patients co-administered a high oral diacetylmorphine dose (amounting to the subject's usual parenteral daily dose) and a low dose (48.5 μmol) of morphine-d3. They were then subjected to repeated blood sampling as described above. In the evening of the last study day (day 3 for naive subjects and day 4 for dependent subjects), the venous or arterial line was removed and the participants were discharged.

Power calculations were based on our prior data for morphine bioavailability following oral diacetylmorphine administration, $67 \pm 19\%$ [11], which corresponded to about three times the expected value of 20%. Expecting a similar SD and given our intention to detect bioavailability differences of $\geq 30\%$ between opioid-dependent patients and healthy volunteers, a sample size of eight patients per group results in a power of 84% ($\alpha = 0.05$, two-tailed). Given the reported relative morphine bioavailability of oral diacetylmorphine vs. oral morphine-d3 of $145 \pm 29\%$ [11], intra-individual comparison in eight subjects between morphine bioavailability of oral

diacetylmorphine vs. oral morphine exhibits a power of 86%.

Determination of the concentrations of diacetylmorphine, diacetylmorphine-d3 and their metabolites

The plasma concentrations of diacetylmorphine, monoacetylmorphine, morphine, morphine-3-glucuronide, morphine-6-glucuronide, diacetylmorphine-d3, monoacetylmorphine-d3, morphine-d3, morphine-d3-3-glucuronide and morphine-d3-6-glucuronide were determined by liquid chromatography–mass spectrometry, as described previously [9]. The quantification limits were 1 nmol l^{-1} for diacetylmorphine, monoacetylmorphine, diacetylmorphine-d3 and monoacetylmorphine-d3, and 2.5 nmol l^{-1} for morphine, morphine-3-glucuronide, morphine-6-glucuronide, morphine-d3, morphine-d3-3-glucuronide and morphine-d3-6-glucuronide. The between-day precision and accuracy for all analytes were <9.5% and between 97.4 and 103.7%, respectively.

Pharmacokinetic calculations

The subjects' plasma half-lives ($t_{1/2}$) were calculated as $t_{1/2} = \ln 2 / \lambda$, where λ represents the slope of the terminal part of the plasma concentration–time curve after i.v. administration, following semilogarithmic transformation. Area under the plasma concentration–time curve (AUC) was calculated by noncompartmental analysis with linear interpolation and log-linear extrapolation. Total plasma clearance (CL) was calculated from the AUC and dose as $\text{CL} = \text{Dose} / \text{AUC}$. The volume of distribution at steady state (V_{ss}) was calculated as $V_{ss} = \text{Dose} \cdot \text{AUMC} / \text{AUC}^2$, in which AUMC is the total area under the first moment of the plasma concentration–time curve. To gain an impression of the formation of metabolites during the different study sessions, we also calculated and compared the ratio between the AUCs of the glucuronides and parent drug ($\text{Ratio}_{\text{G/M}}$) as $\text{Ratio}_{\text{G/M}} = (\text{AUC}_{\text{M3G}} + \text{AUC}_{\text{M6G}}) / \text{AUC}_{\text{morphine}}$.

To adjust for differences in molecular weight between morphine and diacetylmorphine and different preparations used for the parenteral and oral administrations, all diacetylmorphine and morphine doses were converted into micromolar quantities. Bioavailability (F) of morphine was determined as $F = (\text{AUC}_{\text{oral}} / \text{Dose}_{\text{oral}}) / (\text{AUC}_{\text{iv}} / \text{Dose}_{\text{iv}})$, where AUC_{oral} , $\text{Dose}_{\text{oral}}$, AUC_{iv} and Dose_{iv} correspond to the oral and i.v. AUC and dose, respectively. To account for individual dose differences for the high diacetylmorphine administration, those concentrations were normalized to dose (multiplied by mean dose/individual dose). For the figures, morphine concentrations remaining from preceding doses were extrapolated on the basis of the corresponding predose concentration, the subject's terminal morphine half-life, and subtracted from measured concentrations. All calculations and graphics were made in (S)-Plus [13].

