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

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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 (+/-S.D.) immediate and extended release doses were 719 +/- 297 and 956 +/- 404mg, with high absolute morphine bioavailabilities of 56-61%, respectively. Immediate release diacetylmorphine caused rapid morphine absorption, peaking at 10-15min. Morphine absorption was considerably slower and more sustained for extended release diacetylmorphine, with only approximately 30% of maximal immediate release absorption being reached after 10min and maintained for 3-4h, 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.
Oral heroin in opioid-dependent patients:

pharmacokinetic comparison of immediate and extended release tablets

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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 (±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.

Key words

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 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 opioid-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). Diacetylmorphine is usually administered intravenously, but this may not be possible due to venosclerosis or when heroin abuse has occurred via non-intravenous routes (Nordt and Stohler, 2006). Others want to reduce the health risks associated with drug administration (Frick et al., 2006). In the Netherlands, administration by inhalation has been evaluated (Rook et al., 2006, Klous et al., 2005), and oral forms of diacetylmorphine have been developed in Switzerland within the heroin prescription program (HeGeBe — “Heroin Gestützte Behandlung”) conducted by the Swiss Federal Office of Public Health (Frick et al., 2006). In 2006, one third of all diacetylmorphine used in the Swiss heroin prescription program this 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 \textit{in vivo} absorption rate with \textit{in vitro} dissolution profiles (Pitsiu et al., 2001).

We have shown previously that even large doses of oral \textit{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 \textit{extended release} diacetylmorphine in addition to or instead of the \textit{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 \textit{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 HeGeBeSwiss heroin prescription programs. Parenteral dose equivalents were calculated by converting oral doses to parenteral doses by dividing them by 3three 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. Furthermore, oral, in contrast to intravenous, diacetylmorphine does not yield any systemic diacetylmorphine or monoacetylmorphine exposure. Moreover, morphine concentrations after oral diacetylmorphine rise more slowly and produce a subjective opioid effect that depends on the slope of the plasma concentration time curve.

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. We wanted to ensure that volunteers would not be over-sedated or develop withdrawal and require additional opioids during the study sessions or receive excessive doses leading to adverse effects such as oversedation. Therefore, the immediate release diacetylmorphine doses were selected based on the algorithm used successfully during our last study, i.e. a single oral dose of amounted to 1.5-times the individual parenteral diacetylmorphine dose equivalent. Furthermore, and we limited the corresponding study sessions were limited to 7 h and allowed additional diacetylmorphine thereafter. 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 $t_{1/2} = \ln2/\lambda$, where $\lambda$ 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 $\text{AUC}(0-\infty) = \text{AUC}(0-t_{\text{last}}) + C_{\text{last}}/\lambda - C_0/\lambda$, where $t_{\text{last}}$ was the time of the last measurable plasma drug or metabolite concentration above the detection limit, $C_{\text{last}}$ 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 ($t_0$). $\text{AUC}(0-t_{\text{last}})$ was calculated by the trapezoidal rule with linear interpolation.
Total plasma clearances were calculated from AUC and dose (D) for intravenous morphine-d3 as \( CL = \frac{D}{AUC} \). The volumes of distribution at steady state (\( V_{ss} \)) were calculated as 
\[
V_{ss} = \frac{D \cdot (AUMC)^2}{(AUC)^2},
\]
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 
\[
F = \frac{(AUC_1 / D_1)}{(AUC_2 / D_2)}
\]
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 
\[
100 \times \frac{(C_{\text{max}} - C_{\text{min}})}{C_{\text{avg}}} \quad \text{with} \quad C_{\text{avg}} = \frac{AUC_{0-11h}}{11 \text{ h}}
\]
and the percent AUC fluctuation (%AUCF) as 
\[
100 \times \frac{(AUC(\text{above } C_{\text{avg}}) + AUC(\text{below } C_{\text{avg}}))}{AUC}
\]
(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 \( k10, V1, k12, \) and \( k21 \), with interindividual variability on each parameter. A one-compartment model fitted the intravenous data considerably worse: we observed a difference in objective function (\( \Delta OF \)) of 686 points, which is highly significant (the approximate 0.05% confidence level \( \Delta OF \) 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 ± SD) for morphine-d3, morphine-d3-3-glucuronide, and morphine-d3-6-glucuronide was 30.7 ± 5.62, 250 ± 77, and 30 ± 9 min*μmol/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 ± 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 μmol/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% ± 17% (range 44%-88%). The mean relative morphine-3-glucuronide and morphine-6-glucuronide bioavailabilities were 149% ± 64% and 184% ± 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% ± 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 μmol/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 \textit{extended release} diacetylmorphine preparation, with about 1/3 of the maximal absorption rate of the \textit{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 \textit{immediate release}, \textit{extended release} in the fasted condition, and \textit{extended release} after a high-fat breakfast. Panels B and C of Figure 4 compare the estimated \textit{in vivo} morphine absorption rate profile and the \textit{in vitro} release rate profile for the \textit{extended release} and the \textit{immediate release} preparations. Absorption rate shortly after drug delivery rises considerably slower \textit{in vivo} than was predicted by \textit{in vitro} drug release, but the \textit{in vivo} absorption rate – at least for the \textit{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.
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References


