Published in final edited form as:

Eur J Pharm Sci. 2009 March 2; 36(4-5): 421–432. doi:10.1016/j.ejps.2008.11.008.

Oral heroin in opioid-dependent patients: pharmacokinetic comparison of *immediate* and *extended release* tablets

Ludwig Perger¹, Katharina M. Rentsch², Gerd A. Kullak-Ublick³, Davide Verotta⁴, and Karin Fattinger¹

¹ Department of General Internal Medicine, Inselspital – University Hospital Bern and University of Bern, Switzerland ² Institute of Clinical Chemistry, University Hospital Zurich ³ Division of Clinical Pharmacology and Toxicology, Dept. of Medicine, University Hospital Zurich, Switzerland ⁴ Departments of Biopharmaceutical Sciences, Epidemiology and Biostatistics, University of California, Box 0446, San Francisco, USA

Abstract

In diacetylmorphine prescription programs for heavily dependent addicts, diacetylmorphine is usually administered intravenously, but this may not be possible due to venosclerosis or when heroin abuse had occurred via non-intravenous routes. Since up to 25% of patients administer diacetylmorphine orally, we characterised morphine absorption after single oral doses of *immediate* and *extended release* diacetylmorphine in 8 opioid addicts. Plasma concentrations were determined by liquid chromatography-mass spectrometry. Non-compartmental methods and deconvolution were applied for data analysis. Mean ($\pm$ SD) *immediate* and *extended release* doses were 719 ± 297 mg and 956 ± 404 mg, with high absolute morphine bioavailabilities of 56% to 61%, respectively. *Immediate release* diacetylmorphine caused rapid morphine absorption, peaking at 10 to 15 min. Morphine absorption was considerably slower and more sustained for *extended release* diacetylmorphine, with only ~30% of maximal *immediate release* absorption being reached after 10 min and maintained for 3 to 4 h, with no relevant food interaction. The relative *extended* to *immediate release* bioavailability was calculated to be 86% by non-compartmental analysis and 93% by deconvolution analysis. Thus, *immediate* and *extended release* diacetylmorphine produce the intended morphine exposures. Both are suitable for substitution treatments. Similar doses can be applied if used in combination or sequentially.

Keywords

Diacetylmorphine; oral administration; bioavailability; absorption rates; food; deconvolution

1. Introduction

Opioid misuse and addiction embody a grave public health issue. Treatment in most countries is primarily based on methadone and buprenorphine maintenance programs (Van den Brink and Haasen, 2006, Amato et al., 2005). However, treatment response is often incomplete, and

Correspondence: Karin Fattinger, Department of General Internal Medicine, Inselspital - University Hospital Bern and University of Bern, CH - 3010 Bern, Switzerland, Phone + 41 31 632 21 11, ask for 181 8009, Fax + 41 31 632 88 85, Email karin.fattinger@insel.ch.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

many heavily dependent narcotic addicts cannot be included or retained in these programs. Therefore, Switzerland and several other countries now include diacetylmorphine as an additional option for heavily dependent narcotic addicts (Fischer et al., 2007, van den Brink et al., 2003, Sheldon, 2008, Haasen et al., 2007, Brissette, 2001). Based on the three most relevant clinical studies in Switzerland, the Netherlands, and Germany, heroin-assisted treatment is superior to other opiod-assisted treatments such as methadone (Rehm et al., 2001, van den Brink et al., 2003, Haasen et al., 2007, Verthein et al., 2008). In particular, this treatment targets previously untreated intravenous drug users or non-responders to conventional methadone treatments, who subsequently show improvements in health status, often dramatically, less treatment dropout, reduced consumption of other psychotropic substances, and other social improvements. Based on these successful study outcomes, the Swiss and the Dutch health authorities have registered an intravenous diacetylmorphine formulation, and oral formulations have been submitted in Switzerland for marketing approval. In addition, other countries such as Spain, Belgium, Denmark, Canada, and the United Kingdom are planning or have already completed clinical trials with heroin-assisted treatments.

Treatment based solely on injected heroin as a substitution medication can be problematic. While effective, it requires considerable resources as patients usually inject three times a day under supervised conditions at treatment centres, which requires long operating hours and puts high demands on personnel and security. Moreover, not all patients fulfil the admission criteria; in many countries, a considerable fraction of opioid dependents do not inject. In the Netherlands, for instance, most users (i.e. 75% to 90%) inhale heroin by 'chasing the dragon'. Also in other countries, many users do not inject opioids for various reasons, including fear of infection risk or inability to puncture their veins. Moreover, an increasing number of patients participating in heroin-assisted treatment programs suffer from venosclerosis, preventing them from performing intravenous administration. These situations require other means of administering heroin as a substitute medication: oral substitution with diacetylmorphine has been used in Switzerland for a decade. Frick et al. demonstrated that the one year retention rate for solely orally-substituted subjects within the Swiss heroin-assisted treatment programs was 80%, which was above the 70% obtained from historical controls treated intravenously with diacetylmorphine (Frick et al., 2006). In 2006, one third of all diacetylmorphine used in the Swiss heroin prescription program was given as tablets (National Prevention Programmes of the Swiss Federal Office of Public Health, 2007) Furthermore, up to 25% of patients in this program receive diacetylmorphine doses orally (Bundesamt für Gesundheit, 2004).

It is often straightforward to characterise the absorption of oral *immediate release* preparations by model-independent estimation of bioavailability, maximal concentrations (C_{max}), and time of maximal concentration (t_{max}). Alternatively, compartmental analysis may be used under the assumption of zero or first order absorption. For *extended release* preparations, analysis requires parameters describing the extent of fluctuation in plasma concentrations (Steinijans, 1990). Ignorance of the appropriate *in vivo extended release* absorption function often requires the use of deconvolution techniques (Fattinger and Verotta, 1995a, Fattinger and Verotta, 1995b, Fattinger et al., 2000, Pitsiu et al., 2001). This approach provides not only parameter estimates characterising plasma level fluctuations, but also yields the entire drug absorption rate profile over time, allowing comparison of *in vivo* absorption rate with *in vitro* dissolution profiles (Pitsiu et al., 2001).