Results

Adverse events

Despite metoclopramide premedication in all participants, two of the eight opioid-naïve volunteers suffered from nausea and vomiting after the i.v. morphine dose. One of these subjects received a second 10-mg dose of metoclopramide and received two 10-mg doses of metoclopramide on the following 2 days. The other volunteer with nausea did not require any additional measures. One opioid-dependent patient needed an additional diacetylmorphine dose later on study day 2 to treat withdrawal symptoms. To keep schedules comparable for days 2 and 3, this patient received the same additional diacetylmorphine on day 3. All other participants tolerated all of the study doses well.

Morphine disposition after intravenous administration

The pharmacokinetic parameters of intravenously administered morphine in opioid-dependent and opioid-naïve subjects over the 8-h experimental period are reported in Table 2. Intravenous morphine kinetics were similar in both groups as evidenced by comparable values for maximal plasma concentration ($C_{\max}$, 1.17 vs. 1.13 $\mu\text{mol l}^{-1}$), CL (1.69 vs. 1.59 l min^{-1}), V_{ss} (155 vs. 129 l) and terminal half-life (1.8 vs. 1.6 h). Morphine-d3-3-glucuronide concentrations were lower in the naïve than in the dependent subjects with mean AUCs of 1.07 ± 0.42 vs. $1.30 \pm 0.31 \mu\text{mol h}^{-1} \text{l}^{-1}$ and terminal half-lives of 3.02 vs. 3.31 h, respectively. Likewise, morphine-d3-6-glucuronide concentrations were also lower in the naïve than in the dependent subjects, with mean AUCs of 0.21 ± 0.09 vs. $0.26 \pm 0.07 \mu\text{mol h}^{-1} \text{l}^{-1}$ and terminal half-lives of 2.49 vs. 2.11 h. Taken together, these statistically not significant AUC differences resulted in a somewhat lower and highly variable metabolite to parent drug AUC Ratio_{G/N} of 4.96 ± 1.85 in the naïve subjects compared with 6.49 ± 1.72 in dependent subjects ($P = 0.0357$).

Diacetylmorphine and morphine absorption from oral diacetylmorphine and morphine after administration of low doses

Therapeutic concentrations of morphine were detected in the systemic circulation after oral administration of 18.1 mg of diacetylmorphine, whereas neither diacetylmorphine nor monoacetylmorphine could be detected (Table 3). This finding confirms that oral diacetylmorphine should be considered a morphine prodrug. In opioid-dependent subjects, morphine bioavailability for the low oral diacetylmorphine dose was 45.6% (95% confidence interval 40.0, 51.3), which was greater than the 37.2% value observed for an equimolar oral morphine dose (30.1, 44.3) ($P = 0.0499$, Wilcoxon matched pairs test). Morphine entry into the systemic circulation was more rapid after oral diacetylmorphine than after oral morphine, and associated with markedly earlier and almost twofold $C_{\max}$ values (diacetylmorphine 0.26 $\mu\text{mol l}^{-1}$ at 9 min vs. morphine 0.14 $\mu\text{mol l}^{-1}$ at 20 min after drug intake).

Relative to opioid dependents, opioid naïves exhibited lower morphine bioavailability for oral diacetylmorphine, 22.9% (16.4, 29.4), and oral morphine 23.9% (16.5, 31.2). Thus, the difference in morphine bioavailability between oral diacetylmorphine and oral morphine is limited to opioid-dependent volunteers ($P = 0.0379$, Mann–Whitney U -test on bioavailability differences between both groups). However, replicating the pattern observed in opioid dependents, diacetylmorphine resulted in earlier and nearly two-maximal morphine $C_{\max}$ relative to the equimolar morphine dose in opioid naïves (diacetylmorphine 0.10 $\mu\text{mol l}^{-1}$ at 20 min, morphine 0.06 $\mu\text{mol l}^{-1}$ at 36 min; $P = 0.014$ for $C_{\max}$). Due to high interindividual variability, the differences in $t_{\max}$ did not reach statistical significance.

