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Heroin self-administration by means of 'chasing the dragon': pharmacodynamics and bioavailability of inhaled heroin

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Abstract

In this controlled clinical study, the bioavailability and pharmacodynamics of inhaled heroin are evaluated and compared between 'chasing the dragon' and inhalation from a heating device, and at three dose levels, 25, 50 and 100 mg heroin, in two separate study phases. In study phase 1, no differences between the inhalation methods were detected on any of the physiological or behavioral measures, nor in bioavailability. Subjectively, the participants had a strong preference for the method of chasing, which was therefore used in study phase 2. In phase 2, heroin produced a dose-related increase in subjective drug-liking, body temperature and heart rate, and a clear, dose-related decline in reaction time. Linearly dose-related differences were found in the amount of total morphine in urine, amounting to an average of 45% of the parent heroin base received. Based on these findings, it is concluded that chasing is quite an effective route of heroin administration, producing rapid, dose-related subjective and objective effects and a sufficiently high and reproducible bioavailability.

Keywords: Heroin; Addiction; Bioavailability; Pharmacodynamics

1. Introduction

In the Netherlands, a large-scale randomized study is currently being conducted to investigate the effectiveness of medical co-prescription of heroin and methadone, compared to methadone alone, in a population of chronic, treatment-resistant heroin addicts (Van den Brink et al., 1999). The primary goal of the study is to compare the effectiveness and harmful effects of these two treatment regimens, with regard to the somatic and psychiatric status of the patients, their social functioning and social integration, and their illicit drug use. The study, which involves a total of 625 heroin addicted patients, started in the summer of 1998 and is expected to be completed in the beginning of 2002.

In the development of the study protocol for this trial (Central Committee on the Treatment of Heroin Addicts (CCBH), 1997), the researchers were confronted with a typical Dutch phenomenon: the vast majority of the Dutch heroin using population does not inject its heroin, but instead inhales heroin by means of a technique called 'chasing the dragon', or — revealing its Eastern origins — 'chinesing', the common name used in the Netherlands. When chasing, the heroin is put on a piece of aluminum foil, and heated with a cigarette lighter from below. The heroin fumes are then inhaled by the heroin user through a straw.

Originating in Hong Kong in the 1950s, chasing the dragon subsequently spread to other countries in South East Asia in the 1960s and 1970s as well as to the

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Netherlands in the early 1970s, where it became widespread in the course of the 1980s (Grund and Blanken, 1993; Strang et al., 1997). Currently, chasing the dragon has become an established route of heroin self-administration in not only many Asian countries and the Netherlands, but also in certain parts of Spain (among others Andalucia) and regions in the UK (among others London) (Strang et al., 1997). As for the Netherlands, epidemiological studies in both treatment and non-treatment samples of Dutch heroin users have consistently indicated that chasing has been the predominant route of heroin self-administration in the Netherlands in the past 2 decades (Cruts et al., 1997). Currently, 75–85% of Dutch heroin users predominantly or exclusively inhale their heroin (Van Brussel and Buster, 1999; IVV, 1999).

For the trial, the predominance of chasing as the route of heroin self-administration implied that two parallel protocols had to be developed: one in which the heroin would be prescribed in (intravenous) injectable form, and one in which an inhalable form of heroin would be prescribed to the patients. Despite the long tradition of heroin chasing, and the importance of a non-injecting route of heroin administration in the context of HIV/AIDS and hepatitis infection, there has been little systematic investigation of the pharmacokinetic and pharmacodynamic effects of this route of heroin self-administration.

The volatilization of heroin has been investigated in several in vitro studies. Huizer (1987) simulated the practice of chasing the dragon in a laboratory setting by intermittently heating heroin and determined the recovery rate in smoke to be 17% for heroin hydrochloride and 62% for heroin base. Adding caffeine to the heroin base (1:1) enhanced the recovery rate to 76%. In line with these findings, Cook and Jeffcoat (1990) reported a recovery rate of approximately 70% for heroin base at temperatures between 200 and 300°C. Heating the heroin at higher temperatures resulted in substantially increased decomposition. Jenkins et al. (1994) used a computer-assisted smoking device, which delivered as much as 89% of the parent heroin base without decomposition in the smoke, when volatilized at 200°C. In Switzerland, herbal cigarettes impregnated with heroin were investigated by Stalder (1997), as part of the Swiss large-scale study into the effectiveness of medical prescription of heroin to heroin addicts (Uchtenhagen et al., 1997, 1999). Due to decomposition of the heroin at the high temperatures (700–800°C) at the end of the cigarette, a maximum of only 11% of the heroin was delivered in the smoke. Speich (1998) investigated the usefulness of various types of commercially available aerosols for the purpose of heroin inhalation. She determined the maximum output of heroin hydrochloride of a liquid aerosol to be 61%. Using a powder aerosol and a heating device for the volatilization of the heroin base, the maximum output amounted to 53%. In the context of the Dutch trial, Bronner (1997) heated a mixture of heroin base and caffeine at a constant temperature of 300°C, and found a recovery in smoke of 41%. In light of the other findings, this 41% recovery rate seems contradictory. Possibly, the constant — instead of intermittent — heating and the relatively high temperature of 300°C caused the heroin to degrade. In Bronner's study, an average of 6% of the parent heroin was converted to 6-*O*-acetylmorphine, the major pyrolysis product of heroin (Cook and Brine, 1985; Cook and Jeffcoat, 1990), and one of heroin's metabolites with opioid activity. However, 30–40% of the weight of the parent heroin in this study remained behind in the testing-device without determination of its composition, because the applied HPLC method was insufficiently sensitive (Bronner, 1997).

In vivo studies on the bioavailability and dynamic effects of inhaled heroin in humans are rare. Mo and Way (1966) investigated the urinary excretion of heroin as total morphine during 72 h after heroin inhalation by means of chasing ($n=35$) and smoking a heroin cigarette ($n=14$), and found recovery rates of 26% and 14%, respectively. In the study of Jenkins et al. (1994), inhalation of the fumes from a dose of maximum 10.5 mg heroin base by two human subjects resulted in rapid appearance of heroin in blood, with peak concentrations occurring 1–5 min after inhalation. The bioavailability of heroin could not be reliably estimated in this study, as indicated by an apparent overestimation of bioavailability of 130% (Jenkins et al., 1994; Cone, 1998). In the experiments of Stalder (1997), only 5–10% of the heroin dose could be detected in the blood after smoking the heroin cigarettes. In the study of Speich (1998), inhalation of the heroin hydrochloride particles (liquid aerosol) by one subject — who considered the heroin taste to be extremely bitter — resulted in a bioavailability of 58%. Following three inhalation sessions with the powder aerosol by two subjects, the bioavailability of heroin (base) amounted to 35%.

Given the limitations of the currently available data on the effects of inhaled heroin, in terms of low ecological validity, small number of subjects (Jenkins et al., 1994; Speich, 1998), low heroin doses (Jenkins et al., 1994), poor bioavailability (Stalder, 1997) and in general lack of independent replications, the present study was set up to provide more information on the bioavailability and pharmacodynamic effects of this route of self-administration.

The goal of the study was to investigate the inhalation of heroin at dose levels of 25, 50 and 100 mg, and to evaluate two inhalation methods, i.e. chasing the dragon from aluminum foil and inhalation from a heating device. The heating device was developed to standardize the temperature by which the heroin was heated, and — against the background of the randomized clinical study into medically co-prescribed heroin in the Netherlands mentioned before — for its possible usefulness for application in the main trial. The following study questions are asked:

- what is the relative uptake (bioavailability) of heroin in the body after heroin inhalation?