We have shown previously that even large doses of oral *immediate release* diacetylmorphine yield only negligible systemic diacetylmorphine and monoacetylmorphine exposure, but result in an unexpectedly high morphine bioavailability of 67% (Girardin et al., 2003). Since many patients use *extended release* diacetylmorphine in addition to or instead of the *immediate release* form, often switching between formulations, we now characterise and compare morphine absorption of the two formulations in 8 opioid-addicted patients. For the *extended*

release formulation, the study also explores the influence of a high-fat breakfast on morphine absorption.

2. Methods

2.1. Materials

Diacetylmorphine hydrochloride as *immediate* and *extended release* tablets of 200 mg were obtained from DiaMo Narcotics Ltd. (Thun, Switzerland). Deuterium-labelled morphine (morphine-N-methyl-d3, morphine-d3) was obtained from Lipomed (Arlesheim, Switzerland) and doses for intravenous administration were prepared by the canton Zurich pharmacy (Kantonsapotheke Zürich, Switzerland). Diacetylmorphine, monoacetylmorphine, morphine, morphine-3-glucuronide, morphine-6-glucuronide, morphine-d3, morphine-d3-3-glucuronide, morphine-d3-6-glucuronide, and codeine-d3 used as assay standards were purchased from Lipomed (Arlesheim, Switzerland).

2.2. Immediate and extended release diacetylmorphine preparation

The *immediate release* preparation is a coated tablet with 200 mg diacetylmorphine hydrochloride as the active ingredient. At least 80% of the dose is released within 15 min (Conditions: Water, 37°C, Paddle 50 rpm). The *immediate release* preparation shows a fast disintegration within 300 s in water at 37°C. In contrast, the *extended release* preparation is a coated matrix formulation, which releases the 200 mg of diacetylmorphine hydrochloride gradually over 12 h under the same conditions as above. The *in vitro* dissolution is specified with 20–40% release within 1 h, 45–65% within 4 h, and 80–100% within 10 h. Figure 1 shows the *in vitro* dissolution profiles of the two formulations.

2.3. Clinical study

The study protocol was approved by the ethics committee of the canton of Zürich. Volunteers requiring a stable daily parenteral and/or oral diacetylmorphine dose of at least a 300 mg parenteral dose equivalent were recruited from the Swiss heroin prescription programs. Parenteral dose equivalents were calculated by converting oral doses to parenteral doses by dividing them by three and summing them with parenteral doses. The morphine bioavailability of 67% obtained in our previous study (Girardin et al., 2003) suggests that a lower conversion rate may be feasible. However, we again used the previously applied conversion rates (Girardin et al., 2003), since no signs of overdose were observed in the previous study (Girardin et al., 2003) and our main concern was withdrawal symptoms and the need for additional opioid delivery during the 7 or 11 h study sessions. Potential volunteers were first contacted by their treating physician within the program and referred for further evaluation. Among 47 referred volunteers, 37 had to be excluded because of inaccessible veins (16), lack of cooperation (8), elevated transaminases (7), anaemia (3), concomitant medications (2), or impaired gastric emptying (1). Two further volunteers withdrew after the first study day. Written informed consent was obtained from all subjects prior to participation. A total of 8 volunteers, 4 women and 4 men, finished the study and were included in the analysis. All 8 volunteers were heavy smokers, with a mean age of 37 (28 to 50) years and a body weight of 62.3 (59 to 84.5) kg. Two volunteers reported occasional use of cannabis and another two of cocaine. On the first study day, urine drug testing for ethanol, cocaine, methadone, barbiturates, benzodiazepines, amphetamines, and lysergic acid diethylamide (LSD) were negative in all volunteers, but were positive for cannabis in two of them. All volunteers exhibited normal renal function and no signs of liver damage (i.e., normal plasma transaminases, bilirubin, INR, normal abdominal ultrasound examination, and negative hepatitis B and C serology).

Volunteers had been opioid-dependent for 3 to 20 years and had participated in the HeGeBe for an average of 2.9 years (range: 4 weeks to 7 years). The mean daily parenteral

diacetylmorphine dose equivalent amounted to 471 mg/d (300 to 867 mg/d). None of the volunteers took any additional medications for at least 3 days before or during the study. The oral diacetylmorphine doses for the study sessions were selected based on daily parenteral diacetylmorphine dose equivalents. To ensure that volunteers would not be over-sedated or develop withdrawal, *immediate release* diacetylmorphine doses amounted to 1.5-times the individual parenteral diacetylmorphine dose equivalent and the corresponding study sessions were limited to 7 h. To extend the study sessions to 11 h after administration of the *extended release* preparation, we increased doses in this case to 2 times the parenteral diacetylmorphine dose equivalent.