Figure 1 depicts average morphine and Figure 2 average morphine glucuronide concentration–time curves for oral diacetylmorphine and oral morphine in both groups using identical scales so that the data can be compared visually. In contrast to morphine, which produced

Table 2

Morphine disposition: comparison of pharmacokinetic parameters for morphine-d3 administered intravenously to eight opioid-dependent patients and eight opioid-naïve volunteers

	Morphine-d3		Morphine-d3-3-glucuronide		Morphine-d3-6-glucuronide	
	Dependent	Naïve	Dependent	Naïve	Dependent	Naïve
Morphine-d3 Dose (μmol)	24.3	24.3				
$C_{\max}$ ($\mu\text{mol l}^{-1}$)	1.17 ± 0.36	1.13 ± 0.16	0.30 ± 0.09	0.32 ± 0.12	0.07 ± 0.02	0.07 ± 0.03
$t_{\max}$ (min)	5.3 ± 0.9	4.7 ± 0.8	54 ± 40	29 ± 20	68 ± 38	55 ± 14
AUC ($\mu\text{mol h l}^{-1}$)	0.25 ± 0.04	0.26 ± 0.03	1.30 ± 0.31	1.07 ± 0.42	0.26 ± 0.07	0.21 ± 0.09
CL (l min^{-1})	1.69 ± 0.32	1.59 ± 0.17				
V_{ss} (l)	155 ± 60	129 ± 37				
$t_{1/2}$ terminal (h)	1.80 ± 0.32	1.60 ± 0.44	3.31 ± 0.72	3.02 ± 0.63	2.11 ± 0.48	2.49 ± 0.55
Ratio _{G/N}	6.49 ± 1.72	4.96 ± 1.85				

Table 3

Diacetylmorphine (DAM) and morphine absorption: comparison of pharmacokinetic parameters for morphine and its glucuronides after oral diacetylmorphine-d3 and morphine-d3 administration

	Opioid-dependent patients			Opioid-naïve volunteers			Dependent vs. naïve	
	DAM-d3	Morphine-d3	DAM vs. morphine	DAM-d3	morphine-d3	DAM vs. morphine	DAM-d3	morphine-d3
Dose (μmol)	48.5	48.5		48.5	48.5			
DAM-d3 AUC (μmol h l ⁻¹)	<l.d.			<l.d.				
MAM-d3 AUC (μmol h l ⁻¹)	<l.d.			<l.d.				
Morphine-d3								
AUC (μmol h l ⁻¹)	0.22 ± 0.06	0.18 ± 0.07		0.12 ± 0.05	0.12 ± 0.06			
C _{max} (μmol l ⁻¹)	0.26 ± 0.06	0.14 ± 0.11	P = 0.0173	0.10 ± 0.08	0.06 ± 0.05	P = 0.014	P = 0.0046	P = 0.046
t _{max} (min)	9 ± 2	20 ± 11	P = 0.0418	20 ± 14	36 ± 38	P = 0.484	P = 0.0423	P = 0.560
F (%)	45.6 ± 8.1	37.2 ± 10.2	P = 0.0499	22.9 ± 9.3	23.9 ± 10.6	P = 0.327	P = 0.0011	P = 0.0209
Morphine-d3-3-glucuronide								
AUC (μmol h l ⁻¹)	2.83 ± 0.78	2.87 ± 0.72		2.56 ± 0.73	2.29 ± 1.04			
Morphine-d3-6-glucuronide								
AUC (μmol h l ⁻¹)	0.62 ± 0.28	0.55 ± 0.17		0.53 ± 0.18	0.6 ± 0.26			
Ratio _{G/N}	15.7 ± 3.7	19.7 ± 4.3	p = 0.0117	31.3 ± 18.11	29.9 ± 17.5	P = 0.7794	P = 0.0357	P = 0.207

<l.d., below limit of detection, P-values were calculated using Mann–Whitney U-test or Wilcoxon’s matched-pairs test, respectively; n = 8 per group.