- what are the physiological, behavioral and subjective effects during and following heroin inhalation (two inhalation methods; three dose levels)?
- to what extent are the heroin compound, the method of heroin inhalation, and the heroin dose level accepted by the subjects?
- are the bioavailability and pharmacodynamic effects of inhaled heroin reproducible (between administrations; between individuals)?

2. Methods

2.1. Study chemicals and materials

Pharmaceutical grade heroin base was supplied by a reputable pharmaceutical company. The purity of the heroin was validated by infrared and ultraviolet spectroscopy, high-performance liquid chromatography (HPLC), nuclear magnetic resonance, and mass spectrometry. The heroin base was determined to be 99.47% pure, resulting in approval of the heroin (Bronner, 1997). After validation, three types of tablets were manually produced, containing (a) 25 mg heroin base+100 mg caffeine, (b) 50 mg heroin base+100 mg caffeine, and (c) 100 mg heroin base+100 mg caffeine. In addition, a tablet containing only 150 mg caffeine was manufactured for the purpose of practicing the two methods of inhalation in phase 1. Caffeine was added to heroin base, because caffeine has been demonstrated to lower the temperature of volatilization of heroin base, slightly enhance the recovery of heroin, and reduce its pyrolytic decomposition (Huizer, 1987; Cook and Jeffcoat, 1990). In addition, the combination of heroin base and caffeine has been used in illicit street heroin for decades (Grund, 1993; Grund and Blanken, 1993), and has never been observed to produce specific toxicity. Lastly, although the mixtures described above resulted in different heroin–caffeine ratios (1:4, 1:2 and 1:1), the similar amount of caffeine in each tablet has the advantage of keeping possible influences of caffeine on the subjective and objective effects of heroin constant.

2.2. General study design

The study was conducted in two phases. Phase 1 involved five heroin dependent subjects, and focused on a comparison of the effects of heroin inhalation by means of chasing from aluminum foil and from a heating device, using a fixed dose of 50 mg heroin base. At the end of phase 1, a decision was made regarding the best accepted method of heroin inhalation. Based on the strong preference of all subjects for chasing the dragon during phase 1, the method of chasing was utilized in phase 2 of the study, which took place 4 weeks after the end of phase 1. Phase 2 involved five other heroin dependent subjects, and focused on the effects of heroin inhalation at different dose levels (25, 50 and 100 mg).

2.3. Subjects

The study subjects were recruited from the patient population of the methadone maintenance treatment facility of the Municipal Health Service in Amsterdam. Given the relevance of the present study for the Dutch randomized trial into the effectiveness of medically co-prescribed heroin in chronic, treatment-refractory heroin addicts, all subjects had to meet a set of inclusion criteria which closely resembled those for the protocol on inhalable heroin of the main trial (Van den Brink et al., 1999). These included: a history of DSM-IV heroin dependency of at least 5 years duration, at least 25 years of age, inhalation as the predominant route of heroin self-administration, substantial daily or nearly daily use of illicit heroin, currently in treatment in a methadone maintenance program, and poor physical and/or mental health and/or poor social functioning. Subjects were excluded from participating in the study if they had a period of voluntary abstinence from heroin of at least 2 months duration in the previous year, or if they experienced severe medical, psychiatric or psycho–social problems to such an extent that participation in the study would be contraindicated for health reasons.

The study sample (n=5 in phase 1 and n=5 in phase 2) was all male, in order to reduce variations. The mean age was 40.6 years (range 30–55 years), and the mean duration of regular (i.e. at least 3 days a week) heroin use 14.3 years (range 6–24 years). Most subjects had a significant history of additional regular cocaine use, ranging from 2 to 30 years (mean 14.5 years). On average, the subjects had participated in methadone maintenance treatment for 11.1 years (range 2–20 years). Four of the ten subjects were from Dutch non-ethnic background, five Surinamese, and one other. Although some variability of drug metabolism across different ethnic groups has been demonstrated in earlier research (De Wildt et al., 1999), Surinamese subjects were included in the study-sample, because they constitute a sizeable subpopulation of the Dutch heroin users, and they nearly exclusively use heroin by the route of chasing. Prior to the study, all subjects were on a daily maintenance dose of methadone, ranging from 40 to 100 mg.

During both phases 1 and 2 of the study, the subjects remained in a closed clinical research unit for the study period of 6 days. All subjects underwent medical, psycho–social and psychiatric screening, which involved medical history, physical examination, assessment of hematological and biochemical parameters and administration of the Addiction Severity Index (McLellan et al., 1980; Hendriks et al., 1989) and the Composite International Diagnostic Interview (Robins et al., 1988). In addition, dipstick urinalysis on drugs and breath tests on alcohol were performed at study entry. To prevent concomitant illicit drug use during the study period, all personal belongings of the study subjects were screened at study entry and kept in a closed locker.

The study was conducted under the provisions of the Declaration of Helsinki, as amended in Hong Kong (1989), and according to the ICH/EU guidelines for Good Clinical Practice. The study was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam. All subjects received extensive oral and written information about the study and provided informed consent. The subjects each received a financial compensation of Dfl. 500,- for participating in the study.

2.4. Method of heroin inhalation

In both phases of the study, the inhalation sessions were conducted for each subject individually. In phase 1, the commonly practiced technique of heroin chasing from aluminum foil was compared to the inhalation of heroin, volatilized by heating the heroin tablet on a specially developed brass block. In both cases, i.e. when chasing and when using the heating device, the intact tablet was used without crushing. After heating (see below), the tablet melts quickly and the resulting liquid heroin is similar to that of melted heroin powder. In the case of chasing, the heroin base tablet was put on a piece of aluminum foil of approximately 7–15 cm, which the subject had prepared in advance together with a straw for inhaling the heroin fumes. The heroin base tablet on the aluminum foil was heated from below by the subject with a standard cigarette lighter with an adjustable flame. Over the course of 5–15 s, the heroin base tablet started to melt and to vaporize. By simultaneously moving the lighter and straw, keeping the straw just behind the drop of liquid heroin, the subject inhaled the heroin fumes. Typically, the subjects deeply inhaled the heroin fumes and held the fumes for 10–15 s before exhalation. During this period, the lighter was moved away from the foil, resulting in rapid condensation of the liquid heroin–caffeine mixture.

In the case of the heating device, the heroin base tablet was put on a spoon-shaped piece of aluminum foil, which was placed in a cup on top of a brass cube. The brass cube was placed on a standard heating element (RCT Basic IKA, P.M. Tamson), which was set at a temperature of 300°C at least 30 min before the start of the inhalation session. Melting and volatilization of the heroin base tablet started after approximately 15–25 s, and was intermittently stopped by the subject by removing the spoon-shaped piece of aluminum foil from the brass cube. All other procedures, including the types of straws used and the duration of heroin inhalation, were similar to those for the heroin chasing sessions. For both methods of heroin inhalation, the maximum time allowed for inhaling the heroin amounted to 10 min. Besides standardization of inhalation time, heroin dose, tablet form, and study setting, no additional standardization was applied (e.g. number of puffs allowed, duration of holding the heroin fumes before exhalation) in order to mimic the natural situation of heroin smoking as much as possible.

