

## Pharmacokinetics and Pharmacodynamics of High Doses of Pharmaceutically Prepared Heroin, by Intravenous or by Inhalation Route in Opioid-Dependent Patients

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**Abstract:** A pharmacokinetic-pharmacodynamic study was performed in opioid-dependent patients in the Netherlands, who were currently treated with high doses of pharmaceutically prepared heroin on medical prescription. Besides intravenous heroin, heroin was prescribed for inhalation by “chasing the dragon” method. In this technique, heroin base is heated on aluminium foil, and heroin vapours are inhaled into the lungs. Not much is known about the pharmacokinetics profile and bioavailability of this specific administration method. Therefore, a study was performed on pharmacokinetics and pharmacodynamics of heroin inhalation and intravenous use. Eleven patients who injected heroin and 9 patients who inhaled heroin entered the study. They were on steady-state heroin treatment for at least 12 months. For safety reasons, there was no crossing-over between heroin injection or inhalation. In a double-blind randomised study, 67–100–150% of the regular heroin maintenance dose was administered to each patient. Maximal single heroin dose was 450 mg. Plasma concentrations of heroin and its metabolites 6-monoacetylmorphine, morphine and morphine-glucuronides were analysed using LC-MS-MS. Blood pressure, heart rate, skin temperature and reaction time were assessed. Furthermore, visual analogue scales regarding craving and appreciation of heroin effect were scored by the subjects. Both in inhaling and injecting patients, the areas under curve of heroin and all measured metabolites were linearly related to heroin dose. Mean  $C_{max}$  of heroin and its metabolites were 2–6 times lower after inhalation, than after intravenous injection. Bioavailability (F) of heroin inhalation was estimated as 52% (95% CI 44–61%). Heroin was rapidly cleared from plasma.  $Cl/F$  was 930 l/hr (95% CI 799–1061 l/hr) after intravenous administration, and 1939 l/hr (95% CI 1661–2217 l/hr) after inhalation. Heroin  $Cl$  and  $V_d$  were correlated to body weight ( $R^2$  15–19%). Morphine-glucuronides levels were inversely related to creatinine clearance. After heroin administration, the reaction time was significantly prolonged with  $28 \pm 5.3$  msec. in injecting and  $13 \pm 4.9$  msec. in inhaling patients. Cardiovascular changes were only mild after heroin administration. Craving-scores declined immediately after heroin administration in both administration groups. Subjective heroin effect was rated more positively in heroin inhaling than in injecting patients, despite the lower  $C_{max}$  levels following heroin inhalation. In both groups, in this blinded study heroin dose increments were more appreciated than dose reductions. Increments of 50% of the regular heroin dose did not cause any serious side effect.

Diacetylmorphine, or pharmaceutically prepared heroin, is prescribed in several European countries as maintenance treatment for patients with severe heroin addiction, who failed in conventional treatments. In several clinical trials, high doses of heroin have been administered to opioid-addicted patients, under stringent surveillance in special out-patient clinics. Heroin-assisted treatment programs in the UK, Switzerland and The Netherlands have shown good feasibility (Perneger *et al.* 1998; van den Brink *et al.* 2003). The Swiss and Dutch studies provided evidence that treatment with heroin on medical prescription significantly improved mental, social and physical condition of heroin-addicted patients. Compliance and responding rates were high in these studies. Heroin-assisted treatment is currently con-

sidered in other countries e.g. Spain, Germany, Belgium and Canada (Fischer *et al.* 2002).

Beside intravenous use, illicit heroin is also used by a smoking technique called “chasing the dragon”. In chasing the dragon, heroin base is heated on tin foil above a cigarette lighter, controlled by the patient. The heroin vapours generated by heating are inhaled into the lungs, using a straw in the mouth. The name of this smoking technique refers to the way opium was smoked by the Chinese in the 1950’s (Strang *et al.* 1997). Epidemiological studies in heroin addicts have consistently indicated that “chasing the dragon” is nowadays the predominant route with heroin self-administration in The Netherlands (Hartgers *et al.* 1991). Therefore, in the Dutch heroin-assisted treatment programme, heroin hydrochloride for injection and heroin base for inhalation by “chasing the dragon” technique were used in two parallel studies. In this article, heroin inhalation refers to smoking heroin by “chasing the dragon”.

Although heroin administration by “chasing the dragon” appears to be a feasible treatment like intravenous heroin administration, not much is known about the pharmacokinetic profile of this specific administration method. In two studies, estimation of bioavailability of heroin inhalation was based on urine data (Mo & Way 1966; Hendriks *et al.* 2001). Jenkins *et al.* (1994) described the pharmacokinetic features of a single draught of heroin vapours in two addicts, based on plasma data (Jenkins *et al.* 1994). To our knowledge, no pharmacokinetic data of repeated heroin inhalation by chasers based on plasma concentration time curves in human beings are available. Therefore, a pharmacokinetic-pharmacodynamic study was performed on a group of heroin inhalers, who were treated in the Dutch heroin-assisted treatment programme. Furthermore, such data were also collected from intravenous users in a parallel study with similar design.

Heroin is a semi-synthetic morphine ester, with two acetyl groups coupled to the 3- and 6-hydroxyl groups of morphine (fig. 1). Esters like heroin are thought to pass the blood-brain barrier more rapidly than its precursor product morphine, and would therefore account for a larger pharmacodynamic potency compared to morphine (Oldendorf *et al.* 1972). After absorption, heroin is rapidly hydrolysed to 6-monoacetylmorphine and morphine by serum and liver esterases. Furthermore, heroin metabolite morphine is conjugated to glucuronides (fig. 1). Heroin is con-

sidered as a prodrug that mainly acts by its agonistic metabolites 6-monoacetylmorphine (6-MAM), morphine (MOR) and morphine-6-glucuronide (M6G) (Inturrisi *et al.* 1983; Selley *et al.* 2001). The major metabolite, morphine-3-glucuronide (M3G) has virtually no affinity for  $\mu$ -opioid receptors, and therefore displays no agonistic activity. M3G accumulation is thought to be related to neurotoxic effect of long-term morphine use (Smith 2000). Since metabolites of heroin plays an important role in efficacy and toxicity of heroin, not only the pharmacokinetic parameters of heroin, but also those from the major metabolites were investigated in this pharmacokinetic-pharmacodynamic study. To study linearity of heroin kinetics, steady-state heroin doses were varied with a dose increment of plus 50%, and a dose reduction of minus 33%.

Furthermore, the influence of several co-variates such as creatinine clearance, liver function tests, body weight and body surface area, on pharmacokinetics of heroin and its metabolites was studied in this randomised, double blind study. The correlation between plasma levels and subjective appreciation of heroin use or craving could therefore be studied unbiased. Furthermore, reaction time tests, blood pressure, skin temperature and heart rate were assessed.

## Materials and Methods

**Patients.** Male patients, who were on combined heroin with methadone treatment for a period of at least 12 months, and who responded well to this treatment according to the predefined criteria in the protocol of the Dutch Heroin on Medical Prescription Research Project, participated in the study (for criteria, see van den Brink *et al.* (2003)).

For this pharmacokinetic-pharmacodynamic study, the participants had to have reasonable adequate haematological, renal and hepatic functions before entering the study (haemoglobin  $>8.0$  mmol/l, serum creatinine concentration  $<125$   $\mu$ mol/l, serum gamma glutamyl transferase (GGT) and liver amino transferases ASAT and ALAT less than twice the upper limit of normal). Patients who were on treatment with HIV medication, cimetidine or MAO-inhibitors were excluded. All other co-medication besides the prescribed opioids was allowed, if this medication was intended for chronic use, and no dose changes had been made for a period of at least one month before entering the study.

