Effects of High-Dose Heroin versus Morphine in Intravenous Drug Users: A Randomised Double-Blind Crossover Study†

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Abstract—The purpose of this study is to evaluate the effects of high doses of injected opiates as prescribed maintenance in intravenous drugs users. This was accomplished via a randomised double-blind study with crossover at an outpatient clinic in Bern, Switzerland. The subjects were 39 patients with a long history of intravenous opioid use and persistent abuse despite treatment; they were randomly allocated to two groups. Group A was started on controlled injection of graduated doses of morphine up to a satisfying individual dose and was then switched as a double blind to heroin at a randomly determined day between week three and four. Subsequently this group was given heroin for the remaining two to three weeks of the study. Group B was started on heroin and was then switched to morphine in the same manner. Equipotent solutions of 3% morphine and 2% heroin were administered. The main outcome measures were clinical observations, structural interviews and self report of subjective experiences to assess the effects of the drugs. In 16 cases, the study had to be discontinued owing to severe morphine-induced histamine reactions. Thirteen participants in Group B presented these adverse reactions on the day of the switch-over. Full data were thus only obtainable for 17 participants. Average daily doses were 491mg for heroin and 597mg for morphine. The findings indicate that heroin significantly produced a lower grade of itching, flushing, urticaria and pain/nausea. A negative correlation between dose and euphoria was observed for both heroin and morphine. The authors concluded that as heroin produces fewer side effects it is the preferred high-dose maintenance prescription to morphine. The perceived euphoric effects are limited in both substances.

Keywords—double blind method, heroin dependence, intravenous injections, maintenance treatment, morphine, Switzerland

The isolation of morphine from the latex of the poppy was first described by Serthürner in 1803, and heroin was first synthesised in 1874 by Wright. Despite the fact that these substances have been recognised for more than a century, precise clinical data evidencing the effects and side effects in high-dose, steady state application are still lacking. According to the literature, these two substances should be very similar in action, provided equipotent doses are administered. The majority of related studies, however, have been carried out in the field of pain management (Morrison, Payne & Drummond 1991; Robinson, Rowbotham & Smith 1991; Watson et al. 1984; Kaiko et al. 1981; Scott & Orr 1969; Dundee, Loan & Clarke 1966). In pain management, high doses sometimes have to be administered (Bruera et al. 1990), as pain acts as a strong antagonist to opioids

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(Hanks, Twycross & Lloyd 1981). Neither heroin nor morphine was found to be consistently superior in pain management, but strong corroborative data in clinical practice favors intravenous heroin for high-dose injection owing to its higher solubility (Twycross 1977) and lower toxicity (Bruera et al. 1990).

Relatively few studies on the effects of heroin in healthy volunteers have been conducted (Bromage et al. 1982a, b; Smith & Beecher 1962; Smith, Semke & Beecher 1962; Lasagna, von Felsinger & Beecher 1955; von Felsinger, Lasagna & Beecher 1955). To the authors' knowledge, no studies have addressed the administration of heroin to opiate-tolerant addicts, and only a few studies have investigated the administration of this drug to recovering addicts, so-called post-addicts (Jasinski & Preston 1986; Zaks et al. 1969; Martin & Fraser 1961; Lasagna, von Felsinger & Beecher 1955). Generally, only small doses of heroin (not exceeding 30 mg) and morphine were applied in these studies. This is obviously too low for a steady-state dosing as it is needed in a maintenance prescription for addicted patients (Parry 1992).

The most commonly quoted equipotency ratio for the single-dose analgesic effects of morphine and heroin is 2:1 (Robinson, Rowbotham & Smith 1991; Jasinski & Preston 1986; Kaiko et al. 1981; Scott & Orr 1969). Some authors believe that heroin may be even more potent (Hubner & Kornetsky 1992). Only Twycross (1977) found a lower ratio of 1.5:1 in oral application. The findings by one of the authors (RH) in an open clinical trial during which 12 patients were switched from intravenous morphine to intravenous heroin support the appropriateness of a 1.5:1 ratio as opposed to a 2:1 ratio (Haemmig 1997).

Morphine produces substantial side effects when applied in the maintenance of addicts who had previously undergone methadone substitution treatment (Moldovanyi et al. 1996). The reported side effects are of a histaminic type and are attributed to histamine release from mast cells and a histamine-induced central nervous effect. However, Withington, Patrick & Reynolds (1993) found that heroin causes histamine release as frequently as morphine in patients undergoing low-dose pain treatment. Urinary dysfunction seems to be of no clinical importance in tolerant subjects as opposed to nontolerant subjects (Stevens et al. 1991; Bromage et al. 1982a, b).