Figure 1

Morphine-d3 plasma concentration–time profiles in opioid-dependent patients (A) and opioid-naïve volunteers (B) after oral administration of diacetylmorphine-d3 (circles) and morphine d3 (triangles). Plasma concentrations are given as mean ± SEM over an 8-h period following administration of 48.3 μmol diacetylmorphine and 48.3 μmol morphine, respectively

marked differences in exposure (Figure 1, Table 3), glucuronide AUCs (morphine-d3-3-glucuronide and morphine-d3-6-glucuronide, Table 3) were comparable after diacetylmorphine and morphine administration in opioid-dependent patients and opioid-naïve volunteers, suggesting that the overall absorptions of diacetylmorphine and morphine are comparable. Unlike i.v. morphine-d3, oral diacetylmorphine-d3 exhibited a higher AUC Ratio_{G/N} of metabolites to parent drug in opioid naïves than in dependents. Furthermore, the AUC Ratio_{G/N} of oral morphine in opioid dependents exceeded that of oral diacetylmorphine-d3. None of the covariates or patient characteristics such as serological evidence of hepatitis, baseline opioid concentrations, substitution doses, tobacco or cannabis use exhibited any effect on morphine bioavailability from oral diacetylmorphine-d3 or oral morphine-d3 (Figure 3). Thus, previous opioid exposure as

well as the identity of the administered substance, but no other covariates, influenced the amount and time course of morphine absorption after oral administration.

Effect of dose on diacetylmorphine absorption from oral diacetylmorphine

To study the effect of dose on diacetylmorphine absorption, opioid-dependent subjects received two different diacetylmorphine doses: a low dose of 18.1 mg (48.5 μmol) of diacetylmorphine-d3 on day 2 or 3 and a high dose of diacetylmorphine on day 4. The high dose was determined by each subject’s usual daily diacetylmorphine dose and in the range 500–800 mg (average 598 mg = 1601 μmol) of diacetylmorphine HCl, which is approximately 33 times higher than the low dose. Morphine bioavailability increased from 45.6% (40.0, 51.3) for the low diacetylmorphine dose to 64.2% (55.3, 73.1) (P = 0.0117) for the high

Figure 2

Morphine-d3-3-glucuronide (A,B) and morphine-d3-6-glucuronide (C,D) plasma concentration–time profiles in opioid-dependent patients (A,C) and opioid-naïve volunteers (B,D) after oral administration of diacetylmorphine-d3 (circles) and morphine d3 (triangles). Plasma concentrations are given as mean $\pm$ SEM over an 8-h period following administration of 48.3 μ mol diacetylmorphine and 48.3 μ mol morphine, respectively

diacetylmorphine dose (Table 4). After the high diacetylmorphine dose, an average dose-normalized maximal concentration of $3.7 \cdot 10^{-3} \text{ l}^{-1}$ was obtained, which is lower than the $5.3 \cdot 10^{-3} \text{ l}^{-1}$ concentration observed for the low diacetylmorphine-d3 dose at 39 and 9 min (Table 4). Figure 4 compares average dose-normalized morphine concentrations for the 48.5- μ mol and 1601- μ mol diacetylmorphine doses; these data confirm slower, but more sustained morphine absorption for high diacetylmorphine doses. Again, dose-normalized AUCs for morphine-3-glucuronide morphine-6-glucuronides were comparable for both dosages (Table 4), yielding lower metabolite to parent drug AUC Ratio_{G/N} for high compared with low diacetylmorphine doses. These data indicate that in the high diacetylmorphine dose range the fraction absorbed is higher, but absorption takes longer than with low diacetylmorphine doses.

Effect of diacetylmorphine co-administration on morphine absorption

The opioid-dependent subjects received two 14-mg doses of morphine-d3, once alone and once together with the high diacetylmorphine dose. Co-administration of 598 mg of diacetylmorphine (Table 5) increased morphine bioavailability from 37.2% (30.1, 44.3) to 49.0% (45.0, 53.1) ($P = 0.0173$). Maximal concentrations appeared to be

slightly reduced with diacetylmorphine co-administration, but to be reached earlier (Table 5). However, similar to the slightly higher AUCs for morphine-d3-3-glucuronide and morphine-d3-6-glucuronide, these differences did not reach statistical significance. Thus, co-administration of a high dose of diacetylmorphine enhanced morphine absorption.