2.5. Assessments of dependent parameters

The effect parameters were collected 30 min prior to the start of the inhalation session, and then at frequent intervals during and — up to 8 h — following each inhalation session. Effect parameters included: skin temperature (°C), heart rate (bpm), reaction time (in ms), and various ratings of subjective drug effects (see Fig. 1).

The skin temperature was measured with the subject in a sitting position, with a temperature sensor tapered to the inner wrist. The heart rate was also measured in a sitting position, with a sensor tapered to the middle finger of the subject. Reaction time measurements consisted of a simple reaction time test and a digit vigilance task, both presented to the subjects on a computer screen. For the simple reaction time test, the subject was instructed to press a response button as quickly as possible every time the word ‘yes’ appeared on the monitor. In total, 50 stimuli were presented to each subject, with a varying inter-stimulus interval. In the digit vigilance task, a target digit was constantly displayed to the right of the monitor screen and a series of digits was presented in the center of the screen at the rate of 150 per min. The subject was required to press the response button as quickly as possible every time the digit in the series matched the target digit. Whereas simple reaction time measures the power of concentration, the digit vigilance task reflects the continuity of attention. The computerized cognitive assessment system used in this study (Cognitive Drug Research) has been widely used in earlier studies to evaluate the cognitive effects of a broad range of substances and its sensitivity has been established (e.g. Wesnes et al., 1989; Holland et al., 1994).

Concentrations and amounts of total morphine were determined in the urine samples collected over the consecutive 24-h periods by means of gas chromatography–mass spectrometry (GC–MS). GC–MS analyses were performed using a Varian 3400 gas chromatograph.

Ratings of subjective drug effects were collected by means of the ‘Feel’ scale and the ‘Liking’ scale of the single dose questionnaire (SDQ; Fraser et al., 1961). On the SDQ-feel, the subject is asked to rate whether he currently experiences a drug effect (yes, no), and on the SDQ-liking to what extent he likes the drug effect (not at all, slightly, moderately, considerably, extremely). In addition, a 200-mm visual analog scale (VAS) was used to measure ‘good’ versus ‘bad’ effects of the inhaled heroin. Subjectively experienced physiological effects were measured by means of the physiological symptoms questionnaire (PSQ; Powell et al., 1992), which contains a three-item subscale on drug-positive symptoms (pleasant feeling in stomach, itchy nose, feeling ‘high’) and a seven-

time (min)	temperature	heart rate	SDQ-feel	SDQ-liking	VAS	PSQ	reaction time	interview
– 30	•	•	•	•	•	•	•	
+ 1			•	•	•			
2			•	•	•			
5			•	•	•			
10			•	•	•			
+ 11	•	•						
12	•	•						
15	•	•	•	•	•		•	
20	•	•						
25	•	•	•	•	•		•	
40	•	•	•	•	•			
55	•	•						
60	•	•	•	•	•	•	•	
90	•	•						
120	•	•	•	•	•	•	•	
240	•	•	•	•	•	•	•	•
480	•	•	•	•	•	•	•	

Fig. 1. Assessment-schedule of the dependent parameters. The grey-toned area indicates the 10-min inhalation session. SDQ, single dose questionnaire; VAS, visual analog scale; PSQ, physiological symptoms questionnaire; Interview, structured interview on level of control and overall subjective effects.

item subscale on drug-negative symptoms (feeling cold, runny nose, muscular tension, aches and pains, gooseflesh, yawning, restlessness). In both subscales, each item is scored on a four-point scale ranging from 0 (not at all) to 3 (extremely). Lastly, approximately 4 h after each inhalation session, a structured interview was held with each subject to evaluate the perceived level of control and the overall subjective effects of heroin inhalation, with regard to the two inhalation methods (phase 1), and to evaluate the overall subjective effects of heroin inhalation, with regard to the heroin dose received (phase 2). During the inhalation sessions, the subject's psychomotor activity and verbal reactions were constantly registered on audio and video tape.

2.6. Study schedule

Phases 1 and 2 of the study each involved a study period of 6 days. On each day of the study (both phases 1 and 2), the subjects — all methadone maintenance patients — received their oral methadone dose (40–100 mg) between 9.00 and 10.00 am.

2.6.1. Phase 1

On day 1 of the phase 1 study, the two methods of inhalation were practiced by the subjects, utilizing the caffeine only tablet. Day 2 of the phase 1 study was used as a pilot for testing the assessment procedures when subjects had received a 50-mg dose of heroin base. The pharmacodynamic data of this day were therefore not used in the analyses. On the remaining days (days 3–6) of the phase 1 study, the subjects received a daily dose of 50 mg heroin base between 13.00 and 14.00 p.m., chasing or using the heating device on alternating days. Hence, a total of ten observations in five subjects were analyzed for each method of inhalation.

2.6.2. Phase 2

In phase 2 of the study, only the method of chasing was utilized, because the results of phase 1 had indicated that chasing was the best accepted method of heroin inhalation. On the first day of the phase 2 study, the method of chasing was practiced with the caffeine-only tablet. On days 2–6 of the phase 2 study, the subjects received a daily heroin dose of 25 mg (day 2), 50 mg (days 3 and 5), and 100 mg (days 4 and 6) between 13.00 and 14.00 p.m. Hence, the data on the 50- and 100-mg dose are based on ten observations in five subjects. Blinding and/or random ordering of the heroin dose over the days were rejected for safety reasons.

2.7. Data analysis

The analysis of heart rate, skin temperature, reaction time, PSQ, SDQ and VAS scores consisted of simple summary statistics per dose and time point. For the phase 1 data on heart rate, skin temperature, reaction time, SDQ and VAS, an analysis of variance (ANOVA) was conducted to test for differences between the two methods of inhalation, disregarding the order of days. The phase 2 data on heart rate, skin temperature, reaction time, and VAS were analyzed by means of ANOVA to test for differences between dose. The SDQ data of phase 2 were tested by means of Friedman's distribution-free test, due to the non-normal distribution of these data. In each study phase, the analyses are based on five subjects and — with the exception of the 25-mg heroin dose — two (dependent) observations per subject for each method and for the 50- and 100-mg doses.

Change from predose (baseline) was tested (within method or dose) for heart rate and skin temperature by means of the Wilcoxon signed rank test. For the reaction time data of both phases 1 and 2, the general linear models procedure was used to conduct ANOVAs on the main effects of condition (phase 1: inhalation method; phase 2: dose) and of time (time-points of assessments), as well as the interaction between condition and time. A change-test on VAS data was not performed because no baseline data were available. Finally, a change-test for the SDQ-feel data was not performed because all baseline values were negative (do not feel drug effect), and correction was, therefore, not useful.

The interview data (see above) were tested using Fisher's exact test for differences between the two methods of inhalation and between the doses. In all analyses, two-tailed tests were used, and the level of significance was $P \leq 0.05$.

3. Results

3.1. Phase 1

3.1.1. Subjective effects

3.1.1.1. SDQ-feel

Within 1–2 min following the start of the inhalation session, the first subjects began to experience a drug effect (Fig. 2) from the inhaled dose of 50 mg heroin base.

Initial drug effects were reported on the SDQ-feel after 1 min following the start of chasing, and after 2 min when the heating device was utilized. Between 5 and 15 min following the start of inhalation, all subjects reported experiencing a drug effect from chasing. In the case of the heating device, the maximum number of subjects who experienced a drug effect occurred after 10 min, and was reported in 90% of the observations. One hour following the start of the inhalation session, drug effects were still reported in 40% of the observations in the chasing condition, and in 30% of the observations in the heating device condition. Drug effects were reported by a gradually decreasing number of subjects up to 4 h after heroin inhalation. During this time course, less subjects in the heating device condition reported experiencing a drug effect than in the chasing condition. However, no statistically significant differences on the SDQ-feel between the two methods could be detected. After 4 h, (minor) drug effects were still reported in both conditions, in 20% of the observations.