Body mass index was calculated from each participant by dividing weight (in kilograms) by square length (in meters). Body surface area was calculated following the DuBois-DuBois formula. Renal functioning of each participant was calculated from serum creatinine following Cockcroft-Gault equation.

Participation on this study was completely voluntary, and written informed consent before entering the study was obtained from all patients. Protocol and consent form were approved before the start of the study by the Committee of Medical Ethics of the Slotervaart Hospital in Amsterdam. The study was performed according to Good Clinical Practice regulations.

**Design and setting.** Participants were hospitalised in a research clinic, during the 4 day trial (Kendle Clinical Pharmacology Unit, Utrecht, the Netherlands). They were all on steady-state treatment with heroin and methadone for at least 12 months, and received heroin twice daily and methadone once daily. The maximal sustained single heroin dose for entering this study was 300 mg. No limitations in the methadone dose were set. Methadone and heroin dosage regimens had to be constant at least four weeks before en-

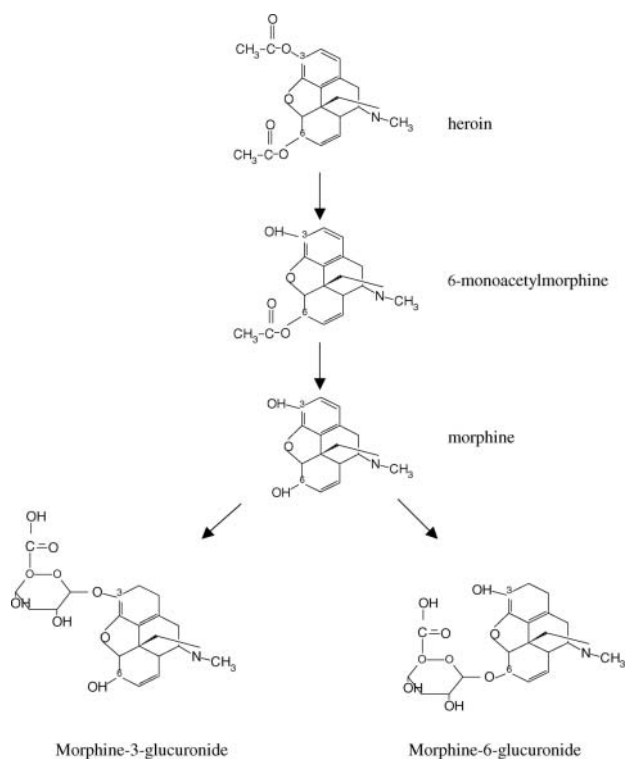


Fig. 1. Metabolism of heroin (diacetylmorphine) and its major metabolites. Heroin is hydrolysed to 6-monoacetylmorphine and morphine. Glucuronides are conjugated to the 3' or 6' position of the phenantrene ring.

tering this study. In this study, regular methadone dosages were given once daily, 2 hr after the heroin morning administration. The dose interval between the heroin morning and evening dose was 8 hr. Pharmacokinetic and pharmacodynamic assessments were performed from 1 hr before to 8 hr after each heroin morning dose.

On the first day of the study, regular steady-state heroin doses for the particular patient were given. On the following three days, heroin morning dose levels were varied double blind from 67–100–150%, in a random order. The heroin evening dose remained unchanged during the study.

Intravenous users were asked to administer heroin by autoinjection, in one fluent movement as a bolus. Heroin inhalers got a period of maximal 30 min. to inhale the heroin dosage. This period of 30 min. is in accordance with the maximal sustained inhalation time in the outpatient clinics. For blinding reasons, heroin base was presented in a scattered way on a piece of tin foil of 10×20 cm. Furthermore, the heroin inhalation dose was offered in two unequal portions of respectively 40% and 60% of the total dose. A 4 min. pause was scheduled when the first portion was completely inhaled. In this pausing period, a blood sample was drawn and some pharmacodynamic assessments took place.

The use of alcohol, cannabis, cocaine, and opiates besides trial medication was not allowed during the trial period. Luggage was checked for these items. The study took place in a closed ward, and visitors were not allowed. Alcohol breath tests were taken before each heroin morning dose during the study. All plasma samples were controlled for cocaine use.

*Plasma sampling and bioanalysis.* Blood samples were drawn from an intravenous cannula, placed in the underarm. In intravenous users, the cannula was placed in the arm opposite to the injection site. Blood samples were taken 10 min. before start of heroin administration and at 2, 5, 10, 15, 30, 45, 60, 115, 180, 240 and 480 min. after heroin administration. For inhalers, an additional sample was collected 2 min. after 40% of the heroin dose was used.

Blood was sampled in 6 ml glass tubes, containing 15 mg sodium fluoride and 12 mg potassium oxalate. The tubes were put in ice water, immediately after sampling. Within 15 min. after sampling, the blood samples were centrifuged at 2000×g for a period of 5 min. The plasma fraction was collected and snap-frozen. Plasma samples were kept at –30°, and defrosted in ice water before bioanalysis. Methadone, heroin and its metabolites 6-MAM, MOR, M3G and M6G were quantified simultaneously, by LC-MS-MS. The lowest limit of quantification (LLQ) was 5 ng/ml, for all quantified analytes. The accuracy, and precision of the analysis method met the current standards of the Food and Drug Administration Guidelines. For further details regarding the bioanalytical method, see Rook *et al.* (2005).

In the same analytical run, cocaine and its metabolites norcocaine and benzoylecgonine were qualitatively detected in plasma to verify whether the subject had used cocaine before or during the study.

*Medication.* All heroin formulations used in this study were similar to the formulations that are normally used in outpatients' settings. Pharmaceutically prepared heroin base for inhalation, and heroin hydrochloride for injection, were produced under Good Manufacturing Practice conditions. For heroin inhalers, caffeine was added to the heroin base formulation in a 1:3 ratio. Caffeine is known to enhance the volatilisation of heroin, by lowering the melting point of heroin (Huizer 1987). Heroin hydrochloride for injection was dissolved in 3 ml Water for Injection, immediate before administration, in a laminar airflow hood under sterile conditions. For blinding reasons, all dosages were dissolved in the same volume of Water for Injection. Racemic methadone syrup came from the hospital pharmacy. Other co-medication besides heroin and methadone came from community pharmacies.

*Pharmacokinetic analysis.* Pharmacokinetic parameters for all compounds were calculated by non-compartmental analysis, using Win-

Nonlin software (Standard Edition Version 3.0, 1999, Pharsight, Mountain View, CA, USA). The area under the curve of the observed concentrations (AUC) was determined by the log-linear interpolated trapezoid rule, with extrapolation to infinity by the elimination constant  $k_e$  (slope of terminal part of the concentration-time-curve on semi-log scale). When the plasma concentrations of the analytes were above the LLQ at the null measurement ( $C_0$ ), the AUC was corrected by subtracting  $C_0/k_e$ .

The bioavailability (F) of heroin by the inhalation route was estimated using the following equation:

$$F = \frac{\text{mean}(\Sigma(\text{AUC}_{\text{heroin inhalation}}))}{\text{mean}(\Sigma(\text{AUC}_{\text{heroin intravenous}}))} \cdot \frac{\text{mean}(\Sigma(\text{AUC}_{\text{heroin intravenous}}))}{\text{mean}(\Sigma(\text{AUC}_{\text{heroin inhalation}}))}$$

Clearance (Cl) and distribution volume (Vd) were calculated for intravenous heroin data, and Cl/F and Vd/F were calculated for inhaled heroin. Since it is known that virtually all heroin is extensively metabolised into 6-MAM, without loss of heroin into urine, the virtual dose of 6-MAM would be practically similar to the actual heroin dose (Yeh *et al.* 1976). Cl/(F) and Vd/(F) were therefore also calculated for the metabolite 6-MAM.