The Swiss Federal Office of Public Health implemented a nationwide research project, the Programme for a Medical Prescription of Narcotics (PROVE), to test the intravenous application of heroin, morphine, and methadone in intravenous drug users. It included a comprehensive assessment and treatment programme. The goal of this project was to determine how patients respond to the maintenance prescription of injectable opiates, to assess the retention rate, which was expected to be high (Hartnoll et al. 1980), and to investigate the pharmacology of these substances as well as the feasibility of controlled dispensing. For this programme, only drug users with a long history of intravenous opioid abuse (at least two years of continuous injecting of illicit heroin prior to entry into the program) were eligible. Further inclusion criteria for participation were at least two failed treatment attempts (detoxification, rehabilitation or methadone maintenance), a minimum age of 20 years of age, and local residency. A description of the full programme (Uchtenhagen, Dobler-Mikola & Gutzwiller 1996; Haemmig 1995) and a synthesis of the results have been published (Uchtenhagen et al. 1999).

Within the context of PROVE, the present double-blind study was performed to test the effects and side effects of high-dose heroin and morphine in a sample of intravenous drug users meeting the criteria to participate in PROVE. This article reports the findings on the relationship between drug effects and substance type and dosage.

MATERIAL AND METHODS

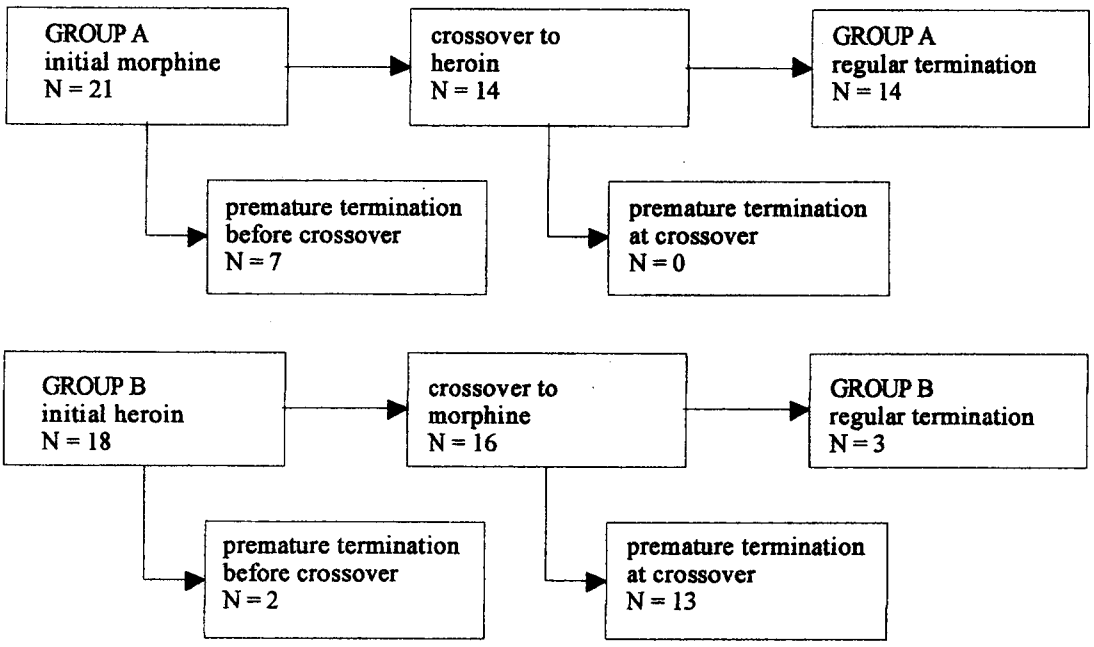
Participants and Treatment Protocol

Thirty-nine applicants were selected for inclusion in this study on the basis of sequential admission in the PROVE program. Other inclusion criteria were as mentioned above. The participants were 31 male (79.5%) and eight female (20.5%) Caucasians with a mean age of 29.9 years (SD: 4.96 years), and a mean duration of heroin use of 10.8 years (SD: 5.08 years). Male participants were older than female participants (mean age 30.7 years, respectively, 26.4 years, Mann-Whitney U-Test: $p<.01$). There was no gender difference, however, in the duration of heroin use. Gender proportion, age, and duration of heroin use in this sample represent the characteristics of the severely addicted drug-user population in Switzerland (Haemmig et al. 1998). Participants were randomly allocated to one of two double-blind study groups.