After an overnight fast (i.e. no food or beverages except water after 11 pm), the volunteers arrived in the hospital at 7 AM and then stayed for 3 days at the Clinical Research Unit. A catheter was placed into the radial artery for blood sampling and into a vein of the other forearm for morphine-d3 administration. On the morning of the first study day, *immediate release* diacetylmorphine was administered orally with 100–200 ml of water. In addition, 15 mg of morphine-d3 dissolved in 30 ml NaCl was infused intravenously over 5 min starting immediately after the oral dose. Arterial blood samples (4.5 mL) were collected prior and 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, 120, 180, 300 and 420 min after the oral diacetylmorphine dose. On one randomly selected morning of the second or third study day, the volunteers first ate a standardized (high fat content) breakfast consisting of 200 ml whole milk, 2 slices of toast, 20 g of butter, 55 g of Emmental cheese, one boiled egg, and 30 g of corn flakes (corresponding to 51 g of fat, 53 g of carbohydrates and 33 g of proteins). Thereafter, or on an empty stomach as on the first study day, the oral diacetylmorphine *extended release* dose was administered with 100–200 ml of water. Four subjects fasted on the second day and 4 were fed, and patients switched groups on the third day. Arterial blood samples were collected prior and 10, 20, 30, 40, 50, 60, 80, 100, 120, 150, 180, 210, 240, 270, 300, 360, 420, 480, 540 and 660 min after the diacetylmorphine dose. All blood samples were collected directly into vials preloaded with sodium fluoride and centrifuged at 4 °C. The plasma was stored at –20 °C until analysis.

Standardized meals were served on each day for lunch (4 h after the dose) and dinner. After the first hour, the volunteers were free to smoke cigarettes. During the period between the last blood sample and 10 PM, the volunteers received additional intravenous or oral *immediate release* diacetylmorphine (on average, 280 mg (day 1) and 230 mg (day 2 and 3) of parenteral dose equivalents) to maintain constant daily diacetylmorphine dosing.

2.4. Determination of morphine, morphine-d3, and metabolite concentrations

Plasma concentrations of diacetylmorphine, monoacetylmorphine, morphine, morphine-3-glucuronide, morphine-6-glucuronide, morphine-d3, morphine-d3-3-glucuronide, and morphine-d3-6-glucuronide were determined by liquid chromatography-mass spectrometry (LC-MS) with a quantification limit of 10 nmol/L as described previously (between-day precision < 9.5%, accuracy for all analytes between 97.4% and 103.7%) (Rentsch et al., 2001, Girardin et al., 2003).

2.5. Non-compartmental pharmacokinetic analysis

Individual morphine and glucuronide plasma half-life ($t_{1/2}$) were calculated from the pharmacokinetic data after intravenous morphine administration as $t_{1/2} = \ln 2 / \lambda$, where λ represents the slope of the terminal part of the plasma concentration-time curve after semi-logarithmic transformation. The areas under the plasma concentration-time curve (AUCs) were calculated as $AUC_{(0-\infty)} = AUC_{(t_0-t_{last})} + C_{last} / \lambda - C_0 / \lambda$, where t_{last} was the time of the last measurable plasma drug or metabolite concentration above the detection limit, C_{last} was the plasma drug or metabolite concentration of this last sample, and C_0 was the plasma drug or

metabolite concentration at the time of drug administration (t_0). $AUC_{(0-tlast)}$ was calculated by the trapezoidal rule with linear interpolation.

Total plasma clearances were calculated from AUC and dose (D) for intravenous morphine-d3 as $CL = D / AUC$. The volumes of distribution at steady state (V_{ss}) were calculated as $V_{ss} = D * (AUMC) / (AUC)^2$, with AUMC being the total area under the first moment of the plasma concentration time curve (Gibaldi and Perrier, 1982). Absolute and relative bioavailability (F) were determined as $F = (AUC_1 / D_1) / (AUC_2 / D_2)$, where AUC_1 , D_1 , AUC_2 and D_2 corresponds to AUC and dose for the oral diacetylmorphine versus the intravenous morphine-d3 dose, the oral *extended* versus *immediate release* dose, or the *extended release* dose administered in the fed and fasted state. To measure the fluctuation of plasma concentrations, we calculated the percent peak trough fluctuation (%PTF) as $100 * (C_{max} - C_{min}) / C_{avg}$ with $C_{avg} = AUC_{0-11h} / 11 h$ and the percent AUC fluctuation (%AUCF) as $100 * (AUC(above C_{avg}) + AUC(below C_{avg})) / AUC$. (Steinijans, 1990). The geometric mean of absolute and relative bioavailabilities and other parameter estimates, as well as the corresponding confidence intervals, were then calculated.

2.6. Deconvolution analysis

If we view each subject as a linear, time-invariant system characterized by its morphine disposition function, $K(t)$, we can relate the serum concentration response $C(t)$ of that subject to an arbitrary morphine or diacetylmorphine dosage using a convolution of the absorption rate function, $A(t)$, with the individual disposition function, $K(t)$:

$$C_j(t) = \int_0^t A(\tau) K_j(t - \tau) d\tau$$

The population (sample) average disposition function was estimated from the plasma concentration data collected after intravenous morphine-d3 administration using a standard two compartment model parameterised as k_{10} , V_1 , k_{12} , and k_{21} , with interindividual variability on each parameter. A one-compartment model fitted the intravenous data considerably worse: we observed a difference in objective function (ΔOF) of 686 points, which is highly significant (the approximate 0.05% confidence level ΔOF is 3.9). No relevant improvement of the fit was achieved with the inclusion of a third compartment. As a by-product of the (population) fit, the individual empirical Bayes estimates for the bi-exponential IV disposition functions were obtained. Drug absorption was described by a positively constrained linear (population) spline function for each study occasion, i.e. the administration of the *immediate release* dose, the *extended release* dose in the fasted state, and the *extended release* dose after a high-fat breakfast, and estimated from the data conditional on the individual bi-exponential disposition functions obtained from the intravenous morphine-d3 data analysis. The breakpoints of the spline were set at the quantiles of the data (Fattinger and Verotta, 1995a, Fattinger and Verotta, 1995b, Fattinger et al., 2000, Pitsiu et al., 2001), and the spline (s) were parameterized to directly estimate absolute or relative bioavailabilities from the data of one or two study occasions combined (The corresponding NONMEM control stream and the data of two patients are given in Appendix 1). The 90% and 95% confidence intervals for the absolute or relative bioavailability estimates were obtained using a likelihood ratio profile (Bates and Watts, 1988).