$\text{AUC}_{0-\text{inf}}$  and elimination half-life ( $T_{1/2}$ ) were calculated for heroin and all its measured metabolites. The maximal plasma concentrations ( $C_{\text{max}}$ ) of heroin and its metabolites and time point at which the  $C_{\text{max}}$  was measured ( $T_{\text{max}}$ ) were derived directly from plasma-concentration-time curves.

*Pharmacodynamic assessments. Simple reaction time (SRT)* was measured by a computerised neuropsychological test battery (FePsy version 6.5, Stichting Epilepsie Instellingen Nederland, Heemstede, The Netherlands). Reaction times to single visual stimuli were measured. In one session, 30 stimuli were presented, both for the dominant and the non-dominant hand. The inter-stimuli intervals varied at random from 2.5 to 4 sec. Stimulus exposure continued until a response, by pushing a button, was given by the subject. The reaction times are expressed in millisecond (msec). Reaction time assessments were taken 20 min. before heroin administration and 20, 100, 150 and 260 min. after heroin administration.

*Blood pressure, heart rate and skin temperature.* Systolic and diastolic blood pressure, and heart rate were measured non-invasively and simultaneously 60 min. before and 13, 28, 70, 110, 145 and 250 min. after heroin administration. Heart rate was derived from lead 2 of the ECG. Heart rate, and blood pressure, were measured after a 3 min. resting period in supine position. To assess the effects of heroin use under orthostatic conditions, blood pressure and heart rate were also measured after standing erect for 1 min.; from the supine position. Orthostatic tension was calculated as the difference between systolic pressure, after orthostatic stress, minus systolic pressure, measured in supine position.

Skin temperature was measured simultaneously with cardiovascular functions, by a sensor tapered on the hand. All assessments were taken with Datex-Ohmeda S/5 light monitor equipment (Datex-Ohmeda Inc, Tewksbury, MA, USA).

*Subjective effects.* Ratings of subjective drug effects were measured by means of visual analogue scales (VAS). The rates of appreciation of the effects of the heroin intake were measured on a scale varying from –10 cm (“very bad effect”) to +10 cm (“extremely good effect”). The appreciation VAS scales were collected in the pre-scheduled pause during the inhalation sessions, and 6, 35, 90 and 260 min. respectively after completely finishing heroin inhalation or injection.

Craving for heroin use was measured on a VAS from 0 (none craving at all) to 20 cm (feelings of extreme craving). Craving was measured 30 min. before heroin morning administration, and 6 and 50 min. after heroin morning administration.

The Physical Symptom Questionnaire (PSQ) contained subscales for withdrawal symptoms (7 items), positive drug effects (3 items)

and signs of overdose (8 items) (Hendriks *et al.* 2001). Withdrawal symptoms that were listed were “feeling cold”, “running nose”, “muscular tension”, “muscular aching”, “gooseflesh”, “yawning”, and “restlessness”. The following positive drug effects, “feeling high”, “pleasant feeling in stomach”, “itchy nose”, and the following overdose symptoms, “giddiness”, “light-headedness”, “sleeping limbs”, “tickling”, “sweating”, “nausea”, “squeezed throat”, and “palpitations”, were listed. The scores for each item varied from zero (no sign at all) to three (extreme). The maximal scores for the subscales were respectively 21, 9 and 24. PSQ was measured at baseline and at 6, 35, 90 and 260 min. after heroin administration.

Inquiries after adverse events took place at base level and respectively 15 min., 2 and 12 hr after heroin intake. Serious adverse events were defined as any symptom that compelled immediate medical intervention. Six hr after each blinded morning dose the subjects were asked to estimate the dose level, for conformation of effectiveness of the blinding procedure.

*Statistical analysis: demographic and pharmacokinetic data.* Differences between inhalers and the intravenous group regarding demographic and pharmacodynamic features were tested with Pearson's correlation tests. Differences in  $t_{1/2}$  of heroin or its metabolites, between the inhalation and the intravenous group, were tested using independent sample t-tests. Pharmacokinetic-pharmacodynamic relationships were studied univariately with linear regression analysis. Significant co-variables were entered in repeated measurements ANOVA or multiple linear regression models.

The inter-subject variability of the pharmacokinetic parameters, were calculated by dividing the standard deviations by the means. The intra-individual variability of the AUC's was based on two AUC outcomes pro person, following regular heroin dosages. The standard error of bioavailability F was calculated by adding the sum of co-variances of the numerator (inhalation AUC's + intravenous dosages) and the sum of co-variances of the denominator (intravenous AUC's + inhalation dosages).

*Statistical analysis: pharmacodynamic data.* Differences between the baseline (E0), and post heroin or methadone administration levels of pharmacodynamic parameters (Et), were tested with paired sample t-tests. The mean percentage of change, after heroin administration, was calculated as  $((Et-E0)/E0)*100$ . When the impact of intravenous use was compared to effects of inhalation, independent sample t-tests were used.

Pharmacodynamic measurements were also analysed with repeated measurements ANOVA, with time-points of assessments and dose-level as within factors and the way of heroin administration and co-administered medication as between factors. Methadone

dose or methadone plasma trough concentrations, were introduced in the repeated measurements ANOVA model as co-variables. Measurements of the subjective VAS and PSQ, taken during the first day of the trial, when regular heroin dosages were administered un-blinded, were not taken into account during analysis.

All statistical calculations were performed with SPSS, version 11 (Statistical Package Service and Solutions Inc., Richmond, CA, USA. 2001). All tests for significance were two tailed and the P-value required for significance was set at 0.05.

## Results

### *Patients.*

Fourteen patients using intravenous heroin, and 10 patients inhaling heroin, were selected for this study. All patients were on a twice-daily heroin administration regimen. Regular blood sampling was not possible from one heroin inhaler and three intravenous users due to serious venous sclerosis. Only the results of the 20 subjects (9 inhalers and 11 intravenous users), whose blood samples could be taken and pharmacokinetic parameters could be assessed, are presented in this article. Baseline demographic data and steady-state doses of both study groups, heroin inhalers and injectors, are shown in table 1. No major differences between inhalers and injectors were detected, except that higher methadone doses were prescribed in heroin injectors compared to heroin inhalers ( $P=0.04$ , Mann-Whitney).

Cocaine was not detected in any plasma sample during the study. Traces of the long-lasting cocaine metabolite, benzoylecgonine, were found in the plasma of 5 participants, but only within the first 24 hr of the study. Benzoylecgonine is biologically inactive and no pharmacodynamic interaction with opioid effects could therefore be expected.

### *Pharmacokinetics.*

#### *Pharmacokinetic parameters after intravenous heroin administration.*

The plasma-concentration time curves of heroin and its metabolites are shown in fig. 2 and 3. Pharmacokinetic parameters of heroin and its major metabolites are summarised

Table 1.