Discussion

This study has demonstrated for the first time that the systemic morphine exposure achieved from oral diacetylmorphine depends upon previous exposure: we observed twice the maximal morphine concentration at about half the maximal time in opioid-dependent compared with opioid-naïve subjects. Doubled bioavailabilities demonstrate that morphine absorption from oral diacetylmorphine is not only faster but also more complete in diacetylmorphine-exposed compared with opioid-naïve subjects. Moreover, morphine absorption from oral diacetylmorphine was found to be faster than from oral morphine, leading to higher C_{max} and shorter t_{max} values in both groups. For opioid-dependent patients, morphine absorption from oral diacetylmorphine was also more efficient, resulting in increased bioavailability. Furthermore, a

Figure 3 Patient characteristics vs. morphine bioavailability for low doses of diacetylmorphine-d3 and morphine-d3. Morphine bioavailability is plotted against daily (parenteral) diacetylmorphine (DAM) maintenance dose. X, opioid-naïve volunteers received no maintenance dose and are thus given at dose = 0; filled diamonds, opioid-dependent patients in case of serological evidence of hepatitis B or C infection/scar; empty diamonds, otherwise

Table 4 Influence of dose on morphine exposure after oral diacetylmorphine-d3/diacetylmorphine (DAM) administration to opioid-dependent patients

DAM-d3/DAM dose (μmol)	Small dose 48.5	Large dose 1601 ± 323	
Morphine-d3/morphine			
AUC (μmol h l ⁻¹)	0.22 ± 0.06	10.2 ± 2.6	
Dose-corrected AUC (10 ⁻³ h l ⁻¹)	4.6 ± 1.1	6.6 ± 2.1	
C _{max} (μmol l ⁻¹)	0.26 ± 0.06	5.8 ± 2.2	
Dose corrected C _{max} (10 ⁻³ l ⁻¹)	5.3 ± 1.2	3.7 ± 1.5	P = 0.0117
t _{max} (min)	9 ± 2	39 ± 37	P = 0.0139
F (%)	45.6 ± 8.1	64.2 ± 12.8	P = 0.0117
Morphine-d3-3-glucuronide/morphine-3-glucuronide			
AUC (μmol h l ⁻¹)	2.83 ± 0.78	102 ± 40	
Dose-normalized AUC (10 ⁻³ h l ⁻¹)	58 ± 16	64 ± 24	
Morphine-d3-6-glucuronide/morphine-6-glucuronide			
AUC (μmol h l ⁻¹)	0.62 ± 0.28	21.7 ± 6.4	
Dose-normalized AUC (10 ⁻³ h l ⁻¹)	13 ± 6	14 ± 3	
Ratio _{G/N}	15.7 ± 3.7	12.3 ± 3.3	P = 0.0499

P-values were calculated using Wilcoxon's matched-pairs test, n = 8.

dose effect was observed for oral diacetylmorphine, with bioavailability increasing from 45.6% at the 18.1-mg dose to 64.2% at the 598-mg dose. Moreover, co-administration of diacetylmorphine increased morphine bioavailability from 37.2 to 49% (Table 5). Thus, our study has demonstrated that morphine bioavailability depends on (i) prior

opioid exposure, (ii) the particular drug administered, and (iii) dose.
Drug absorption, in general, depends upon the physicochemical properties of the substance being absorbed and its interaction with processes governing its absorption, including presystemic elimination, e.g. drug metabo-

lism and transport at apical and basolateral enterocyte membranes and in hepatocytes. Morphine has polar hydroxyl groups that interact with the adjacent amino group, whereas diacetylmorphine has acetyl groups that preclude intramolecular bonding [14, 15]. Thus diacetylmorphine HCl is orders of magnitude more water soluble (1 g in 1.6 ml) than morphine HCl (1 g in 24 ml) [14, 15]. Despite its higher water solubility, however, diacetylmorphine is more lipophilic than morphine [14, 15], and the higher lipophilicity should favour more rapid transmembrane passage of diacetylmorphine than of morphine.

With respect to presystemic elimination, deacetylation of diacetylmorphine, glucuronidation of morphine [16]

and intestinally expressed drug transporters such as P-glycoprotein/MDR1 [17, 18] should be considered. Diacetylmorphine is not stable at physiological pH or at moderately elevated temperatures and thus might be deacetylated in part to monoacetylmorphine in the intestinal lumen. Given that monoacetylmorphine is chemically more stable, further deacetylation to morphine should occur only within intestinal epithelia, portal blood and/or hepatocytes.