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

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**Morphine**

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<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (µmol/L)</strong></td>
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<td><strong>C&lt;sub&gt;max&lt;/sub&gt; / D (10&lt;sup&gt;-3&lt;/sup&gt;/L)</strong></td>
<td>2.42 ± 0.88</td>
<td>1.23 ± 0.47</td>
<td>1.14 ± 0.22</td>
<td>0.51 (0.41, 0.63)</td>
<td>0.97 (0.81, 1.15)</td>
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<td><strong>C&lt;sub&gt;min&lt;/sub&gt; (µmol/L)</strong></td>
<td>0.11 ± 0.12</td>
<td>0.44 ± 0.24</td>
<td>0.50 ± 0.31</td>
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<tr>
<td><strong>C&lt;sub&gt;min&lt;/sub&gt; / D (10&lt;sup&gt;-3&lt;/sup&gt;/L)</strong></td>
<td>0.05 ± 0.05</td>
<td>0.18 ± 0.06</td>
<td>0.20 ± 0.09</td>
<td>4.9 (3.1, 7.7)</td>
<td>1.04 (0.87, 1.25)</td>
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<td><strong>t&lt;sub&gt;max&lt;/sub&gt; (min)</strong></td>
<td>76 ± 52</td>
<td>157 ± 71</td>
<td>263 ± 33</td>
<td>2.29 (1.62, 3.24)</td>
<td>1.96 (1.32, 2.93)</td>
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<tr>
<td><strong>AUC&lt;sub&gt;0-∝&lt;/sub&gt; (mmol*min/L)</strong></td>
<td>0.63 ± 0.29</td>
<td>0.72 ± 0.32</td>
<td>0.76 ± 0.33</td>
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<tr>
<td><strong>F (%)</strong></td>
<td>61 ± 17</td>
<td>53 ± 15</td>
<td>56 ± 15</td>
<td>86</td>
<td>106</td>
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<tr>
<td><strong>%PTF</strong></td>
<td>450 ± 227</td>
<td>235 ± 122</td>
<td>202 ± 78</td>
<td>0.52 (0.45, 0.61)</td>
<td>0.89 (0.70, 1.13)</td>
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<tr>
<td><strong>%AUCF</strong></td>
<td>0.664 ± 0.233</td>
<td>0.428 ± 0.104</td>
<td>0.428 ± 0.127</td>
<td>0.66 (0.58, 0.76)</td>
<td>0.99 (0.85, 1.14)</td>
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**Morphine-3-glucuronide**

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<td><strong>AUC&lt;sub&gt;0-∝&lt;/sub&gt; (mmol*min/L)</strong></td>
<td>11.1 ± 4.5</td>
<td>12.9 ± 7.3</td>
<td>14.6 ± 6.0</td>
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<td><strong>AUC&lt;sub&gt;0-∝&lt;/sub&gt; / D (min/L)</strong></td>
<td>6.68 ± 2.31</td>
<td>5.51 ± 2.08</td>
<td>6.42 ± 2.30</td>
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<td><strong>F&lt;sub&gt;rel&lt;/sub&gt; (%)</strong></td>
<td>149 ± 64</td>
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<td>81 (58, 113)</td>
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**Morphine-6-glucuronide**