3.1.1.2. SDQ-liking

Concurrently with the SDQ-feel, subjects were asked to rate the extent to which they appreciated the drug effect (if experienced) on the SDQ-liking scale. As Fig. 3 shows the subjects were not very enthusiastic and generally rated their appreciation of the drug effect between the categories 'slightly' and 'moderately'. Only minor and non-significant differences occurred between both inhalation conditions.

3.1.1.3. VAS

As with the SDQ-liking, subjects in both inhalation conditions generally rated their appreciation of the drug effects slightly below the average of the VAS-scale ('good' versus 'bad' effects), with the maximum appreciation occurring between 15 and 40 min after the start of the inhalation session. No statistically significant differences occurred between the two inhalation methods (Fig. 4).

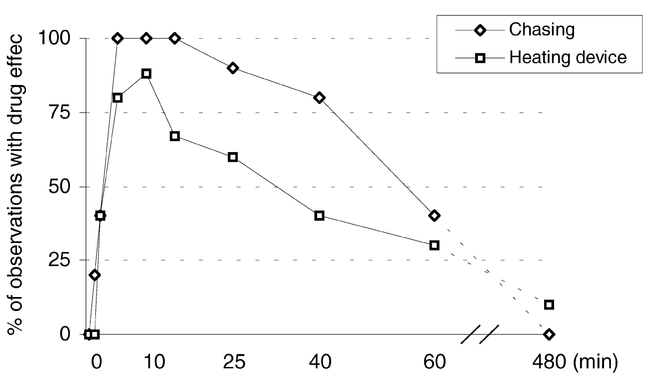

Fig. 2. Percentage of observations in which a drug effect was reported on the SDQ-feel following 50 mg heroin inhalation by means of chasing and from a heating device ($n=5$). Notably, the heroin inhalation session took place in the first 10 min.

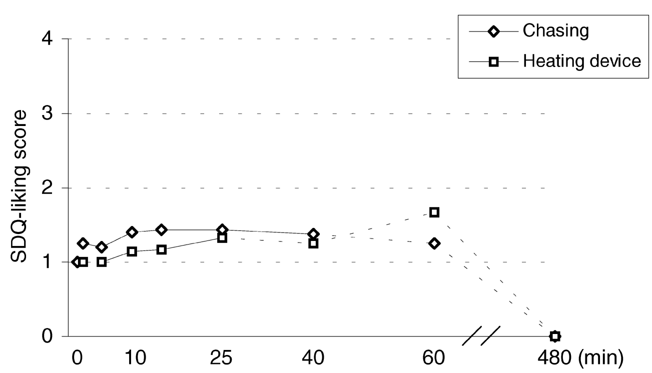

Fig. 3. Appreciation of the drug effect following 50 mg heroin inhalation, rated on the SDQ-liking ($n=5$). 0, not at all; 1, slightly; 2, moderately; 3, considerably; 4, extremely. The intermittent line represents the situation in which less than half of the subjects actually reported a drug effect.

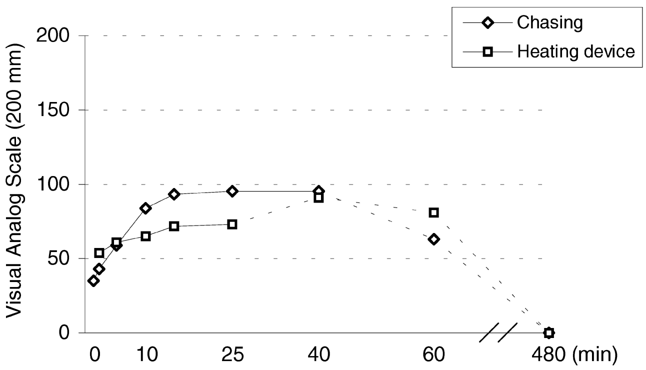

Fig. 4. Subjective rating of 'good' drug effect following 50 mg heroin inhalation, rated on a 200 mm VAS (n=5). The intermittent line represents the situation in which less than half of the subjects actually reported a drug effect.

3.1.1.4. PSQ

Drug-positive symptoms occurred approximately twice as much in the chasing condition than in the heating device condition. The symptom that was reported most often was 'feeling high'. Conversely, drug-negative symptoms occurred almost twice as much when the heating device was used. From these, 'restlessness' was most often reported.

3.1.1.5. Interview on overall judgement of inhalation method

When retrospectively asked about the level of control the subject felt he could exert over the inhalation method utilized that day, the subjects generally gave a much — and statistically significant (P<0.000) — higher rating to the method of chasing than to the method in which the heating device was used (Fig. 5).

On a scale ranging from 0 ('very bad') to 4 ('very good') the average score in the chasing condition amounted to 2.9 ('good'), and in the heating device condition to 0.3 ('very bad'–'bad'). Similar results were obtained when retrospectively asked about the quality of the perceived drug effects from either chasing or inhalation by means of the heating device, although the preference for the effects following chasing did not reach statistical significance (P>0.05). In line with the SDQ-liking and VAS data, none of the subjects were very positive about the perceived drug effect.

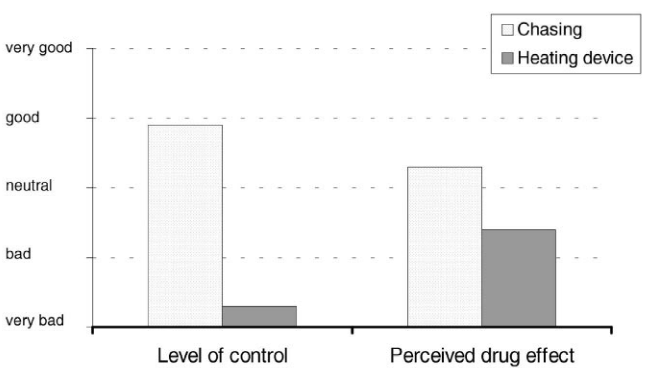

Fig. 5. Rating of perceived level of control when chasing or when using the heating device and overall rating of perceived drug effect following 50 mg heroin inhalation by these two methods (n=5).

Verbal comments of the subjects indicated that heating by means of the heating device was considered too slow to finish the tablet completely within 10 min. The subjects generally considered the heroin dose (50 mg) to be too low, they did not like the 'taste' of the heroin, and they reported that the heroin contained too much caffeine, which affected the inhalation properties of the heroin.

3.1.2. Physiological and behavioral effects

3.1.2.1. Skin temperature

Following the end of the inhalation session (11 min after the start), a mean increase of skin temperature was observed of 0.34°C for subjects in the chasing condition, and of 0.82°C for subjects in the heating device condition. During the subsequent hour, there was a slight tendency towards a decreasing skin temperature. However, the observed differences did not reach statistical significance, neither between the two methods, nor in change from predose level.

3.1.2.2. Heart rate

In both inhalation conditions, a sharp increase in heart rate was observed 10–11 min after the start of heroin inhalation, followed by a rapid return to preinhalation levels during the following 15 min. The observed changes from predose heart rate did not reach statistical significance, although there was a trend towards significance for subjects in the chasing condition, and only directly following the end of the inhalation session (at t=11 min; P=0.07).