The absence of detectable diacetylmorphine or monoacetylmorphine in the peripheral blood in this study indicates that all ingested diacetylmorphine was presystemically deacetylated to morphine. The very high systemic diacetylmorphine and monoacetylmorphine clearances of 8.7 l min⁻¹ and 6.7 l min⁻¹ [9] suggest that the intestine, liver and blood may all contribute to first-pass metabolism to morphine. Intestinal glucuronidation might contribute to the observed effects of the drug administered on absorption parameters, but cannot explain all differences observed. The lower AUC Ratio_{G/N} of metabolites to parent drug for diacetylmorphine-d3 than morphine-d3 would suggest differences in metabolism by UDP-glucuronosyltransferases. However, comparing glucuronide concentrations from oral diacetylmorphine-d3 and morphine-d3 (Figure 2a,c) during the initial 1.5–2 h, i.e. when the compounds are absorbed from the intestine, we find higher glucuronide concentrations after diacetylmorphine-d3 compared with morphine-d3. Thus, the bulk of glucuronides leading to the higher AUC Ratio_{G/N} of morphine-d3 comes into the circulation only after the majority of the dose has been absorbed, suggesting that other mechanisms such as drug transporters should also be considered. Morphine’s status as a substrate of the intestinal efflux transporter P-glycoprotein [17, 18] may enable its more efficient intestinal first-pass elimination relative to diacetylmorphine. However, in contrast to opioid-dependent subjects, opioid naïves exhibited com-

Figure 4
Morphine plasma concentration–time profiles in opioid-dependent patients after low and high doses of diacetylmorphine. Plasma concentrations were normalized to dose and are given as mean ± SEM over an 8-h period following administration of low-dose diacetylmorphine, 48.3 µmol (circles), and after high-dose diacetylmorphine, average dose of 1601 µmol (diamonds)

Table 5
Influence of diacetylmorphine (DAM) co-administration on morphine exposure after oral administration of a small dose of morphine d3 to opioid-dependent patients

DAM co-administration	No	Yes (1601 ± 323 µmol)	
Morphine-d3 dose (µmol)	48.5	48.5	
Morphine-d3			
AUC (µmol h l ⁻¹)	0.18 ± 0.07	0.24 ± 0.05	
C _{max} (µmol l ⁻¹)	0.14 ± 0.11	0.10 ± 0.03	P = 0.1614
t _{max} (min)	20 ± 11	13 ± 4	P = 0.1468
F (%)	37.2 ± 10.2	49.0 ± 5.8	P = 0.0173
Morphine-d3-3-glucuronide			
AUC (µmol h l ⁻¹)	2.87 ± 0.72	3.02 ± 0.66	
Morphine-d3-6-glucuronide			
AUC (µmol h l ⁻¹)	0.55 ± 0.17	0.65 ± 0.16	
Ratio _{G/N}	19.7 ± 4.3	23.8 ± 6.5	P = 0.1614

P-values were calculated using Wilcoxon’s matched-pairs test, n = 8.

parable bioavailabilities for diacetylmorphine and morphine. If physicochemical differences had been mainly responsible for the observed absorption differences, they should be manifested similarly in both groups. Hence, the differences we observed between the subject groups favour the interpretation that active processes, such as glucuronidation and transport across membranes, underlay the differential absorptions observed.

Our experiments have revealed bioavailability for diacetylmorphine and morphine in opioid-dependent subjects that were two and 1.5 times greater than that in opioid-naïve subjects. Accordingly, $C_{\max}$ in the opioid-dependent group was more than twice as high and occurred at about half the $t_{\max}$ as that in the opioid-naïve group. Animal studies on morphine kinetics in rats and on presystemic morphine elimination in rabbits suggest that extraction and/or metabolism in the intestine contribute approximately two-thirds of overall first-pass elimination of morphine, and the liver the remaining one-third [19, 20]. Furthermore, morphine's systemic clearance depends mainly on hepatic glucuronidation [21]. One would thus expect that any differences in hepatic glucuronidation would result in differences in morphine's disposition. Therefore, hepatic morphine handling as possible causes of the differential results seems unlikely based on identical morphine kinetics in both groups after i.v. administration. On the other hand, it remains possible that previous opioid exposure may influence intestinal first-pass mechanisms, such as the expression and activity of drug-metabolizing enzymes and transporters. These differences could well be explained by prior opioid use decreasing expression or function of UDP-glucuronosyltransferases and/or drug efflux carriers or increasing expression of uptake carriers in the intestine.