All calculations and drawings were done in Microsoft Excel and (S)-Plus 6.1 for Windows (Insightful Corporation, 2002) or with NONMEM VI under Windows or Unix (Beal and Sheiner, 1992).

3. Results

3.1. Adverse events

All study doses were well tolerated. Only one adverse event was observed in which one volunteer requested one dose of paracetamol for a headache during the second night. Diacetylmorphine dosing was considered adequate on all study days.

3.2. Non-compartmental pharmacokinetic analysis

Intravenous morphine-d3—The AUC(0- ∞) (mean $\pm$ SD) for morphine-d3, morphine-d3-3-glucuronide, and morphine-d3-6-glucuronide was 30.7 ± 5.62 , 250 ± 77 , and 30 ± 9 min* μ mol/l, respectively. Morphine-d3 exhibited a clearance of 1.7 ± 0.3 l/min, a volume of distribution at steady state of 151 ± 42 l, and a terminal half-life of 1.74 ± 0.5 h.

Oral immediate release diacetylmorphine—The diacetylmorphine dose (mean $\pm$ SD) was 719 ± 297 mg (1.77 ± 0.73 mmol). Similar to our previous study (Girardin et al., 2003), diacetylmorphine and monoacetylmorphine plasma concentrations were negligible. Morphine plasma concentrations peaked at 15 to 180 min, with maximal concentrations of 4.0 ± 1.27 μ mol/l (Table 1, Figure 2A). The 7-h sampling period covered at least 80% of the morphine AUC. If we determine morphine bioavailability by comparing oral diacetylmorphine with intravenous morphine-d3, (absolute) morphine bioavailability was $61\% \pm 17\%$ (range 44%–88%). The mean relative morphine-3-glucuronide and morphine-6-glucuronide bioavailabilities were $149\% \pm 64\%$ and $184\% \pm 96\%$, respectively.

Oral extended release diacetylmorphine—The mean *extended release* diacetylmorphine dose was 956 ± 404 mg (2.36 ± 1.0 mmol). Diacetylmorphine and monoacetylmorphine concentrations were again negligible. The 11-h sampling period covered at least 85% of the morphine AUC. Morphine bioavailability on an empty stomach was $53\% \pm 15\%$ (range 37%–79%) (Table 1, Figure 2B and C). Morphine bioavailability for *extended release* diacetylmorphine was lower in 4, higher in 3, and the same in 1 volunteer compared to *immediate release* diacetylmorphine. The geometric mean relative bioavailability of morphine after *extended* vs. *immediate release* diacetylmorphine was 86% (90% CI, 73%–103%). Relative bioavailabilities for the morphine-glucuronides (81% and 86%) were close to the values for morphine. A high-fat breakfast did not affect morphine bioavailability, yielding geometric mean relative bioavailabilities (fed/fasted) of 106%, 119%, and 93% for morphine, morphine-3-glucuronide, and morphine-6-glucuronide. The relative fed vs. fasted morphine bioavailability has a rather narrow 90% confidence interval from 96% to 117%, which excludes any relevant food effect.

Plasma concentration fluctuation was characterised by percent peak through fluctuation and percent AUC fluctuation. The peak-through fluctuation for the *extended release* preparation was about half that of the *immediate release* formulation (90% CI of 45% to 61%). The percent AUC fluctuation for the *extended release* formulation was only 0.66 (90% CI, 0.58 to 0.76) of the *immediate release* formulation. The presence of food did not increase either of these variability parameters. Maximal morphine concentrations were observed at 0.4 to 4.5 h in fasted and at 3 to 4.5 h in fed conditions, with peak morphine concentrations of 2.98 ± 1.72 and 2.62 ± 1.06 μ mol/l (Table 1, Figure 2B and C). Thus, dose-normalised maximal morphine plasma concentrations for *extended release* diacetylmorphine averaged about half of the *immediate release* diacetylmorphine, and were observed after about double the period of time.

3.3. Deconvolution Analysis

The three panels of Figure 3 compare data and the (population) prediction (solid line) for morphine plasma concentration after the *immediate* (A) and the *extended release*

diacetylmorphine preparation in the fasted state (B) and after a high-fat breakfast (C). Panel A of Figure 4 compares the (population) morphine absorption rate profiles obtained from the deconvolution analysis. For the *immediate release* diacetylmorphine preparation, the morphine absorption rate rapidly peaks at about 10 to 15 min and more than 50% of the dose is absorbed after about 1.5 hours, with more than 90% absorbed at 4.7 h. Morphine absorption was considerably slower and more sustained after administration of the *extended release* diacetylmorphine preparation, with about 1/3 of the maximal absorption rate of the *immediate release* preparation observed from 10 min to 3.5 h after drug intake, with at least 50% of the dose absorbed after 3 hours and at least 90% absorbed after 8.5 h. Administration after a high-fat breakfast slightly delayed initial morphine absorption for about 20 to 30 min, without much effect on later morphine absorption rates.

The absolute and relative bioavailability estimates for the different preparations are given in Table 2, with point estimates of 0.57, 0.55 and 0.57 for *immediate release*, *extended release* in the fasted condition, and *extended release* after a high-fat breakfast. Panels B and C of Figure 4 compare the estimated *in vivo* morphine absorption rate profile and the *in vitro* release rate profile for the *extended release* and the *immediate release* preparations. Absorption rate shortly after drug delivery rises considerably slower *in vivo* than was predicted by *in vitro* drug release, but the *in vivo* absorption rate – at least for the *extended release* formulation – subsequently catches up.