3.1.2.3. Reaction time test

Both methods of inhalation produced a clear time dependent effect of heroin on simple reaction time (P<0.05). However, there were no significant time dependent effects on the percentage of targets correctly detected by the subjects in the digit vigilance accuracy task, although a trend towards decreased accuracy could be observed in both conditions. The decline in simple reaction time was identifiable after 25 min following the start of the inhalation session, reached its maximum after approximately 25–60 min, and gradually diminished during the following hours. No differences between the two inhalation methods were observed for either simple reaction time, or digit vigilance accuracy. In addition, there were no significant effects for the interaction between inhalation method and time.

3.1.3. Urinary excretion of total morphine

Concentrations and amounts of total morphine were determined in the urine samples by GC–MS. In the case of chasing, a mean of 14.7 mg total morphine was found per 24-h urine sample (S.D.=6.8; range 1.7–23.7 mg). For the heating device, the mean total morphine per sample amounted to 15.0 mg (S.D.=8.3; range 3.7–26.1 mg). Expressed as percentage of the (50 mg) heroin dose received, a mean of 38% of the heroin was recovered as total morphine for the chasing condition, and a mean of 39% for the heating device condition. No significant differences were detected between the two inhalation methods.

Intra-individual variations in recovery rates were moderate, with maximum differences between the inhalation sessions of the same individual ranging from 16% for subject 4 to 26% for subject 5. Inter-individual variations were larger, the mean recovery rates for the five subjects amounting to 13, 26, 43, 53 and 57%.

At the end of phase 1, a decision was made regarding the best accepted method of heroin inhalation. Based on the strong preference of all subjects for the method of chasing, and in the absence of clinically relevant differences between both methods with regard to physiological and behavioral effects and bioavailability, the method of chasing was used for phase 2, which focused on the effects of heroin inhalation at different dose levels.

3.2. Phase 2

3.2.1. Subjective effects

3.2.1.1. SDQ-feel

First drug effects occurred 1–2 min after the start of the inhalation (chasing) session for all heroin doses (25, 50 and 100 mg). At the end of the inhalation session, all subjects reported to experience a drug effect (Fig. 6). After 25 min, a stepwise, dose-related difference was observed in the percentage of subjects who experienced a drug effect after inhaling 25, 50 and 100 mg of heroin base, respectively, and this difference was maintained during the first 2–3 h. However, due to the small number of subjects, these differences did not reach statistical significance.

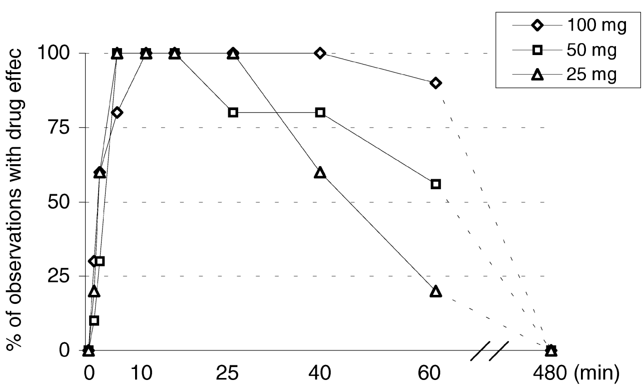

Fig. 6. Percentage of observations in which a drug effect was reported on the SDQ-feel following 25, 50 and 100 mg heroin inhalation (n=5). Notably, the heroin inhalation session took place in the first 10 min.

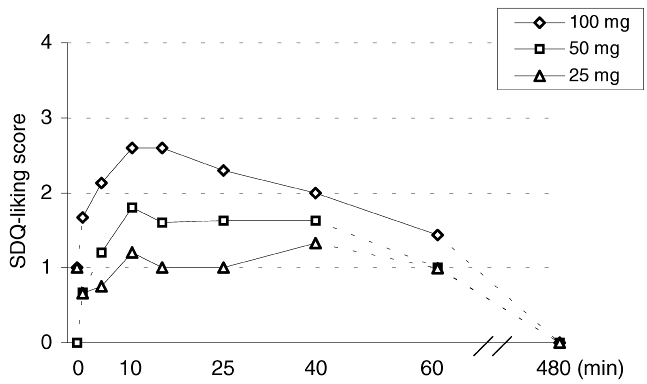

Fig. 7. Appreciation of the drug effect following 25, 50 and 100 mg heroin inhalation, rated on the SDQ-liking (n=5); 0, not at all; 1, slightly; 2, moderately; 3, considerably; 4, extremely. The intermittent line represents the situation in which less than half of the subjects actually reported a drug effect.

3.2.1.2. SDQ-liking

Similar changes in, and differences between the extent to which the subjects liked the drug effect were observed on the SDQ-liking, with peak values occurring between 10 and 15 min for all doses, and with scale-scores increasing from 25 to 50 to 100 mg (Fig. 7). Statistically significant differences were observed at 10 min ($P<0.05$) and 25 min ($P=0.001$) after the start of the inhalation session.

3.2.1.3. VAS

The VAS-data ('good effects') also showed a direct correlation with heroin dose, a higher dose being associated with an increased VAS score (Fig. 8). Significant differences between dose-level were detected at all time points, from 5 min up to 2 h after the start of the inhalation session ($P<0.001$).

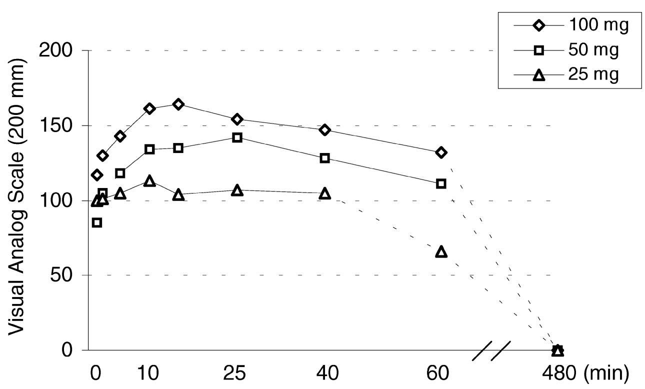

Fig. 8. Subjective rating of 'good' drug effect following 25, 50 and 100 mg heroin inhalation, rated on a 200-mm VAS (n=5). The intermittent line represents the situation in which less than half of the subjects actually reported a drug effect.

3.2.1.4. PSQ

In line with the other results of the phase 2 study, drug-negative symptoms showed a clear dose-related increase from 100 to 50 to 25 mg of heroin, being absent in the 100-mg condition and occurring approximately half as much in the 50-mg condition than in the 25-mg condition. However, drug-positive symptoms occurred with a similar frequency in the three dose conditions.

3.2.1.5. Interview on overall judgement of heroin dose

When retrospectively asked about the perceived effect of the heroin inhaled that day, all subjects gave a more positive evaluation as the heroin dose increased (Fig. 9), the difference being significant at $P<0.05$.

None of the subjects reported the 50- or the 100-mg dose-effect to be 'bad', whereas the 100-mg effect was considered to be 'good' or 'very good' in seven observations. Conversely, the 25-mg dose–effect was not rated as 'good' or 'very good' by any of the subjects.

Remarks made by the subjects consistently indicated that they felt the heroin contained too much caffeine. Although the effect of the 100-mg heroin tablet, with a 1:1 heroin–caffeine ratio, was reported to be closest to the subjects' desired effect, all subjects felt that a reduction of the amount of caffeine in the tablet would enhance this desired effect considerably.