Characteristics of participants (median, range).

|                                      | Intravenous (n=11) | Inhalation (n=9) |
|--------------------------------------|--------------------|------------------|
| Age (years)                          | 40 (32–54)         | 45 (34–48)       |
| Ethnicity (number of Caucasians)     | 9                  | 8                |
| Weight (kg)                          | 73 (57–101)        | 73 (62–132)      |
| Length (cm)                          | 1.81 (170–189)     | 1.80 (165–190)   |
| Body mass index (kg/m <sup>2</sup> ) | 22.0 (19.2–30.5)   | 24.1 (19.6–38.6) |
| Body surface area (median)           | 1.78 (1.49–2.26)   | 1.78 (1.58–2.75) |
| Hb (mmol/l)                          | 8.7 (7.3–9.8)      | 8.7 (8.2–10)     |
| ALAT (U/l)                           | 36 (13–69)         | 21 (14–48)       |
| ASAT (U/l)                           | 34 (11–92)         | 18 (5–41)        |
| GGT (U/l)                            | 27 (15–45)         | 19 (15–100)      |
| Creatinine (μmol/l)                  | 67 (56–110)        | 69 (45–101)      |
| Creatinine clearance (ml/min.)       | 125 (66–110)       | 131 (61–165)     |
| Steady-state heroin dose (mg)        | 287.7 (225–300)    | 283.3 (200–300)  |
| Methadone dose (mg)                  | 70 (40–100)        | 55 (30–70)       |
| Benzodiazepine co-medicated (n)      | 5                  | 3                |

Table 2.

AUC,  $C_{\max}$  and  $t_{1/2}$  (mean $\pm$ S.E.) of heroin and its metabolites after intravenous heroin administration or heroin inhalation. AUC and  $C_{\max}$  are presented after reduction of regular heroin dose (67%), after steady-state dose (100%) and after heroin dose increment (150%).  $t_{1/2}$  is calculated from terminal elimination constants of data of all dose levels together.

|        | AUC iv<br>hr $\cdot$ $\mu$ mol/l | AUC inh<br>hr $\cdot$ $\mu$ mol/l | $C_{\max}$ iv<br>$\mu$ mol/l | $C_{\max}$ inh<br>$\mu$ mol/l | $t_{1/2}$ iv<br>min. | $t_{1/2}$ inh<br>min. |
|--------|----------------------------------|-----------------------------------|------------------------------|-------------------------------|----------------------|-----------------------|
| Heroin |                                  |                                   |                              |                               | 3.77 $\pm$ 0.39      | 3.24 $\pm$ 0.26       |
| 67%    | 0.80 $\pm$ 0.08                  | 0.40 $\pm$ 0.07                   | 7.54 $\pm$ 0.97              | 1.70 $\pm$ 0.23               |                      |                       |
| 100%   | 0.89 $\pm$ 0.06                  | 0.47 $\pm$ 0.07                   | 8.43 $\pm$ 0.60              | 1.85 $\pm$ 0.23               |                      |                       |
| 150%   | 1.04 $\pm$ 0.11                  | 0.79 $\pm$ 0.23                   | 9.48 $\pm$ 1.05              | 2.83 $\pm$ 0.96               |                      |                       |
| 6-MAM  |                                  |                                   |                              |                               | 21.98 $\pm$ 0.85     | 25.59 $\pm$ 0.85      |
| 67%    | 0.94 $\pm$ 0.05                  | 0.38 $\pm$ 0.06                   | 3.81 $\pm$ 0.45              | 0.60 $\pm$ 0.07               |                      |                       |
| 100%   | 1.47 $\pm$ 0.06                  | 0.54 $\pm$ 0.06                   | 5.28 $\pm$ 0.39              | 0.88 $\pm$ 0.06               |                      |                       |
| 150%   | 2.22 $\pm$ 0.14                  | 0.81 $\pm$ 0.12                   | 8.02 $\pm$ 1.08              | 1.19 $\pm$ 0.16               |                      |                       |
| MOR    |                                  |                                   |                              |                               | 176.78 $\pm$ 5.68    | 184.31 $\pm$ 7.16     |
| 67%    | 6.73 $\pm$ 0.60                  | 2.70 $\pm$ 0.33                   | 1.91 $\pm$ 0.14              | 0.67 $\pm$ 0.7                |                      |                       |
| 100%   | 9.07 $\pm$ 0.61                  | 3.65 $\pm$ 0.34                   | 2.90 $\pm$ 0.13              | 0.95 $\pm$ 0.07               |                      |                       |
| 150%   | 13.06 $\pm$ 1.41                 | 4.76 $\pm$ 0.74                   | 4.73 $\pm$ 0.42              | 1.32 $\pm$ 0.15               |                      |                       |
| M3G    |                                  |                                   |                              |                               | 275.86 $\pm$ 6.17    | 282.75 $\pm$ 10.06    |
| 67%    | 54.13 $\pm$ 4.42                 | 25.46 $\pm$ 2.05                  | 6.92 $\pm$ 0.36              | 3.65 $\pm$ 0.45               |                      |                       |
| 100%   | 69.76 $\pm$ 2.91                 | 34.38 $\pm$ 2.23                  | 9.29 $\pm$ 0.47              | 4.95 $\pm$ 0.36               |                      |                       |
| 150%   | 94.81 $\pm$ 7.69                 | 50.11 $\pm$ 6.20                  | 14.71 $\pm$ 1.22             | 6.83 $\pm$ 0.88               |                      |                       |
| M6G    |                                  |                                   |                              |                               | 267.56 $\pm$ 9.06    | 240.26 $\pm$ 8.38     |
| 67%    | 7.06 $\pm$ 0.83                  | 3.91 $\pm$ 0.31                   | 0.99 $\pm$ 0.16              | 0.66 $\pm$ 0.06               |                      |                       |
| 100%   | 9.31 $\pm$ 0.68                  | 5.80 $\pm$ 0.46                   | 1.47 $\pm$ 0.13              | 1.00 $\pm$ 0.07               |                      |                       |
| 150%   | 12.13 $\pm$ 1.39                 | 8.09 $\pm$ 0.07                   | 2.17 $\pm$ 0.30              | 1.45 $\pm$ 0.18               |                      |                       |

(iv=intravenous, inh=inhalation, 6-MAM=6-monoacetylmorphine, MOR=morphine, M3G=morphine-3-glucuronide, M6G=morphine-6-glucuronide).

in table 2. Heroin plasma concentration declined rapidly after an intravenous injection of a bolus, and could not be detected after 45 min. The decline in heroin plasma concentration curve is biphasic: an initial ultra-rapid distribution phase ( $t_{1/2}$ : mean 2.0, 95% CI 1.8–2.2 min.) followed by a rapid elimination phase ( $t_{1/2}$ : mean 3.7, 95% CI; 3.0–4.4 min.). 6-MAM was immediately formed after intravenous injection of a bolus of heroin.  $C_{\max}$  was already measured 2 min. after intravenous administration. The mean CI of heroin was estimated as 930 l/hr (95% CI 799–1061 l/hr) and of 6-MAM as 607 l/hr (565–648 l/hr). The mean volume of distribution was estimated as 96 l (95% CI 51–141 l) in heroin and as 325 l (95% CI 284–367 l) in 6-MAM. Neither heroin nor 6-MAM was detected in baseline measurements, 16 hr after the last heroin intake the evening before. However, MOR was detectable at baseline in most cases. MOR concentration rose sharply after intravenous administration and  $C_{\max}$  was reached between 2–45 min. (mean 7.8). All plasma samples at baseline contained M3G and M6G. Peak concentrations of M3G and M6G were reached at approximately one hour after heroin injection. The curves of M3G and M6G were parallel on log-linear scale (fig. 3). M3G concentrations exceeded by far the concentrations of heroin and other metabolites.

#### Pharmacokinetic parameters after heroin inhalation.

The inhalation sessions took on average 16 min. (95% CI 14.8–17.2), without considering the pre-scheduled pausing period of 4 min. The mean measured peak concentrations

of heroin after inhalation were about 4 times lower than after intravenous injection. Bioavailability of heroin by inhalation was estimated as 52.3% (95% CI 44–61%). The mean heroin plasma concentration remained stable during the inhalation session, while the mean 6-MAM plasma concentration accumulated during the inhalation period.