4. Discussion

This study compared the morphine absorption characteristics of orally administered *immediate* and *extended release* diacetylmorphine in the high dose range required by opioid addicts. Both preparations exhibited a high mean absolute morphine bioavailability in the range of 56% to 61%. The *immediate release* preparation resulted in rapid morphine absorption, with the absorption rate peaking at 10 to 15 min after dosing. For the *extended release* formulation, morphine absorption rates were considerably lower and more sustained, with only about 30% of the maximal absorption rate (of the *immediate release* preparation) being reached after 10 min and then maintained for 3 to 4 h, with no relevant food interaction. The relative bioavailability of the two preparations was 86% for the non-compartmental or 93% for the deconvolution analysis. Therefore, it can be concluded that these two diacetylmorphine preparations produce the intended morphine exposures and are suitable for substitution with similar dosages when given sequentially or in combination to the same patient. The part of the dose given as an *immediate release* formulation will assure a rapid opioid effect, whereas the part given in an *extended release* form maintains opioid availability until the patient's next visit to the treatment center.

The rapid absorption and concentration rise of the *immediate release* preparation is advantageous, since the pharmacodynamic effects of opioids depend on both the substance and the initial slope of the plasma concentration. Two factors probably contribute to the rapid initial rise in drug absorption: diacetylmorphine produces a more rapid rise in morphine levels than oral morphine (Girardin et al., 2003) and a pharmaceutical formulation designed for rapid disintegration of the tablets. Based on this absorption rate profile, a rapidly disintegrating *immediate release* formulation might be especially suited for addicted patients that used opioids parenterally, by inhalation, or nasally.

The *extended release* diacetylmorphine preparation produces a lower but more sustained morphine exposure, which could avoid a drug-related "high". Morphine absorption reached 90% only after 8.5 hours, allowing for an extended dosing interval that could improve compliance, as dosing requires scheduled visits to treatment centres. Flexible dosing can also be achieved as food does not affect drug absorption. Clinically, these findings confirm the

indications of *extended release* diacetylmorphine, which are recommended for situations requiring the absence of a drug “high,” such as working patients, or in patients preparing for diacetylmorphine withdrawal. Furthermore, the *extended release* preparation allows for prolonged dosing intervals and thus enhances the ability for employment.

In vivo absorption profiles differ clearly from the *in vitro* dissolution profile for both the *immediate* and the *extended release* preparations (Figure 4B and 4C). Similar differences also occur with the *slow release* oxybutynin OROS (Pitsiu et al., 2001), stressing the importance of *in vivo* studies even for drugs with high water or lipid solubility, such as diacetylmorphine.

Deconvolution analysis enabled us to characterise and visually compare the time courses of drug absorption for the different preparations, and to compare them to the *in vitro* dissolution profiles, as well as calculating absolute and relative bioavailability. Most parameter estimates and confidence intervals matched closely in both data analysis approaches, i.e. the standard AUC calculation and the deconvolution approach. In deconvolution analysis, the 90% confidence interval for the relative bioavailability of the *extended release* preparation was more narrow (80.5% to 107.2%) than AUC calculations (73.1% to 105.0%), suggesting that deconvolution analysis may be more robust with respect to outliers. The reason for the observed (but probably clinically irrelevant) differences in the point bioavailability estimates of 61% vs. 57% (*immediate release*) and 53% vs. 55% (*extended release*) for the two data analysis approaches remains unresolved.

The slightly lower bioavailability of *extended* as compared to *immediate release* diacetylmorphine could result from lower maximal concentrations leading to more efficient first pass elimination in the intestine and liver, or lower mucosal diacetylmorphine and/or morphine permeability in the distal than the proximal intestine.

In conclusion, orally administered *immediate* and *extended release* diacetylmorphine both exhibit a high absolute morphine bioavailability of 56% to 61% in the dose range required by opioid addicts. The *immediate release* preparation produces rapid morphine absorption, whereas absorption rates are considerably lower and more sustained for the *extended release* formulation, with 90% of morphine absorption reached only after 8.5 h, which would allow for extending dosing intervals. Morphine absorption was not significantly affected by a high-fat breakfast. The relative bioavailability of the two preparations was 86% (non-compartmental analysis) or 93% (deconvolution analysis), indicating they can be substituted for each other with a one to one ratio. The absorption characteristics could improve outcomes in patients switching from parenteral opioids or for well-integrated patients under chronic treatment to enhance employability.

Acknowledgments

We thank Mathias Markert, Andreas Ryser, and the physicians involved in the Swiss heroin trials for their help with volunteer recruitment and all volunteers for their good cooperation. We also thank the physicians of the Division of Clinical Pharmacology in Zürich for their help during the study sessions.

The study was funded by the Swiss Federal Office of Public Health. Karin Fattinger was supported by a Swiss National Science Foundation Grant, 3200B0-109352. Davide Verotta was supported by a National Institutes of Health Grant, RO1 A150587.

References

- Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat* 2005;28:321–9. [PubMed: 15925266]