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<td><strong>AUC&lt;sub&gt;0-∝&lt;/sub&gt; (mmol*min/L)</strong></td>
<td>1.7 ± 1.0</td>
<td>1.9 ± 1.0</td>
<td>1.8 ± 0.8</td>
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<tr>
<td><strong>AUC&lt;sub&gt;0-∝&lt;/sub&gt; / D (min/L)</strong></td>
<td>1.02 ± 0.50</td>
<td>0.81 ± 0.22</td>
<td>0.75 ± 0.18</td>
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<tr>
<td><strong>F&lt;sub&gt;rel&lt;/sub&gt; (%)</strong></td>
<td>184 ± 96</td>
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<td>86 (63, 119)</td>
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<sup>a</sup> Values are given as mean ± SD
<sup>b</sup> Values are given as geometric mean and 90% confidence interval
<sup>c</sup> For the extended release preparation, C<sub>min</sub> corresponds to the minimal concentration observed after C<sub>max</sub> during the 11 h sampling period, and for the immediate release preparation to the extrapolated concentration at 11 h after drug administration
<sup>d</sup> Morphine bioavailability was determined by comparing dose-normalized morphine AUCs after oral diacetylmorphine and intravenous morphine-d<sub>3</sub> administration.
<sup>e</sup> Relative morphine-glucuronide bioavailabilities were determined by comparing dose- normalized morphine-glucuronide AUCs from oral diacetylmorphine and intravenous morphine-d<sub>3</sub> administration.
<sup>f</sup> %PTF percent peak trough fluctuation, i.e. 100 * (C<sub>max</sub>-C<sub>min</sub>) / Cavg with Cavg = AUC<sub>0-11h</sub> / 11h
<sup>g</sup> %AUCF percent AUC fluctuation, i.e. 100 * (AUC(above Cavg) + AUC(below Cavg) ) / 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.

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<td>(0.49, 0.65)</td>
<td>(0.48, 0.67)</td>
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<td>0.55</td>
<td>(0.50, 0.59)</td>
<td>(0.50, 0.59)</td>
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<tr>
<td>ER with food</td>
<td>0.57</td>
<td>(0.53, 0.62)</td>
<td>(0.53, 0.62)</td>
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<tr>
<td>ER vs. IR</td>
<td>0.93</td>
<td>(0.805, 1.072)</td>
<td>(0.783, 1.100)</td>
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<tr>
<td>ER with food vs. fasted</td>
<td>1.08</td>
<td>(0.988, 1.192)</td>
<td>(0.971, 1.211)</td>
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* 90% and 95% confidence intervals are based on a likelihood ratio profiles.
Figure Legends

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 ± 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.
Figure 1
Figure 2

A

B

C

Morphine [umol/l]

Time (h)
Figure 3

A

B

C
Figure 4
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 LV DNOM TIME EVID RATE DOSE=AMT SS CONT ET1 ET2 ET3 ET4

$DATA DataFile IGNORE=#

$SUBROUTINES ADVAN6 TOL=5

$MODEL

COMP=(CENTRAL,DEFDOSE)

COMP=(PERIPH)

$PK

; two cmp disposition model: population (Tn) individual (Et, obtained from data) pk parameters from disposition analysis

TH1=8.50
TH2=12.5
TH3=10.3
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 quartiles 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.BDES2.AND.T.LT.BDES3) BDESV2=THETA(2)*(T-BDES2)/(BDES3-BDES2)
IF (T.GE.BDES3.AND.T.LT.BDES4) BDESV3=THETA(3)*(T-BDES3)/(BDES4-BDES3)
IF (T.GE.BDES4.AND.T.LT.BDES5) BDESV4=THETA(4)*(T-BDES4)/(BDES5-BDES4)
IF (T.GE.BDES5.AND.T.LT.BDES6) BDESV5=THETA(5)*(T-BDES5)/(BDES6-BDES5)
IF (T.GE.BDES6.AND.T.LT.BDES7) BDESV6=THETA(6)*(T-BDES6)/(BDES7-BDES6)
IF (T.GE.BDES7.AND.T.LT.BDES1) BDESV7=THETA(7)*(T-BDES1)/(BDES1-BDES7)
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 0.01)
(0 0.01)
(0 0.6) ; bioavailability

$OMEGA .3
$EST
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