3.2.2. Physiological and behavioral effects

3.2.2.1. Skin temperature

Paralleling the reported subjective effects, a stepwise, dose-related increase in mean skin temperature was observed from 25 to 50 to 100 mg. Differences in skin temperature between the doses were notable after 10 min and maintained during the first hour after administration (Fig. 10). At $t=25$ min ($P<0.05$), $t=40$ min ($P<0.01$), and $t=60$ min ($P<0.05$), differences in skin temperature between the dose levels reached statistical significance. Increase in skin temperature from baseline level was significant at $t=25$ min ($P<0.05$), $t=40$ min ($P<0.01$), $t=55$ min ($P<0.05$), and $t=8$ h ($P<0.05$) in the 50-mg condition, and at $t=20$ min ($P=0.01$), $t=25$ min ($P<0.05$), and $t=40$ min ($P=0.01$) in the 100-mg condition. No significant changes from predose level occurred in the 25-mg condition.

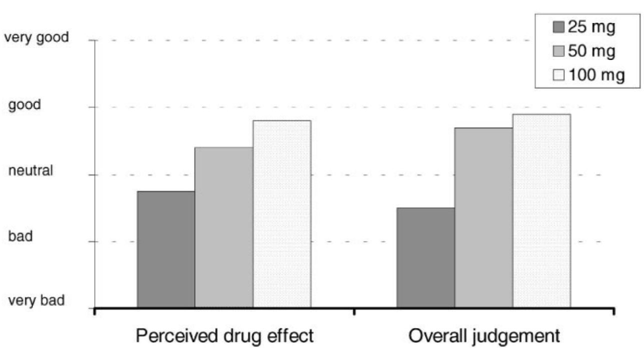

Fig. 9. Rating of perceived drug effect and overall judgement of the 25-, 50- and 100-mg heroin dose-level ($n=5$).

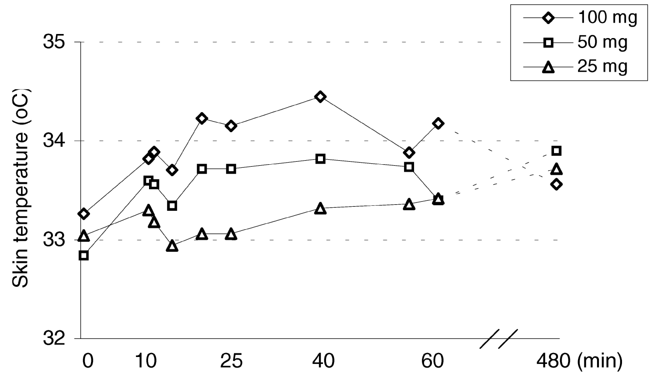

Fig. 10. Skin temperature (°C) following 25, 50 and 100 mg heroin inhalation ($n=5$).

3.2.2.2. Heart rate

All heroin doses produced a rapid increase in heart rate after 10–11 min, followed by a dose-related difference in heart rate during the first hour after inhalation. The change from predose level was only significant in the 50-mg condition and only at $t=60$ min ($P<0.05$). A significant difference between the dose levels occurred at $t=55$ min ($P<0.01$). Notably, subjects' heart rates in the 25-mg dose condition remained lowered during the first 2–3 h (Fig. 11).

3.2.2.3. Reaction time test

The three heroin doses produced linearly dose-dependent differences in both simple reaction time ($P<0.05$) and percentage of correctly identified targets in the digit vigilance accuracy task ($P<0.05$), the 25-mg dose having little or no effect compared to the 50- and 100-mg doses (Fig. 12). For simple reaction time, although the interaction term was non-significant, the effects did seem to be time-dependent. Whereas the three doses were overlapping

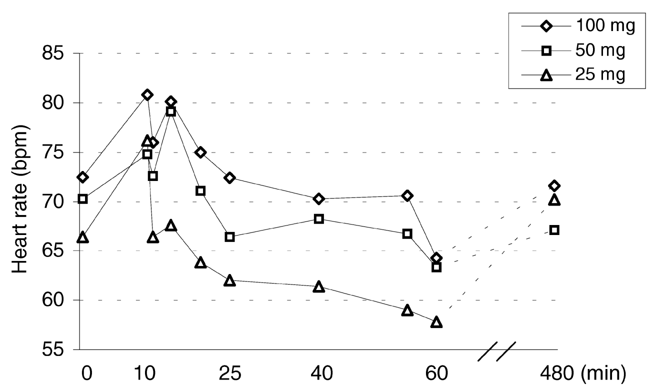

Fig. 11. Heart rate (bpm) following 25, 50 and 100 mg heroin inhalation ($n=5$).

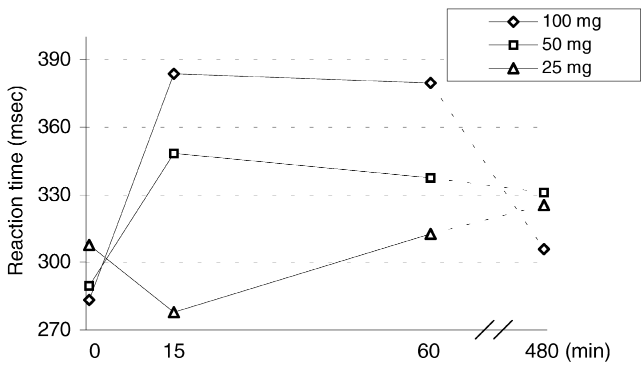

Fig. 12. Simple reaction time (ms) following 25, 50 and 100 mg heroin inhalation (n=5).

at the 4- and 8-h measurements, the doses showed a clear separation at the 1-h measurement.

3.2.3. Urinary excretion of total morphine

As in phase 1, total morphine concentrations and amounts were determined in urine by GC–MS. To prevent interference from the 100-mg heroin dose provided on day 4, the 50-mg dose on day 5 was left out of the analysis. In addition, the 100-mg dose on day 6 was left out, because no 24-h urine was collected following that dose. The three heroin doses (days 2, 3 and 4) resulted in linearly dose-related differences in amount of total morphine. For the 25-mg heroin dose, a mean of 8.4 mg of total morphine was detected in the urine samples (S.D.=3.3; range 6.1–14.0 mg). For the 50-mg dose, total morphine amounted to 17.0 mg (S.D.=8.1; range 8.4–28.9 mg), and for the 100-mg dose to 37.2 mg (S.D.=12.9; range 24.1–53.8). Within-subject variations in recovery rates were small to moderate, the maximum difference between the inhalation sessions of the same individual ranging from 5% for subject 1 to 24% for subject 3. Between-subject variations were larger, the mean recovery rates for the five subjects amounting to 28, 31, 44, 55 and 67%, respectively. Overall, a mean of 45% of the heroin dose received was recovered as total morphine in the urine samples. This percentage was similar across the three doses (43, 44 and 48% for the 25-, 50- and 100-mg doses, respectively).

4. Discussion

Although some studies have been conducted on the bioavailability and pharmacodynamic effects of inhaled heroin, the available literature on this subject is scarce and limited by low ecological validity, small sample sizes, low heroin doses, and lack of replications (Jenkins et al., 1994; Stalder, 1997; Speich, 1998). In the present study, ten heroin-dependent subjects inhaled heroin doses up to 100 mg, the inhalation sessions were conducted twice per method (phase 1) or per dose (phase 2) by each subject, and the heroin was inhaled by means of a naturalistic and common practice, chasing the dragon, or — in the case of the heating device — by a method that closely resembled this practice.