- Bates, DM.; Watts, DG. Nonlinear regression analysis and its applications. John Wiley and Sons; New York: 1988.
- Beal, SL.; Sheiner, LB. NONMEM user guides. NONMEM Project Group; San Francisco: 1992.
- Brisette S. Medical Prescription of Heroin. Canadian HIV/AIDS Policy & Law 2001;6:92–8.
- Bundesamt Für Gesundheit. HeGeBe Info: Konsumformen von Diacetylmorphin 2004. 2004 [accessed on August 19th 2008].
<http://www.bag.admin.ch/themen/drogen/00042/00629/00798/01191/index.html?lang=de>
- Fattinger K, Benowitz NL, Jones RT, Verotta D. Nasal mucosal versus gastrointestinal absorption of nasally administered cocaine. Eur J Clin Pharmacol 2000;56:305–10. [PubMed: 10954344]
- Fattinger KE, Verotta D. A nonparametric subject-specific population method for deconvolution: II. external validation. J Pharmacokinet Biopharm 1995a;23:611–34. [PubMed: 8733949]
- Fattinger KE, Verotta D. A nonparametric subject-specific population method for deconvolution: I. description, internal validation and real data examples. J Pharmacokin Biopharm 1995b;23:581–610.
- Fischer B, Oviedo-Joekes E, Blanken P, Haasen C, Rehm J, Schechter MT, Strang J, Van Den Brink W. Heroin-assisted treatment (HAT) a decade later: a brief update on science and politics. J Urban Health 2007;84:552–62. [PubMed: 17562183]
- Frick U, Rehm J, Kovacic S, Ammann J, Uchtenhagen A. A prospective cohort study on orally administered heroin substitution for severely addicted opioid users. Addiction 2006;101:1631–9. [PubMed: 17034443]
- Gibaldi, M.; Perrier, D. Pharmacokinetics. Marcel Dekker, Inc.; New York: 1982.
- Girardin F, Rentsch KM, Schwab MA, Maggiorini M, Pauli Magnus C, Kullak Ublick GA, Meier PJ, Fattinger K. Pharmacokinetics of high doses of intramuscular and oral heroin in narcotic addicts. Clin Pharmacol Ther 2003;74:341–52. [PubMed: 14534521]
- Haasen C, Verthein U, Degkwitz P, Berger J, Krausz M, Naber D. Heroin-assisted treatment for opioid dependence: randomised controlled trial. Br J Psychiatry 2007;191:55–62. [PubMed: 17602126]
- Insightful Corporation. S-PLUS 6.1. for Windows. 6.1. Seattle: Mathsoft; 2002.
- Klous MG, Huitema AD, Rook EJ, Hillebrand MJ, Hendriks VM, Van Den Brink W, Beijnen JH, Van Ree JM. Pharmacokinetic comparison of two methods of heroin smoking: ‘chasing the dragon’ versus the use of a heating device. Eur Neuropsychopharmacol 2005;15:263–9. [PubMed: 15820414]
- National Prevention Programmes of the Swiss Federal Office of Public Health. Heroin-assisted treatment/treatment with diacetylmorphine (HAT) in 2006. 2007 [accessed on March 13 2008].
<http://www.bag.admin.ch/themen/drogen/00042/00629/00798/01191/index.html?lang=en>
- Nordt C, Stohler R. Incidence of heroin use in Zurich, Switzerland: a treatment case register analysis. Lancet 2006;367:1830–4. [PubMed: 16753485]
- Pitsiu M, Sathyan G, Gupta S, Verotta D. A semiparametric deconvolution model to establish in vivo-in vitro correlation applied to OROS oxybutynin. J Pharm Sci 2001;90:702–12. [PubMed: 11357173]
- Rehm J, Gschwend P, Steffen T, Gutzwiller F, Dobler-Mikola A, Uchtenhagen A. Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study. Lancet 2001;358:1417–23. [PubMed: 11705488]
- Rentsch KM, Kullak Ublick GA, Reichel C, Meier PJ, Fattinger K. Arterial and venous pharmacokinetics of intravenous heroin in subjects who are addicted to narcotics. Clin Pharmacol Ther 2001;70:237–46. [PubMed: 11557911]
- Rook EJ, Van Ree JM, Van Den Brink W, Hillebrand MJ, Huitema AD, Hendriks VM, Beijnen JH. Pharmacokinetics and pharmacodynamics of high doses of pharmaceutically prepared heroin, by intravenous or by inhalation route in opioid-dependent patients. Basic Clin Pharmacol Toxicol 2006;98:86–96. [PubMed: 16433897]
- Sheldon T. Substance misuse: More than a quick fix. Bmj 2008;336:68–9. [PubMed: 18187719]
- Steinijans VW. Pharmacokinetic characterization of controlled-release formulations. Eur J Drug Metab Pharmacokinet 1990;15:173–81. [PubMed: 2200687]
- Van Den Brink W, Hendriks VM, Blanken P, Koeter MW, Van Zwieten BJ, Van Ree JM. Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. Bmj 2003;327:310. [PubMed: 12907482]

- Van Den Brink W, Haasen C. Evidenced-based treatment of opioid-dependent patients. *Can J Psychiatry* 2006;51:635–46. [PubMed: 17052031]
- Verthein U, Bonorden-Kleij K, Degkwitz P, Dilg C, Kohler WK, Passie T, Soyka M, Tanger S, Vogel M, Haasen C. Long-term effects of heroin-assisted treatment in Germany. *Addiction* 2008;103:960–6. [PubMed: 18422829]discussion 967–8

Appendix

Appendix 1

Example of a NONMEM control stream used in the deconvolution analysis

\$PROBLEM DAM absorption - estimate input function for SR using a linear spline in B-spline representation

\$INPUT XID DV DMOL TIME EVID RATE DOSE=AMT SS CMT ET1 ET2 ET3 ET4

\$DATA Datapape IGNORE=#

\$SUBROUTINES ADVAN6 TOL=5

\$MODEL

COMP=(CENTRAL, DEFDOSE)

COMP=(PERIPH)

\$PK

; 2 cmp disposition model: population (THn) individual (ETn, obtained from data) pk parameters from disposition analysis

; the system ist set to steady state with the first data record of each individual at his/her measured Co

TH1=8.50

TH2=12.5

TH3=10.8

TH4=0.847

K10 = TH1*EXP(ET1)

V1= TH2*EXP(ET2)

K12 = TH3*EXP(ET3)

K21 = TH4*EXP(ET4)