Group A was started on a small dose of a 3% morphine solution. The dose was gradually increased up to an individual maintenance dose and adjusted to meet the participants' subjective needs for opiates. On a randomly determined day in the third or fourth week of the study the participants were switched as a double blind to the same volume of a 2% heroin solution. The study lasted a total of six weeks for each participant. All drug injections took place on the premises of the outpatient drug clinic KODA-1 in Bern and were applied under close observation of the trained medical staff. Group B started with heroin and was later switched to morphine using the same protocol. A disclosure of the double-blind design was foreseen in the event of severe adverse effects being observed. Participants were obliged to pay CHF 15 (approx. US$ 9) per day to obtain the substances.

Randomisation was carried out by the pharmaceutical department of the Swiss Federal Office of Public Health, which also prepared the study substances. Morphine solution has a slightly different color from heroin solution.

FIGURE 1
Overview of Termination



Therefore, to prevent recognition of the applied substance by both the users and the medical staff, the substances were supplied in brown plastic syringes with black pistons.

Applicants gave written informed consent after having been appropriately informed about their participation in the study. The study design was approved by the Ethical Committee of the Medical Faculty of the University of Bern and by the Swiss National Ethical Committee.

Data Acquisition

After each injection of either heroin or morphine, various aspects of drug effects were recorded using 24 different measures. One part of the data was collected by the nurse or physician administering the injection. This person rated side effects such as flushing, hives, edema, itching, "pins and needles" sensation, and other adverse reactions according to their location, intensity, and duration. Location and intensity were coded respectively on three-point scales (localised/circumscribed/general, or perceptible/moderate/strong). Duration was measured in minutes.

Additional data on side effects were gathered from the participants' self-ratings, which were coded on seven-point Likert scales. The following items were recorded: perceptibility of drug effects; "rush"; euphoria or relief; feeling clear-headed or functioning better than before; feeling well-balanced or relaxed; inner warmth; frustration or disappointment; itching or prickly sensation ("pins and needles"); nausea; vertigo, sweating, heart palpitations or difficulties in breathing and headache.

Data Processing

The data set, comprising 24 items of drug side effect measures and drug effect measures, was factor-analysed by principal component analysis in order to summarise and reduce the number of variables before further analyses were performed. Thus, for each participant in the study, factor values were obtained at each point of measurement, i.e. at the time the injection was given. There was considerable variation in the individual levels of drug response in both the heroin and the morphine condition. This variance was assessed by cross-sectional comparisons of the mean factor levels (finding what proportion of the variance can be attributed to the substance administered) and by linear regression (finding whether there was a significant relationship between drug response and dosage in the heroin and morphine condition).

RESULTS

Premature Termination of the Study

In Group A (starting on morphine with a subsequent crossover to heroin), 14 of 21 participants (66.7%) completed the study, whereas in Group B (starting on heroin with a subsequent crossover to morphine), only three of 18

TABLE 1
Linear Regression of Dosage and Mean Factor Values

	Substance	N	Standardised beta weight	*t*	R square
Euphoria	heroin	31	-.47	2.85*	21.9%
	morphine	21	-.56	2.97*	31.7%
Itching	heroin	31	-.27	1.49 ns	7.1%
	morphine	21	.27	1.23 ns	7.3%
Objective side effects	heroin	31	-.05	.25 ns	0.2%
	morphine	21	.49	2.48*	24.5%
Pain/nausea	heroin	31	.10	.52 ns	0.9%
	morphine	21	.15	.65 ns	2.2%

*$p < .001$

participants (16.7%) completed it. In 16 cases, premature termination was due to excessive histamine reactions, all of which occurred in the morphine condition. Histamine reactions were particularly acute in the crossover phase from heroin to morphine (13 of 16 cases). Symptoms included severe itching and prickly sensations, flushing, swelling, urticaria, extreme headaches, nausea, general malaise, drop in blood pressure, tachycardia, and even collapse. All participants experiencing severe symptoms of histamine release after the critical injection recovered within half an hour. They were kept under clinical observation and further medical intervention proved unnecessary. Only 43.6 % of the patients terminated the study regularly, 14 who were getting heroin at the end, and only three getting morphine (Wilcoxon W = 323.0, $p < .001$). An overview of the regular and premature terminations of the study is given in Figure 1.

In two cases the study had to be discontinued owing to the poor condition of the veins (one instance in the morphine group (A) and one in the heroin group (B). One participant was excluded as a disciplinary measure (theft). Three participants left the study for unknown reasons (two in the morphine group, one in the heroin group).

Dosages

The average daily dose per participant in the heroin group was 491 mg (SD: 198.8 mg) and in the morphine group 597 mg (SD: 337.5 mg).

Factor Analysis

Principal component analysis yielded seven factors with eigen values larger than one. The scree test, however, pointed to a smaller number of meaningful factors; four factors were extracted which account for approximately 59.4% of the sample's total variance. The factors were obtained using varimax rotation. The rotated factors were labeled as follows:

- euphoria (22.5% explained variance)
- itching (13.9%)
- objective side effects (11.8%)
- pain/nausea (11.2%).