The mean CI/F of heroin was estimated as 1939 l/hr (95% CI 1661–2217 l/hr) and of 6-MAM as 1826 l/hr (95% CI 1601–2051 l/hr). Vd/F of heroin and 6-MAM were estimated as 147 l (95% CI 120–174 l) and 1085 l (95% CI 960–1210 l), respectively. All baseline samples contained MOR and morphine-glucuronides.

The ratio between the AUC of M6G and M3G differed between both administration groups from 1:8 in the intravenous group and 1:5.8 in the inhalers (independent t-test:  $P < 0.0001$ ). The terminal half-life of heroin and all measured metabolites after inhalation did not differ significantly from the intravenous data (table 2).

The inter-individual variability in heroin AUC was larger in inhalers than injectors, 31% and 12%, respectively. The intra-individual variability of the AUC in inhalers varied from 9–51% (median 32%), indicating that exposure to heroin was reasonable reproducible for the each individual, following different inhalation sessions.

#### Pharmacokinetic parameters after methadone.

Inhalers received significant lower methadone dosages than injectors (table 1). The mean plasma methadone trough concentration, measured 5 min. before the next methadone

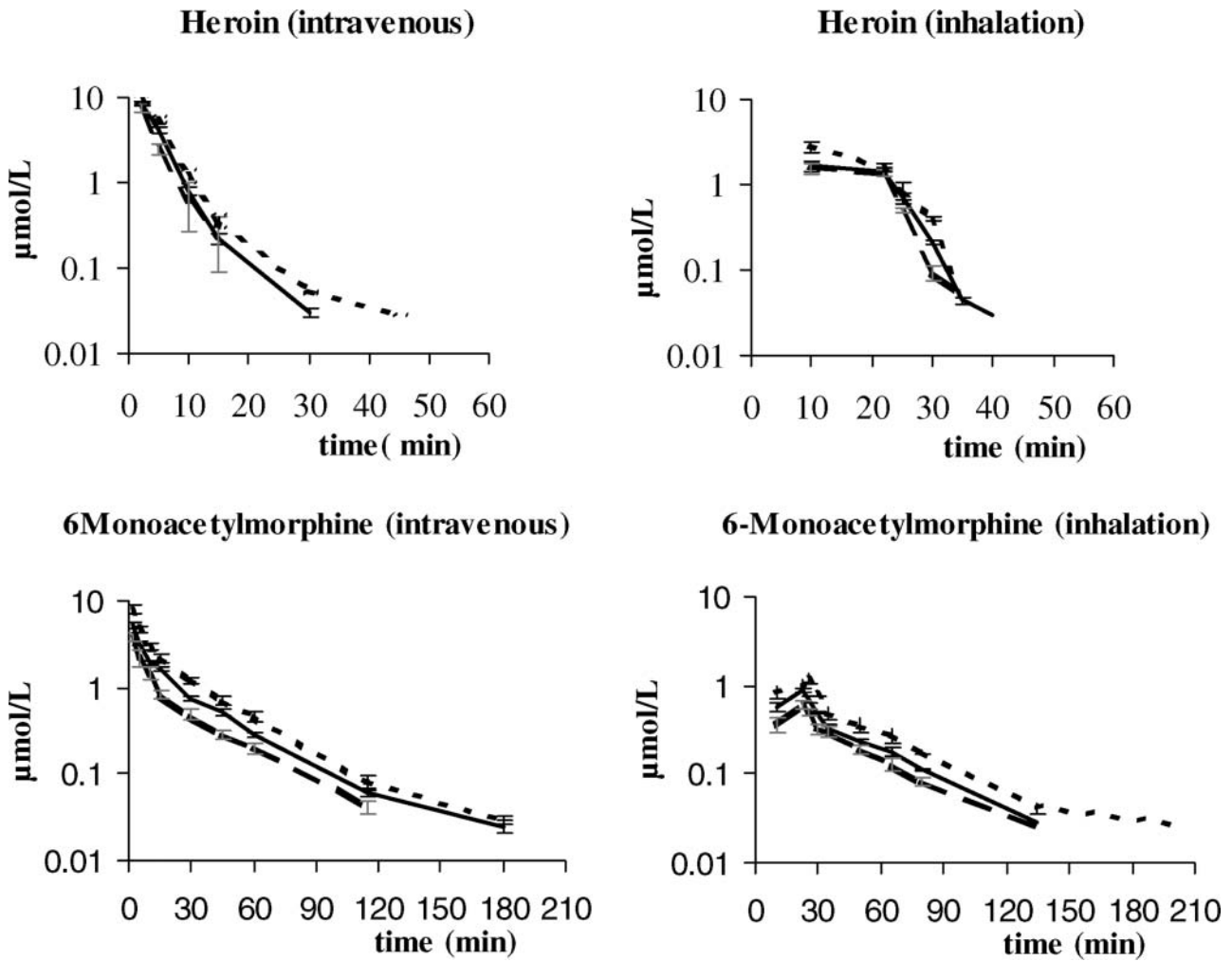


Fig. 2. Mean plasma concentrations ( $\pm$ S.E.) of heroin and 6-monoacetylmorphine at three dose levels after intravenous heroin administration and after heroin inhalation. The intravenous injection ended at  $t=0$ , while the inhalation session started at  $t=0$ . At  $t=10$ , 40% of the heroin dose is inhaled, at  $t=20$ , 100% of the heroin dose is inhaled. In reality, inhalation times varied between subjects, but for clarity are all scheduled measurements are depicted independently of the individual inhalation time. — steady state heroin dose, --- heroin dose reduction -33%, . . . heroin dose increment +50%.

administration, was 230  $\mu\text{g/l}$  (95% CI 193–267  $\mu\text{g/l}$ ) in injectors and 158  $\mu\text{g/l}$  (95% CI 134–183  $\mu\text{g/l}$ ) in inhalers.  $T_{\text{max}}$  of methadone was similar in heroin inhalers and injectors (mean 3.6, 95% CI 3.2–4.0 hr). Methadone concentrations rose on average 70% (95% CI 64–76%) after oral intake.

#### *Dose-linearity.*

Both in inhalers as in the intravenous group, AUC's of heroin and all measured metabolites were linearly related to heroin dose, with significant linear regression coefficients. Analyses with non-linear regression did not improve the fits.

#### *Correlation pharmacokinetic parameters and demographics, biochemistry and creatinine clearance.*

Cl and Vd of heroin were significantly related to body weight. No relationships were found between any pharmacokinetic parameter and other co-variables like age, haemoglobin and liver enzymes levels and benzodiazepine use.

The exposition to morphine glucuronides was inversely related to creatinine clearance. The AUC of M3G increased with on average 8.0% (95% CI 3.3–12.7%) and the AUC of M6G increased with 6.7% (95% CI 2.2–11.4%), when creatinine clearance declined with 10 ml/min. The AUC's of heroin, 6-MAM and MOR were not related to creatinine clearance.

#### *Pharmacodynamics.*

The pharmacodynamic changes after heroin intake are shown in figure 4, 5 and table 3. The changes in pharmacodynamic effects following heroin administration were not statistically significant related to the heroin dose level.