S1 = V1

\$DES

; define breakpoints BDES 1 to 7 at the quantiles of the time data

```
BDES1=0.0

BDES2=0.2361667

BDES3=0.639

BDES4=1.1665

BDES5=3.166667

BDES6=5.166667

BDES7=11

; reset basis values to zero

BDESv1=0

BDESv2=0

BDESv3=0

BDESv4=0

BDESv5=0

BDESv6=0

BDESv7=0

IDES=0

IF (T.GE.BDES1.AND.T.LT.BDES2) BDESv1=THETA(1)*(BDES2-T)/(BDES2-
BDES1)

IF (T.GE.BDES1.AND.T.LT.BDES2) BDESv2=THETA(2)*(T-BDES1)/(BDES2-
BDES1)

IF (T.GE.BDES2.AND.T.LT.BDES3) BDESv2=THETA(2)*(BDES3-T)/(BDES3-
BDES2)

IF (T.GE.BDES2.AND.T.LT.BDES3) BDESv3=THETA(3)*(T-BDES2)/(BDES3-
BDES2)

IF (T.GE.BDES3.AND.T.LT.BDES4) BDESv3=THETA(3)*(BDES4-T)/(BDES4-
BDES3)

IF (T.GE.BDES3.AND.T.LT.BDES4) BDESv4=THETA(4)*(T-BDES3)/(BDES4-
BDES3)

IF (T.GE.BDES4.AND.T.LT.BDES5) BDESv4=THETA(4)*(BDES5-T)/(BDES5-
BDES4)

IF (T.GE.BDES4.AND.T.LT.BDES5) BDESv5=THETA(5)*(T-BDES4)/(BDES5-
BDES4)
```

```

IF (T.GE.BDES5.AND.T.LT.BDES6) BDESV5=THETA(5)*(BDES6-T)/(BDES6-
BDES5)

IF (T.GE.BDES5.AND.T.LT.BDES6) BDESV6=THETA(6)*(T-BDES5)/(BDES6-
BDES5)

IF (T.GE.BDES6.AND.T.LE.BDES7) BDESV6=THETA(6)*(BDES7-T)/(BDES7-
BDES6)

IF (T.GE.BDES6.AND.T.LE.BDES7) BDESV7=THETA(7)*(T-BDES6)/(BDES7-
BDES6)

A1= THETA(1)*(BDES2-BDES1)/2

A2= THETA(2)*(BDES3-BDES1)/2

A3= THETA(3)*(BDES4-BDES2)/2

A4= THETA(4)*(BDES5-BDES3)/2

A5= THETA(5)*(BDES6-BDES4)/2

A6= THETA(6)*(BDES7-BDES5)/2

A7= THETA(7)*(BDES7-BDES6)/2

AREA=A1+A2+A3+A4+A5+A6+A7

BIO=THETA(8)

IDES = DMOL/AREA * BIO * 1000 * (BDESV1+BDESV2+BDESV3+BDESV4+BDESV5
+BDESV6+BDESV7)

DADT(1)=K21*A(2)-A(1)*(K10+K12)+IDES

DADT(2)=K12*A(1)-K21*A(2)

$ERROR

Y=F*EXP(ERR(1))

$THETA

(0 0.01)

(0 0.02)

(0 0.05)

(1 FIXED); fix one theta (expected not to go to 0) to 1 so that we have
1 parameter left to estimate bioavailability

(0 0.03)

(0 0.05)

```

(0 0.01)

(0 0.6); bioavailability

\$OMEGA .3

\$EST

Example of af the corresponding data set (first two patients)

Figure 1. *In vitro* diacetylmorphine dissolution profiles of immediate and extended release tablets
Six single tablets of *immediate* (IR) or *extended release* (ER) diacetylmorphine were subjected to dissolution profiling with a standard USP dissolution apparatus. Values are given as mean $\pm$ standard deviations.

Figure 2. Individual morphine plasma concentration–time profiles after orally administered *immediate* (A) and *extended release* diacetylmorphine in the fasted (B) and the fed (C) state Solid lines connect measured plasma concentrations, dashed lines correspond to plasma concentration extrapolations based on the last sample (at 7 h) and the subject's terminal morphine elimination rate estimated from the intravenous morphine-d3. Identical symbols are used for the same patient in all 3 panels. The mean diacetylmorphine doses were 719 mg (1.77 mmol) for *immediate* and 956 mg (2.36 mmol) for *extended release* diacetylmorphine.

Figure 3. Goodness-of-fit plots for *immediate* (A) and *extended release* diacetylmorphine in the fasted (B) and the fed (C) state from deconvolution analysis using a bi-exponential disposition and a linear spline absorption function

The (X) represents the observed data and the solid lines correspond to the average predictions.

Figure 4. Population morphine absorption rate function for *immediate* (dashed-dotted line) and *extended release* diacetylmorphine in the fasted (solid line) and the fed (short dashed line) state estimated by deconvolution analysis using a bi-exponential disposition and a linear spline absorption function

Panel A gives the estimated absorption rate functions obtained by deconvolution analysis for the oral *immediate* and *extended release* diacetylmorphine preparation. Panel B and C compare the morphine absorption rate functions obtained by deconvolution analysis from the drug concentration data and the corresponding diacetylmorphine release profiles from the *in vitro* experiments (long dashed line) for the *extended release* (B) and the *immediate* (C) preparations.

Table 1
Pharmacokinetic comparison of oral immediate (IR) and extended (ER) release diacetylmorphine.