The data presented in this report, 35–45% of the parent heroin being available to the subject, clearly indicate that chasing is an effective means of heroin self-administration, in particular in light of earlier findings on the amount of heroin base in smoke after heating (Huizer, 1987; Cook and Jeffcoat, 1990; Bronner, 1997). The effects of inhaled heroin by this route of administration appeared rapidly, within 1–5 min of inhalation, and occurred on physiological, behavioral and subjective measures. Inhaled heroin produced clear dose-related changes on each of these dimensions, including stepwise, dose-related increases in subjective drug-liking, body temperature and heart rate, and decline in reaction time. In terms of magnitude, the decline in reaction time produced by the 50-mg heroin dose was comparable to that produced by 0.7 g/kg alcohol (Wesnes et al., 1994). In general, the observed changes occurred similarly across and between the objective and subjective measures collected. These changes, in turn, clearly paralleled the dose-related differences in amount of total morphine in the subjects' urine.

With regard to the reproducibility of the pharmacodynamic effects of heroin and its bioavailability, the data indicate that the general pattern of effects and bioavailability is similar after repeated administrations. Perhaps most clearly, the pharmacodynamic and bioavailability data of the fixed 50-mg heroin dose in phase 1 correspond well with those of the 50-mg dose in phase 2 (e.g. 38 vs. 44% bioavailability). Furthermore, the reproducibility of inhaled heroin's effects is indicated by the nearly perfect linear relationship between heroin dose and amount of heroin that entered the body. Intra-individual differences in effects and bioavailability were generally moderate, the maximum difference in bioavailability between inhalation-sessions of the same individual ranging from 5 to 26%. Between subjects however, larger differences in total morphine excretion were found. Large inter-individual differences are frequently found in excretion studies with opiate compounds (Pelders and Ros, 1996; Cone et al., 1996). In addition, these differences may well have been due to differences in the specific technique of heroin chasing by the participants. For example, some subjects used a soda straw during the sessions to inhale the heroin fumes, while others folded a straw made out of aluminum foil and cardboard from a pack of cigarette paper, depending on their usual inhalation ritual. Whereas these different practices were allowed in order to resemble the naturalistic circumstances as much as possible, it is very likely that they affect the output of heroin being inhaled by the subject (Grund, 1993). In addition, and also observed by the first author during the sessions, some heroin users are just more efficient smokers than others, making sure that as little as possible of the heroin fumes escapes from the end of the straw, and being careful not to 'hurt' the heroin by keeping the cigarette lighter too close to the foil.

The 35–45% bioavailability of inhaled heroin is somewhat higher than that of another non-injecting route of heroin administration, intranasal snorting. For the intranasal route, Cone et al. (1993,1996) obtained recovery rates of total morphine of 27–31%, which are in the same range as those for intramuscular injection (34%). Despite its common practice in various countries, although not in the Netherlands, a review of the literature revealed no published data on the bioavailability of subcutaneously ('skin popping') self-administered heroin. When compared with the intramuscular route, the relative potency of intranasally administered heroin was estimated to be approximately 50% (Cone et al., 1996). In another study, Comer et al. (1999) used a choice-paradigm and determined the relative potency of intranasal heroin to be approximately one-quarter of that of intravenously administered heroin. To date, no data are available on the relative potency of inhaled heroin.

The two methods of heroin inhalation evaluated and compared in phase 1 did not differ from each other on any of the objective or subjective parameters, although some measures showed a trend towards more subjective effect in the chasing condition. Notably, the heroin uptake in the body was similar in both conditions, and the extent to which the subjects liked the effects of the heroin was rated 'slightly' to 'moderately' for both chasing and for the heating device. When retrospectively asked about their experiences however, all subjects strongly preferred their usual method of inhalation from aluminum foil and rejected the heating device.

As indicated by the subjective measures, the participants had very limited appreciation of the 25-mg heroine dose and — to some lesser extent — the 50-mg dose, but were quite satisfied about the effects of the 100-mg dose. For the two lower doses, tolerance due to the methadone doses the subjects received in their methadone maintenance program (ranging from 40 to 100 mg), and due to their habit, usually involving higher daily doses of illicit heroin, very likely limited the subjects' appreciation. In the Netherlands, with the purity of street heroin in the bigger cities ranging from 20 to 50% (Korf et al., 1994), 50 mg of pharmaceutical grade heroin would be equivalent to 0.1–0.25 g of street heroin, which is well below the modal daily heroin dose for most heroin addicts (Blanken et al., 1996). In addition, many studies have pointed out the importance of the combination of 'drug, set and setting' factors (Zinberg, 1984) in the experience of a drug's effect. Although much effort was taken to mimic the natural circumstances around the chasing ritual as much as possible, the clinical research setting combined with the frequent assessments may have negatively affected the appreciation of the effects.

In conclusion, chasing the dragon has been the predominant route of heroin administration for most heroin addicts in the Netherlands in the past decades. In this study, chasing has been demonstrated to be a rather effective route of administration, producing rapid, dose-related subjective and objective effects and sufficiently high and reproducible bioavailability. Based on these properties, the similar range of intra- and inter-individual differences in recovery rates between the two inhalation methods, and the good acceptance of chasing by the drug users, chasing from aluminum foil was chosen as the route of heroin self-administration for the inhalable protocol of the Dutch trial into the effectiveness of medically prescribed heroin.

Limitations of the present study include the following. Although this study involved more subjects than previous studies on the effects of inhaled heroin, a total of ten subjects is still quite small and generalizations must be made with caution. Secondly, since neither the two inhalation methods, nor the heroin doses were (single- or double-) blinded, expectations on drug-effects may have influenced the results, particularly those regarding the subjective effects. Thirdly, since large between-subjects variations in total morphine are often found in excretion studies with opioids, it is unclear to what extent the inter-individual differences in bioavailability are caused by the determination in urine, differences in inhalation techniques between the subjects, or reflect true differences in bioavailability. Estimation of the bioavailability from blood samples may provide more exact results. Fourthly, the relative potency of inhaled heroin, compared to intravenous injection was not investigated in this study. For this, it would have been necessary for the subjects to concomitantly inject heroin, and both quantitatively and qualitatively compare the physiological and behavioral effects at different dose levels.

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References

Blanken, P., Barendregt, C., Vollemans, L., Hendriks, V.M., 1996. Druggebruikers in Feijenoord (Drug Users in Feijenoord). Erasmus University Rotterdam/Addiction Research Institute, Rotterdam.