#### *Reaction time, cardiovascular parameters and skin temperature.*

Intravenous administration of heroin on average had a stronger and more prolonged effect on reaction time than

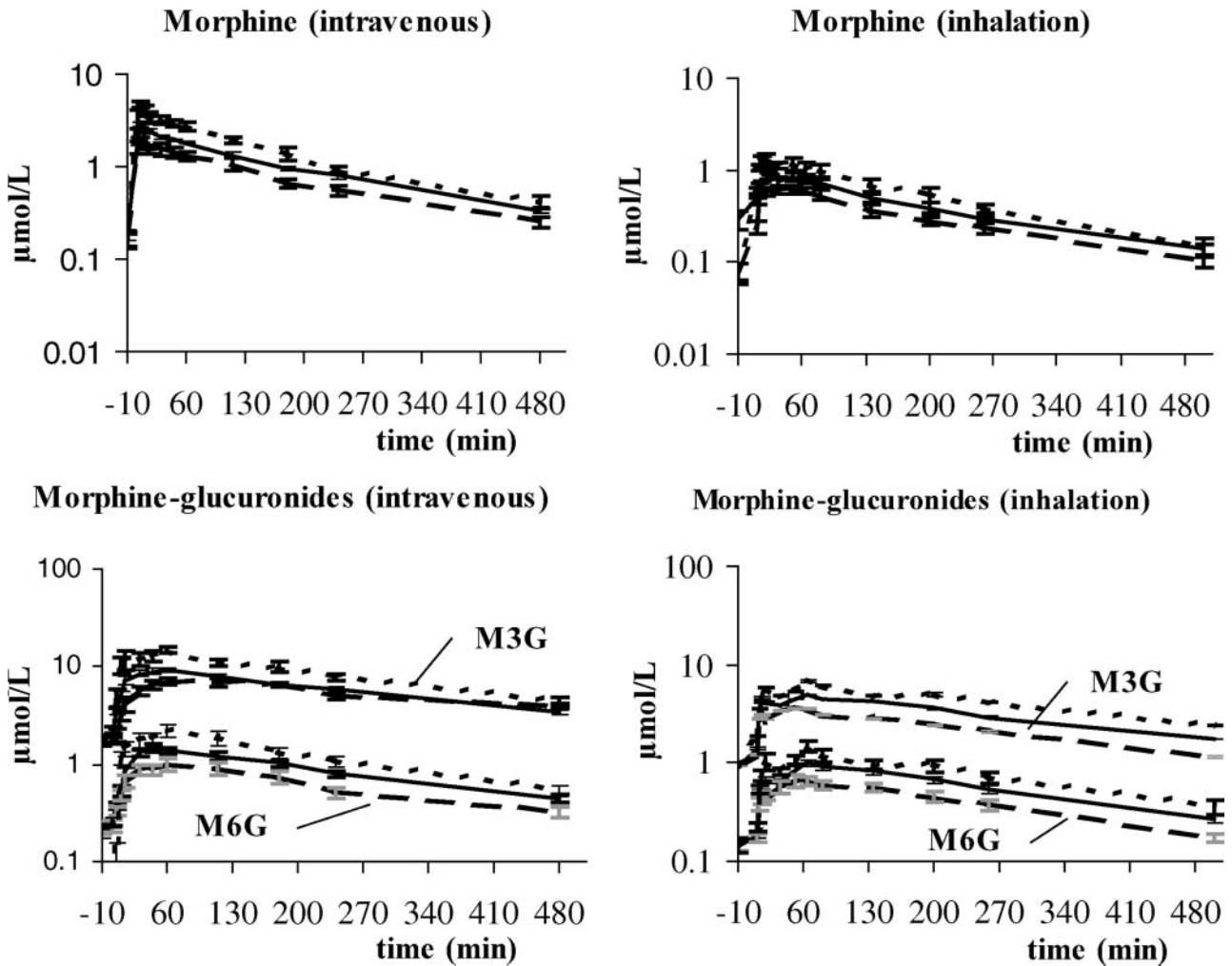


Fig. 3. Mean plasma concentrations ( $\pm$ S.E.) of morphine and morphine-glucuronides at three dose levels after intravenous heroin administration and after heroin inhalation. The intravenous injection ended at  $t=0$ , while the inhalation session started at  $t=0$ . At  $t=10$ , 40% of the heroin dose is inhaled, at  $t=20$ , 100% of the heroin dose is inhaled. In reality, inhalation times varied between subjects, but for clarity are all scheduled measurements are depicted independently of the individual inhalation time. — steady state heroin dose, --- heroin dose reduction -33%, - · - heroin dose increment +50%.

inhalation (independent  $t$ -test  $P=0.03$ ); the mean reaction time increased with 27.8 msec. (95% CI 5–38) in intravenous users versus 12.7 msec. (95% CI 2.4–23) in inhalers.

Changes in heart rate, systolic and diastolic blood pressure, and skin temperature were marginal, less than 5%. At the 150% dose level in heroin injectors, the heart rate initially increased. At lower heroin dose levels and in heroin inhalers, the heart rate declined after heroin administration. Changes in heart rate and blood pressure only reached statistical significance in intravenous users (table 3). Heroin intake had a mild, but statistically significant, declining effect on orthostatic blood pressure, both in inhalers and intravenous users.

#### *Craving and rating heroin effect.*

Craving and subjective heroin effect rating scores are depicted in fig. 4. The rate of craving was neither related to the heroin administration method, the methadone dose, nor

to methadone trough plasma concentrations in this study. Only in heroin inhalers, relief in craving was (reverse) related to heroin dose.

In this double-blind study design, higher doses of heroin were more appreciated than dose reductions, both by inhalers and by injectors (repeated measurements ANOVA;  $P<0.01$ ). The mean VAS scores for appreciation of heroin effect were higher in inhalers than in injectors, despite lower heroin plasma concentrations in inhalers (repeated measurements ANOVA;  $P=0.014$ ).

#### *Physical symptoms and adverse events.*

Physical symptoms, measured by PSQ, were equally rated in the two administration groups and showed no dose-dependency. At baseline, scores of withdrawal symptoms were rather low (median 4, inter quartile range 2–7). Most mentioned item was "feeling restless". The withdrawal symptoms score, declined drastically after heroin administration.

Table 3.

Pharmacodynamic effects of heroin administration. The changes in pharmacodynamic parameters following heroin administration are expressed as mean percentage of change from baseline.  $T_{Emax}$  is the time when the mean maximal effect was measured. Since the changes in pharmacodynamic effects following heroin administration were not statistically significant related to heroin dose level, the pharmacodynamic data of different dose levels, 67–100–150%, were pooled together. The changes from baseline are tested with paired t-test.

|                             |            | Percentage of change<br>(mean, 95% CI) | $T_{Emax}$<br>(min.) | P-value<br>paired t-test |
|-----------------------------|------------|--|----------------------|--------------------------|
| Simple reaction time        | iv         | +10.8 (7.2–14.4)                       | 20                   | 0.022*                   |
|                             | inhalation | +4.5 (1.1–8.1)                         | 20                   | <0.0001*                 |
| Skin temperature            | iv         | +1.9 (0.9–2.9)                         | 15                   | 0.001*                   |
|                             | inhalation | +1.9 (1.0–2.8)                         | 15                   | <0.0001*                 |
| Diastolic blood pressure    | iv         | -3.4 (-5.5 to -1.3)                    | 70                   | 0.002*                   |
|                             | inhalation | -1.3                                   | 70                   | ns                       |
| Systolic blood pressure     | iv         | -2.2 (-4 to -0.4)                      | 30                   | 0.025*                   |
|                             | inhalation | -1.4                                   | 30                   | ns                       |
| Orthostatic tension         | iv         | -3.1 (-4.2 to -1.2)                    | 30                   | <0.0001*                 |
|                             | inhalation | -6.4 (-10.9 to -1.9)                   | 30                   | 0.001*                   |
| Heart rate (initial effect) | iv         | +4.9 (1.2–8.6)                         | 15                   | 0.035*                   |
|                             | inhalation | -1.1                                   | 15                   | ns                       |
| Heart rate (delayed effect) | iv         | -2.1                                   | 30                   | 0.054                    |
|                             | nhalation  | -2.9                                   | 30                   | ns                       |

ns=not statistically significant.