Bioavailability increased from 45.6% with a low dose of diacetylmorphine to 64.5% with the high dose. This marked dose-dependent increase in bioavailability could have resulted from saturation of glucuronidation and/or active drug transport by intestinal efflux systems under the high diacetylmorphine dose condition. Saturation of an intestinal first-pass system could also explain why concomitant diacetylmorphine administration increased morphine bioavailability from 37.2 to 49.0%.

The observed group differences in morphine exposure cannot be explained by differences in metabolic capacity for morphine: the two groups displayed similar dispositions of morphine-d3 after being subjected to equivalent treatments despite considerable predose opioid concentrations in opioid-dependent patients. Furthermore, the clearance estimates in both groups correspond well to previously reported values [12, 22, 23]. The terminal half-life values observed here were also within the previously reported range [12, 24]. The congruence between disposition parameters determined in our studies using deuterium-labelled morphine and reported values obtained with unlabelled morphine indicates that deute-

rium does not affect morphine pharmacokinetics. This supposition was confirmed in a preliminary pilot study, in which we observed identical morphine and morphine-d3 concentrations after a combined i.v. dose of both compounds (data not shown). Thus, the results from the i.v. study day indicate that opioid-dependent and opioid-naïve subjects did not differ with respect to morphine distribution or elimination in liver, kidney and other tissues.

Data on morphine absorption and bioavailability in patients undergoing chronic pain treatment with high-dose morphine are scarce. Säwe *et al.* [25] determined repeated AUCs in two cancer patients who received increasing oral morphine up to 2000–2500 mg day⁻¹ over six to eight doses. Thus, each dose in that study was in the range 300–350 mg, which is about half of the dose level used in this study. They concluded that there was no evidence for autoinduction or dose dependence of morphine metabolism. However, in their AUC vs. dose plots for morphine and glucuronide AUCs, the data points corresponding to the highest doses lay considerably above those of the other doses in a manner suggestive of increased exposure and thus possibly of greater bioavailability for the highest doses tested. Another study [26] comparing two slow-release preparations in four patients receiving 230–800 mg per 24 h for pain relief did not include i.v. doses, and thus bioavailability was not estimated. Therefore it is not yet clear whether the dose- and exposure-dependency of morphine absorption we observed in opioid-dependent patients can be generalized to patients chronically exposed to diacetylmorphine or morphine for pain relief. Nevertheless, our study has provided a clear demonstration that oral diacetylmorphine exhibits pharmacokinetic advantages over oral morphine for substitution treatment in opioid addicts, especially if we consider that pharmacodynamic effects depend predominantly upon the slope of the concentration rise after drug administration. Utilization of a rapid drug absorption preparation may, however, also be advantageous for rescue doses in pain treatment.

In conclusion, we have demonstrated that oral diacetylmorphine should be regarded as a prodrug of morphine and that it produces considerably more rapid and complete morphine entry into the systemic circulation of diacetylmorphine-exposed people than oral morphine. Furthermore, morphine bioavailability from oral diacetylmorphine increases with dose. The same may hold true for oral morphine, since co-administration of large diacetylmorphine doses increased morphine bioavailability. Furthermore, morphine absorption from oral diacetylmorphine and from oral morphine was also faster and more efficient in diacetylmorphine-exposed subjects than in opiate-naïve volunteers. Taken together, our findings indicate that drug absorption for diacetylmorphine and morphine is substance-, dose- and patient collective-dependent and implicates further the involvement of active processes, such as by UDP-glucuronosyltransferases and drug transporters in the absorption of these opioids.

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