Bronner, G.M., 1997. Ontwikkeling Rookvorm Van Heroïne. Eindrapport

(Development of an Inhalable Form of Heroin). Apotheek Slotervaart-tziekenhuis, Amsterdam.
Central Committee on the Treatment of Heroin Addicts (1997, 1999). Investigating the medical prescription of heroin. Utrecht: CCBH.
Comer, S.D., Collins, E.D., MacArthur, R.B., Fischman, M.W., 1999. Comparison of intravenous and intranasal heroin self-administration by morphine-maintained humans. Psychopharmacology 143, 327–338.
Cone, E.J., Holicky, B.A., Terrance, M.G., Darwin, W.D., Goldberger, B.A., 1993. Pharmacokinetics and pharmacodynamics of intranasal 'snorted' heroin. J. Anal. Toxicol. 17, 327–337.
Cone, E.J., Jufer, R., Darwin, W.D., Needleman, S.B., 1996. Forensic drug testing for opiates. VII. Urinary excretion profile of intranasal (snorted) heroin. J. Anal. Toxicol. 20, 379–392.
Cone, E.J., 1998. Recent discoveries in pharmacokinetics of drugs of abuse. Toxicol. Lett. 102–103, 97–101.
Cook, C.E., Brine, D.R., 1985. Pyrolysis products of heroin. J. Forensic Sci. 30 (1), 251–261.
Cook, C.E., Jeffcoat, A.R., 1990. Pyrolytic degradation of heroin, phencyclidine, and cocaine: identification of products and some observations on their metabolism. In: Chiang, C.N., Hawks, R.L. (Eds.). Research Findings on Smoking of Abused Substances, Vol. NIDA Research Monograph 99. National Institute on Drug Abuse, Baltimore, MD, pp. 97–120.
Cruts, A.A.N., Ouwehand, A.W., vandeWijngaart, G.F., 1997. Trendmatig: Trendcijfers Verslavingszorg 1986 T/m 1996 En Prognoses Voor Het Jaar 2006 Op Basis Van Het Landelijk Alcohol En Drugs Informatie Systeem (ladis) (Trends in the Addiction Care 1986–1996 and Prognoses For the Year 2006 on the Basis of the National Alcohol and Drugs Information System (ladis)). Houten: IVV, Utrecht: CVO.
De Wildt, S.N., Kearns, G.L., Leeder, J.S., van den Anker, J.N., 1999. Glucuronidation in humans. Pharmacogenetic and developmental aspects. Clin. Pharmacokinet. 36 (6), 439–452.
Fraser, H.F., van Horn, G.D., Martin, W.R., Wolbach, A.B., Isbell, H., 1961. Methods for evaluating addiction liability. (a) Attitude of opiate addicts toward opiate-like drugs (b) A short-term direct addiction test. J. Exp. Anal. Behav. 133, 371–387.
J-PC. Grund (1993). Drug use as a social ritual: Functionality, symbolism and determinants of self-regulation. Doctoral thesis. Rotterdam: Erasmus University Rotterdam/Addiction Research Institute.
Grund, J.-P.C., Blanken, P., 1993. From Chasing the Dragon to Chinezen: the Diffusion of Heroin Smoking in the Netherlands. Erasmus University Rotterdam/Addiction Research Institute, Rotterdam.
Hendriks, V.M., Kaplan, C.D., van Limbeek, J., Geerlings, P., 1989. The Addiction Severity Index: reliability and validity in a Dutch addict population. J. Subst. Abuse Treat. 6, 133–141.
Holland, R.L., Wesnes, K., Dietrich, B., 1994. Single dose human pharmacology of umespirone. Eur. J. Clin. Pharmacol. 46, 461–468.
Huizer, H., 1987. Analytical studies on illicit heroin. V. Efficacy of volatilization during heroin smoking. Pharmaceutisch Weekblad, Sci. Edn. 9, 203–211.
IVV, 1999. Landelijk Alcohol en Drugs Informatie Systeem: Kerncijfers verslavingszorg 1999 (National Alcohol and Drugs Information System: Core figures in the addiction care 1999). IVV, Houten.
Jenkins, A.J., Keenan, R.M., Henningfield, J.E., Cone, E.J., 1994. Pharmacokinetics and pharmacodynamics of smoked heroin. J. Anal. Toxicol. 18, 317–330.
Korf, D.J., Biemond, R., Jellema, R., 1994. Prijs En Kwaliteit Van Illegale Drugs in Amsterdam (Price and Quality of Illicit Drugs in Amsterdam). University of Amsterdam/Criminologic Institute Bonger, Amsterdam.
McLellan, A.T., Luborsky, L., Cacciola, J. et al., 1980. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. J. Nerv. Mental Dis. 168 (1), 26–33.
Mo, B.P., Way, E.L., 1966. An assessment of inhalation as a mode of administration of heroin by addicts. J. Pharmacol. Exp. Ther. 154, 142–151.
Pelders, M.G., Ros, J.J.W., 1996. Poppy seeds: differences in morphine and codeine content and variation in inter- and intra-individual excretion. J. Forensic Sci. 41 (2), 209–212.
Powell, J., Bradley, B., Gray, J., 1992. Classical conditioning and cognitive determinants of subjective craving for opiates: an investigation of their relative contribution. Br. J. Addict. 87 (8), 1133–1144.
Robins, L.N., Wing, J., Wittchen, H.U. et al., 1988. The Composite International Diagnostic Interview: An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch. Gen. Psychiatry 45, 1069–1077.
Speich, A., 1998. Heroin-flüssiginhalation Und Heroin-pulverinhalation: In Vitro und in Vivo Studien Im Rahmen Der Versuche Zur ärztlich Kontrollierten Verschreibung Von Betäugungsmitteln (dissertation) (Heroin Liquid Aerosol Inhalation and Heroin Powder Aerosol Inhalation: In Vitro and in Vivo Studies in the Context of the Swiss Heroin-assisted Treatment Program). Department of Clinical Research of the University of Bern, Bern.
Stalder, A.B., 1997. Heroin-zigaretten: in Vitro und in Vivo Rauchstudien (dissertation) (Heroin Cigarettes: in Vitro and in Vivo Smoking Experiments). Department of Clinical Research of the University of Bern, Bern.
Strang, J., Griffiths, P., Gossop, M., 1997. Heroin smoking by 'chasing the dragon': origins and history. Addiction 92 (6), 673–683.
Uchtenhagen, A., Gutzwiller, F., Dobler-Mikola, A., 1997. Versuche Für Eine ärztliche Verschreibung Von Betäugungsmitteln. Abschlussbericht Der Forschungsbeauftragten. Synthesebericht (Medically Controlled Prescription of Narcotics. Final Report of the Research Committee). Institut für Suchtforschung in Verbindung mit der Universität Zürich, Zürich.
Uchtenhagen, A., Dobler-Mikola, A., Steffen, T., Gutzwiller, F., Blätter, R., Pfeifer, S., 1999. Prescription of Narcotics For Heroin Addicts: Main Results of the Swiss National Cohort Study. Karger, Basel.
Van Brussel, G.H.A., Buster, M., 1999. Zorg Voor De Toekomst: Opiaatverslaafden in Amsterdam. Trends En Figuren: 1996, 1997 En 1998 (Care for the Future: Opiate Addicts in Amsterdam. Trends and Figures: 1996, 1997 and 1998). Municipal Health Service, Amsterdam.
Van den Brink, W., Hendriks, V.M., van Ree, J.M., 1999. Medical co-prescription of heroin to chronic, treatment-resistant methadone patients in the Netherlands. J. Drug Issues 29 (3), 587–608.
Wesnes, K.A., Simpson, P.M., Christmas, L., 1989. A microcomputerised system for evaluating the cognitive actions of drugs in the young, elderly and demented. Eur. J. Clin. Pharmacol. 36, A38.
Wesnes, K.A., McEwen, J., Pritchard, G., 1994. The dose and time dependent profile of cognitive impairments of alcohol in young volunteers. J. Clin. Pharmacol. 34, 1021.
Zinberg, N.E., 1984. Drug, Set and Setting: the Basis for Controlled Inoxicant Use. Yale University Press, New Haven.