Most mentioned items from PSQ after heroin administration were “sweating”, “light-headedness” and “feeling giddy”, all in a mild degree.

The study physician noted four cases of “face blushing” and one case of “tremors” as observed adverse events that were probably related to heroin use. All events occurred after intravenous administration. No serious adverse events occurred during the study.

*Dose estimation.*

On each day patients were asked to estimate the size of heroin dose that they had received 6 hr earlier. Mismatches of dose-estimations occurred in 41% and 49% of all blinded dosages in inhalers and injectors respectively, indicating that the blinding procedures turned out to be equally successful in both administration groups.

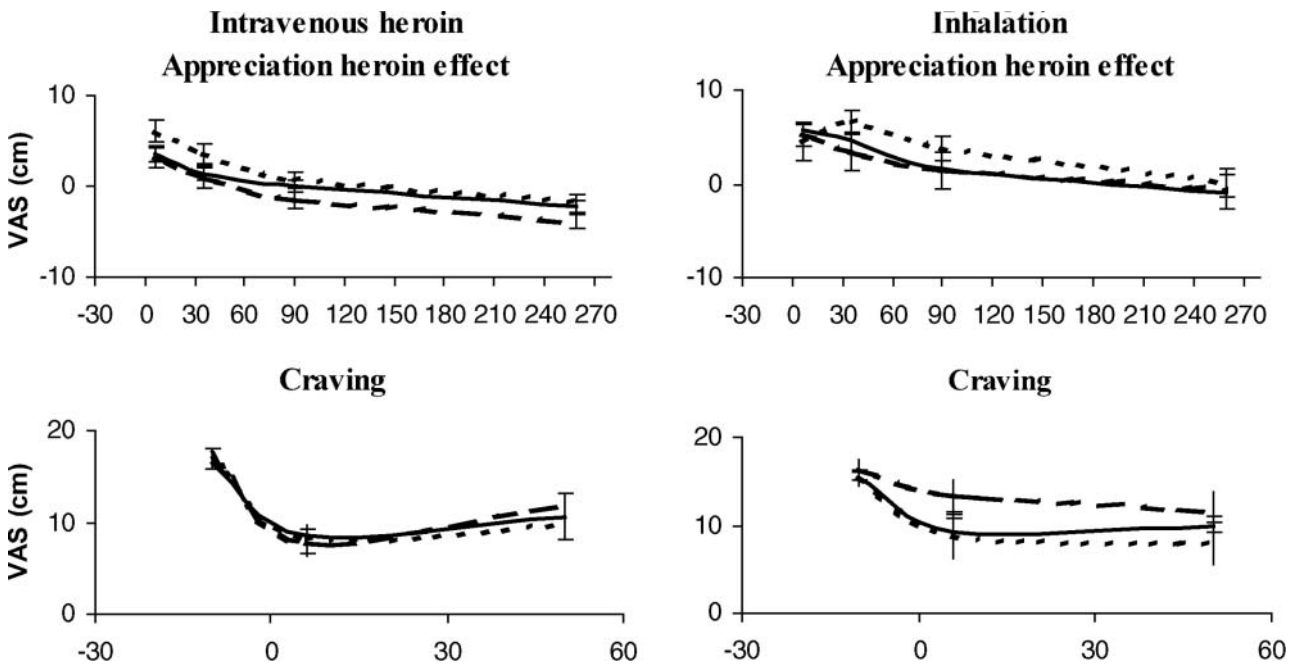


Fig. 4. Scores on visual analogue scales (VAS) of subjective appreciation and craving (means, S.E.). The ratings of the effects of the heroin intake were measured on a scale, varying from -10 cm (“very bad effect”) to +10 cm (“extremely good effect”). Craving for heroin use, was measured on a scale from 0 (none craving at all) till 20 cm (feelings of extreme craving). At t=0 heroin is administered (at 3 dose levels) and at t=120 methadone. — steady state heroin dose, --- heroin dose reduction -33%, - - - heroin dose increment +50%.

### *Pharmacokinetic-pharmacodynamic relationships.*

The relationships between the pharmacodynamic outcomes of this study and pharmacokinetic features like AUC,  $C_{\max}$  of heroin and its metabolites or the duration of administration by inhalation were investigated univariably with linear regression analysis. No clear significant pharmacokinetic-pharmacodynamic relationships were found in this opioid-tolerant population.

Methadone administration caused no significant pharmacodynamic changes. Co-administration of benzodiazepines did not influence reaction time significantly, nor any other pharmacodynamic variable. It should however be noted that the participants using benzodiazepines during this study, were on steady-state treatment with benzodiazepines for a long time. Probably therefore, no significant effects of concurrent benzodiazepine use were found.

### **Discussion**

In this study, the pharmacokinetics of heroin and its major metabolites were studied after heroin inhalation with the “chasing the dragon” technique (n=9) or intravenous heroin injection (n=11).

All participating patients were on long-term heroin-assisted treatment for severe opiate addiction. Heroin doses were varied double blind, 67–100–150% of the regular heroin dose. The heroin doses varied from 67–450 mg in this study. The effects of heroin intake on physiologic functions, such as heart rate, blood pressure and reaction time were studied. In this double-blind study, the subjective ratings of different intravenous or inhaled heroin dosages were assessed as well. The results of this study are discussed below.

### *Pharmacokinetics.*

The bioavailability of the heroin after inhalation was estimated to be 52% (95% CI 44–61%). This estimate of the bioavailability of heroin inhalation is slightly higher compared to estimations of 38 and 45% by Mo & Way (1966) and Hendriks *et al.* (2001), respectively. In these two studies, bioavailability estimates were based on total morphine urine data instead of heroin plasma concentrations like in our study, and total morphine was measured with gas-chromatography after hydrolysis of morphine glucuronides. Underestimation of the total amount of morphine excreted into urine may have occurred in these studies, due to incomplete hydrolysis of morphine glucuronides before analysis (Hackett *et al.* 2002).

Our estimate of the bioavailability was obtained by comparing the AUC's of a group of inhalers to the AUC in a group of heroin injectors (after dose correction). A better estimate of bioavailability might have been made if each individual person had both injected and inhaled heroin. However, all were accustomed to either heroin injection or inhalation before entering this study. Because of the greater health risks associated with intravenous heroin use, it was

decided that crossing-over from inhalation to intravenous use was not allowed in this study.

A part of the heroin dosage is suspected to be lost during “chasing the dragon” procedure due to disintegration of heroin during the heating. The recovery of heroin base in several *in vitro* heroin heating experiments mimicking the “chasing the dragon” method varied from 40 to 75% (Huizer 1987; Brenneisen & Hasler 2002), which resembles the estimated bioavailability rate. This indicates that inhalation over the lungs was a rather efficient heroin administration method, probably because of the large alveolar absorption area ( $\pm 100 \text{ m}^2$  in adults) and the extensive perfusion rate of the lungs of approximately 5 l/min. in adults. Furthermore, the lipophilic character of heroin, and the low ionisation rate at physiological pH ( $\text{pK}_a=7.6$ ) may have contributed to rapid absorption of heroin after inhalation. After absorption in the lung capillaries, inhaled heroin is thought to be transported directly into the arterial brain circulation. The first-pass effect of the liver, which contains many esterase enzymes, is avoided by this administration route.