Formulation	Parameter Estimate ^a			Ratio ^b	
	IR	ER	ER	ER / IR	ER / ER
Condition	fasted	fasted	fed	fasted	fed / fasted
Dose (D, mmol)	1.77 ± 0.73	2.36 ± 1.00	2.36 ± 1.00	---	1
Morphine					
C _{max} (μmol/L)	4.00 ± 1.27	2.98 ± 1.72	2.62 ± 1.06	---	---
C _{max} / D (10 ⁻³ /L)	2.42 ± 0.88	1.23 ± 0.47	1.14 ± 0.22	0.51 (0.41, 0.63)	0.97 (0.81, 1.15)
C _{min} (μmol/L) ^c	0.11 ± 0.12	0.44 ± 0.24	0.50 ± 0.31	---	---
C _{min} / D (10 ⁻³ /L)	0.05 ± 0.05	0.18 ± 0.06	0.20 ± 0.09	4.9 (3.1, 7.7)	1.04 (0.87, 1.25)
t _{max} (min)	76 ± 52	157 ± 71	263 ± 33	2.29 (1.62, 3.24)	1.96 (1.32, 2.93)
AUC _{0-∞} (mmol*min/L)	0.63 ± 0.29	0.72 ± 0.32	0.76 ± 0.33	---	---
F (%) ^d	61 ± 17	53 ± 15	56 ± 15	86 (73.1, 105)	106 (96, 117)
%PTF ^f	450 ± 227	235 ± 122	202 ± 78	0.52 (0.45, 0.61)	0.89 (0.70, 1.13)
%AUCF ^g	0.664 ± 0.233	0.428 ± 0.104	0.428 ± 0.127	0.66 (0.58, 0.76)	0.99 (0.85, 1.14)
Morphine-3-glucuronide					
AUC _{0-∞} (mmol*min/L)	11.1 ± 4.5	12.9 ± 7.3	14.6 ± 6.0	---	---
AUC _{0-∞} / D (min/L)	6.68 ± 2.31	5.51 ± 2.08	6.42 ± 2.30	---	---
F _{rel} (%) ^e	149 ± 64	---	---	81 (58, 113)	119 (100, 142)
Morphine-6-glucuronide					
AUC _{0-∞} (mmol*min/L)	1.7 ± 1.0	1.9 ± 1.0	1.8 ± 0.8	---	---
AUC _{0-∞} / D (min/L)	1.02 ± 0.50	0.81 ± 0.22	0.75 ± 0.18	---	---
F _{rel} (%) ^d	184 ± 96	---	---	86 (63, 119)	93 (79, 110)

^aValues are given as mean ± SD

^b Values are given as geometric mean and 90% confidence interval

^c For the extended release preparation, C_{min} corresponds to the minimal concentration observed after C_{max} during the 11 h sampling period, and for the immediate release preparation to the extrapolated concentration at 11 h after drug administration

^d Morphine bioavailability was determined by comparing dose-normalized morphine AUCs after oral diacetylmorphine and intravenous morphine-d3 administration.

^e Relative morphine-glucuronide bioavailabilities were determined by comparing dose- normalized morphine-glucuronide AUCs from oral diacetylmorphine and intravenous morphine-d3 administration.

^f %PTF percent peak trough fluctuation, i.e. $100 * (C_{\text{max}} - C_{\text{min}}) / C_{\text{avg}}$ with $C_{\text{avg}} = \text{AUC}_{0-11\text{h}} / 11\text{h}$

^g %AUCF percent AUC fluctuation, i.e. $100 * (\text{AUC}(\text{above Cavg}) + \text{AUC}(\text{below Cavg})) / \text{AUC}$

Table 2

Absolute and relative bioavailability estimates for *immediate* (IR) and *extended release* (ER) diacetylmorphine from the deconvolution analysis in NONMEM and their 90% and 95% confidence intervals.

	Point estimate	90% CI ^a	95% CI ^a
IR	0.57	(0.49, 0.65)	(0.48, 0.67)
ER fasted	0.55	(0.50, 0.59)	(0.50, 0.59)
ER with food	0.57	(0.53, 0.62)	(0.53, 0.62)
ER vs. IR	0.93	(0.805, 1.072)	(0.783, 1.100)
ER with food vs. fasted	1.08	(0.988, 1.192)	(0.971, 1.211)

^a 90% and 95% confidence intervals are based on a likelihood ratio profiles.

#	I	DV	Dmol	Time	EVID	RATE	AMT	SS	CMT	ET1	ET2	ET3	ET4
3		.	1601	0.0000	4	43730	0	1	1	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	330		1601	0.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	795		1601	0.1667	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	985		1601	0.3333	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1075		1601	0.5000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1060		1601	0.6667	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1105		1601	0.8333	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1028		1601	1.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1260		1601	1.3333	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1753		1601	1.6667	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1994		1601	2.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1243		1601	2.5000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1338		1601	3.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1301		1601	3.5000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	990		1601	4.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	941		1601	4.5000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	1023		1601	5.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	795		1601	6.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	615		1601	7.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	510		1601	8.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	384		1601	9.0000	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
3	289		1601	11.2583	0	.	.	.	.	1.62E-01	5.89E-02	-8.78E-02	5.07E-01
4	.		1971	0.0000	4	41838	0	1	1	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4	404		1971	0.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4	426		1971	0.1667	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4	655		1971	0.3333	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4	696		1971	0.5000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4	922		1971	0.6667	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4	425		1971	0.8458	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4	593		1971	1.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01

#	I	DV	Dmol	Time	EVID	RATE	AMT	SS	CMT	ET1	ET2	ET3	ET4
4		765	1971	1.3333	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		1573	1971	1.6667	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		4493	1971	2.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		1788	1971	2.5000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		1179	1971	3.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		1002	1971	3.5000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		1123	1971	4.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		1034	1971	4.5000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		842	1971	5.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		706	1971	6.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		431	1971	7.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		401	1971	8.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		293	1971	9.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01
4		269	1971	11.0000	0	.	.	.	.	2.02E-01	-2.28E-01	-7.39E-02	1.54E-01