The values of *euphoria* were based on the participants' evaluation of the desired drug effect; examples of the corresponding questionnaire items were "Are you experiencing relief or do you feel free or euphoric?" or "Do you feel relaxed, well-balanced?" The factor *itching* was based on the participants' self-reported itching and tingling sensations, especially the intensity and spreading of itching sensations. *Objective side effects* comprised histamine-induced skin reactions observed by the medical staff. This factor included the intensity and spread of flushing, hives, and edema. *Pain/nausea* summarised a number of self-reported symptoms such as headache, vertigo, nausea, and sweating.

Regression Analysis of Factor Values and Dosage

In this first series of statistical tests the effect of dosage on the mean levels for the factors euphoria, itching, objective side effects, and pain/nausea were examined. The mean levels were computed over all factor values of a participant in either substance condition. Linear regressions of dosage to the mean levels were computed separately for heroin and morphine (see Table 1).

Table 1 shows that euphoria was clearly associated with the administered dosage. Surprisingly, this association proved to be inverse, i.e. the higher the mean dosage, the less euphoric the participants felt. With regard to drug side effects, only the factor objective side effects correlated significantly to dosage in morphine.

Fit of Mean Factor Values by Substance

The paired *t*-tests of factor levels by substance are summarized in Table 2. A significant advantage of heroin over morphine in all factors which assessed undesired drug ef-

TABLE 2
Paired *t*-Tests of Factor Levels by Drug Type

		Heroin versus Morphine	
	N	*t*	*p*
Euphoria	17	2.06	.057
Itching	17	-6.77	<.001
Objective side effects	17	-4.06	<.001
Pain/nausea	17	-2.20	.043

fects was found. Euphoria was more prominent in the heroin condition, but this effect missed the 5%-level of a two-tailed test.

DISCUSSION

The distinguishing feature of the present study in comparison to other empirical studies is that the effects of high doses of opioids in addicts were examined. These findings clearly indicate that heroin and morphine gave rise to markedly different drug effects. This observation was not expected since the profiles of action of both substances are very similar, and morphine is a main active metabolite of heroin. Nonetheless, high-dose morphine produced more adverse effects in this sample. Cases in which it became necessary to prematurely terminate the study because of dramatic histamine-type reactions occurred only in the morphine condition. In contrast to controlled studies of pain management that yielded no differences in histamine-type reactions between morphine and diamorphine (Withington, Patrick & Reynolds 1993), the present study found histamine-induced cardiovascular reactions only in the morphine condition within the high-dose range investigated. Most particularly, the switch-over from full-dose heroin to full-dose equipotent morphine proved to be highly problematic. The gradual increase in the morphine dose (Group A) led to fewer complications but nevertheless a higher rate of premature termination was recorded in this group. To summarise, heroin was clearly better tolerated than morphine, and the incidence of medical or other premature termination was lower. This main result made further processing of data somewhat difficult.

The difference between the substances can be partially explained by the dissimilarity of lipophily in heroin and morphine. However, the tolerance mechanism, the effects of heroin and its metabolite 6-mono-acetylmorphine, and of morphine on the μ-receptors and various receptor subtypes still remain substantially puzzling and require further investigation.

Only a statistical trend was found indicating that heroin produces a more intense feeling of euphoria than morphine in steady state dosing. The present findings reveal, however, that high-level doses of either substance do not induce greater euphoria—on the contrary, an inverse association between euphoria and dosage was found. This contradicts a commonly held belief among addicts and professional caregivers that higher drug levels heighten desired effects.

The authors can only speculate on an explanation for this phenomenon. Several interdependent physiological processes are involved. First, a *saturation* of the μ-receptors may occur with opiates. The sigmoid shape of the semi-logarithmic dose-effect curve reflects that beyond a certain (high-level) dose, no further increase in effects is possible. Secondly, saturation may combine with an increase in *tolerance* whereby, after repeated applications, drug-induced effects are diminished. Consequently, the combined mechanisms of saturation and tolerance should explain the occurrence of an inverse association between euphoria and dosage in steady-state dosing. An important corollary is that the subsequent weakening of the reinforcing quality of the substances exerts a regulatory effect on self-dosing.

Ultimately, these results have implications not only for the treatment of drug users but also for parenteral pain management. They support, for example, the results of Bruera and colleagues (1990), who found a decreased local toxicity of heroin. The authors' finding of the superiority of injected heroin over morphine in steady-state dosing could support the choice of heroin in the treatment of severe pain by general practitioners and specialists as well.

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