Several other studies have been published where the pharmacokinetic profile of heroin was studied on the basis of plasma concentration data (Inturrisi *et al.* 1984; Gyr *et al.* 2000; Rentsch *et al.* 2001; Girardin *et al.* 2003). Heroin doses in these studies varied from 5–210 mg. Values for CI and  $t_{1/2}$  after intravenous heroin doses in our study were approximately similar to the other studies on heroin pharmacokinetics, indicating the linearity of the pharmacokinetics of heroin.

In our study, relatively more M6G was formed in the inhalers compared to the intravenous users. The M3G/M6G ratio of 5.8 in inhalers is comparable to data from studies with sublingual morphine administration (Faura *et al.* 1998). The M3G/M6G ratio of 8.0 in our intravenous data is similar to the mean ratio of 7.6, based on 20 intravenous morphine administration studies (Faura *et al.* 1998).

We have chosen to let the participating patients self-administer heroin, in order to mimic the usual out-patient clinical setting of heroin administration as much as possible. In experienced heroin inhalers, the inter-individual variation in the AUC of heroin was estimated to be 31%. Variation in the chasing technique, depth of inhalation and alveolar-capillary capacity between participants may account for this variability.

In auto-injection, the individual speed and force of injection could account for extra variability. However, the inter-individual variability of heroin AUC, on average 12% after auto-injection in our study, is relatively low compared to other studies, where heroin was not auto-administered (Inturrisi *et al.* 1984; Rentsch *et al.* 2001).

In principle variability of pharmacokinetic parameters could also have been related to genetic variance of relevant enzymes, such as serum esterases, which are involved in the hydrolysis of heroin and 6-MAM into morphine, and uridine 5'-diphosphate-glucuronosyltransferases (UGT) that are involved in the glucuronidation process of metabolite morphine (Löttsch *et al.* 2004). Polymorphism of esterase en-

zymes has been described in literature. However, to what extent genetic differences in expressing esterase account for variability in heroin metabolism is not reported. Considering the large availability of esterases throughout the human body, and the broad spectrum of esterases that are involved in heroin metabolism, it is not very likely that low expression rate of one of these enzymes would lead to clinical relevant changes of heroin metabolism.

Mainly UGT 2B7, and to minor extent UGT 1A1 are involved in morphine glucuronidation. However, polymorphisms in the expression of these enzymes did not contribute significantly to the variability of morphine/morphine-glucuronides ratio *in vitro* in human liver cells (Court *et al.* 2003) or *in vivo* in cancer patients (Holthe *et al.* 2002).

#### *Pharmacokinetic parameters, body weight and renal clearance.*

The AUC, Vd and Cl of heroin and 6-MAM were significantly related to body weight and to body weight related properties, like body mass index and body surface area. Probably this is due to the strong lipophilic character of heroin and 6-MAM. To our knowledge, the relationship between the pharmacokinetic parameters of heroin and body weight has not been described before. Considerable weight gain often occurs during heroin-assisted treatment, probably because of decline in drug-seeking behaviour (van den Brink *et al.* 2003). The AUC of heroin and 6-MAM were inversely related to body weight, and weight gain could be a possible contributing factor in diminishing pharmacodynamic effects in continuing heroin-assisted treatment.

A reverse relationship was found between the AUC of the morphine glucuronides and the creatinine clearance. Renal excretion is the main route of clearance of morphine glucuronides. In the target patient population of heroin abusers, a higher prevalence of renal impairment could be expected. Intravenous drug users are known to be at risk for nephropathy as a result of injection contaminants of illicit heroin or as side-effects of HIV or HIV therapy (Dettmeyer *et al.* 1998). Adverse side-effects of morphine like myoclonus and neuroexcitatory behaviour are associated with high plasma concentrations of M3G (Jayawardena & Hill 1991; Smith 2000). Therefore, carefulness in heroin dose elevation in patients with high creatinine serum levels should be exercised.

#### *Pharmacodynamics.*

Both in injectors as in inhalers, the visual simple mean reaction times increased slightly above normal reference value. For inhalers, this change in reaction time was on average 4–5 times smaller than in a similar study, where heroin doses up to 100 mg were administered to treatment-naïve heroin dependents (Hendriks *et al.* 2001). All the subjects in the current study were on heroin-assisted treatment for at least 12 months, and probably tolerance for the heroin effects on reaction time had occurred.

Intravenous administration had a larger and more prolonged effect on reaction time than heroin inhalation in this study. Heroin base-caffeine mixtures (3:1) were adminis-

tered to inhalers, whereas the heroin for injection formulation lacked caffeine. Caffeine is known to improve reactive power and concentration, and adding caffeine to the heroin base formulation may have accounted for differences in reaction time between inhalers and injectors (Sawynok 1995). The bioavailability of inhaled caffeine was estimated as approximately 60% in experienced heroin smokers (Zandvliet *et al.* 2005).

Opiates are known to reduce heart rate and blood pressure after an initial stimulating effect (Schug *et al.* 1992; Mildh *et al.* 2000). Morphine is known to cause orthostatic hypotension in non-addicted patients (Schoenberger 1991), although no exact quantified data concerning this phenomenon has been found in the literature. The effect of opioids on blood pressure is thought to be related to  $\mu$ -opioid receptors in central vasomotoric centre, a reduced sympathetic discharge of the CNS, and peripheral vasodilatation after opioid-induced histamine release. Skin temperature increased significantly after heroin administration in this study, which may be considered as a sign of peripheral vasodilatation due to histamine release (Schug *et al.* 1992).

In this study, the changes in blood pressure, orthostatic tension, heart rate and skin temperature after heroin administration were very small. However, due to the full time schedule of the pharmacokinetic assessments, the first pharmacodynamic measurement took place only after 13 min. after heroin administration. The acute heroin effects were therefore probably missed in this study. Some side-effects in our study, like giddiness after heroin use, were possibly related to the orthostatic pressure lowering effect of heroin.

Although  $C_{max}$  heroin levels were considerable lower in heroin inhalers, the mean VAS scores for rating of heroin effect were significantly higher in inhalers than in injectors. However, there was no cross-over between the two heroin administration methods in this study. Therefore, it is difficult to assess the efficacy of both heroin administration methods.

The highest heroin dose levels of 150% got the highest ranking in our blinded study.

Immediately before heroin use, craving scores were higher in heroin injectors than in heroin inhalers. This is remarkable, since methadone dosages and plasma levels were higher in the heroin injectors group compared to heroin inhalers.

Serious venous sclerosis is very common in patients after long-term intravenous use of illicit substances, and intravenous heroin-assisted treatment may become impossible for some heroin injectors. For these patients, heroin inhalation by “chasing the dragon” is an alternative, provided that patients would get enough opportunity to get used to the inhalation method. Compared to injection, heroin inhalation might have a lower risk of overdosing, because of the more gradual and patient-controlled heroin intake.

Heroin inhalation by “chasing the dragon” resulted in considerable and consistent heroin plasma levels in this study. Alternative parenteral heroin applications in other

studies, such as oral, rectal and subcutaneous administration, resulted in low or non-detectable heroin and 6-MAM plasma levels (Gyr *et al.* 2000; Girardin *et al.* 2003). Heroin and its metabolite 6-MAM are thought to be related to the acute euphoric effects of heroin use, which are appreciated by the users (Seidenberg & Honegger 1998). The lack of sufficient heroin and 6-MAM levels in other parenteral routes of administration might reduce therapy adherence.

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