

Pharmacokinetic comparison of two methods of heroin smoking: 'chasing the dragon' versus the use of a heating device

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Abstract

In preparation for a trial on co-prescription of inhalable heroin and methadone, two methods for inhalation of heroin/caffeine tablets were compared: the commonly used method of 'chasing the dragon' and a standardised procedure for inhalation of volatilised heroin, using a heating device. Five male addicts inhaled a tablet of smokable heroin daily for 5 days, alternating the inhalation method. Plasma concentrations of heroin, 6-acetylmorphine, morphine and morphine-3- and -6-glucuronide were determined using a liquid chromatography method with tandem mass spectrometric detection. The exposure to heroin and its metabolites (expressed as areas under the concentration–time curve) was significantly lower after smoking via the heating device than after 'chasing the dragon': heroin 80% and 6-acetylmorphine 73% lower ($p < 0.05$). Maximal concentrations of heroin and 6-acetylmorphine were also 80% and 70% lower ($p < 0.05$) after using the heating device. 'Chasing the dragon' is a more efficient inhalation method than inhalation via the heating device.

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1. Introduction

Heroin (3,6-diacetylmorphine) is a well-known drug of abuse, that is usually administered intravenously, but smoking heroin has gained popularity since it was first described in Shanghai in the 1920s (Strang et al., 1997). After some refinement, the use of an inhalation procedure called 'chasing the dragon' spread to South East Asia, India and some parts of Europe in 1960–1980 (Strang et al., 1997). In this procedure, drug users heat heroin powder on a piece of aluminium foil with a cigarette lighter until it melts

and evaporates. The fumes are subsequently inhaled through a straw.

A clinical trial was performed in the Netherlands to evaluate the effect of medical co-prescription of heroin and methadone on mental and physical health and social functioning of chronic treatment-resistant heroin-dependent patients (Van den Brink et al., 2003). Since in the Netherlands 75–85% of the heroin addicts use heroin by 'chasing the dragon' (Hendriks et al., 2001), two separate study protocols were developed: one trial testing the efficacy of the prescription of an inhalable form of heroin and another trial testing the efficacy of the prescription of injectable heroin. In preparation for the first trial, an inhalable form of pharmaceutical heroin was developed to be used by 'chasing the dragon', containing 50 mg diacetylmorphine base and

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100 mg caffeine anhydrate in tablets, obtained via direct compression. Caffeine was added because it is commonly found in street heroin samples (de la Fuente et al., 1996; Huizer et al., 1977; Kaa and Bent, 1986; Risser et al., 2000) and has been shown to improve the volatilisation of heroin (Huizer, 1987). Since ‘chasing the dragon’ might not be the most effective and reproducible method for inhalation of volatilised heroin, an alternative method was developed. A heating device fitted with a sample holder was proposed as a method for inhaling heroin that allowed for improved control of the volatilisation temperature and thereby for standardisation of the inhalation process. The latter was considered important for the future acceptance of inhalable heroin prescription as an authorised treatment for heroin-dependent patients. The method of preference would be used in the abovementioned clinical study and in the future in heroin prescription programs (after obtaining market authorisation for diacetylmorphine for inhalation after volatilisation).

A pharmacodynamic comparison of ‘chasing the dragon’ and inhalation via the heating device has been reported by Hendriks et al.: no significant differences in physiological and behavioural effects were found between the two inhalation methods, but participants expressed a strong preference for ‘chasing the dragon’ (Hendriks et al., 2001). In this paper, the pharmacokinetics of inhalation of volatilised diacetylmorphine/caffeine tablets by addicts via ‘chasing the dragon’ and via a heating device were compared.

2. Experimental procedures

2.1. Inhalation methods

On five consecutive days, the patients alternately used pharmaceutical heroin for inhalation via ‘chasing the dragon’ (the commonly used method on the street) or via the heating device. The maximum time allowed for inhalation was 10 min. In the procedure of ‘chasing the dragon’, patients placed the heroin tablet on a piece of aluminium foil and heated it carefully with a lighter until it melted and evaporated. The liquefied substance was moved around on the aluminium foil and patients followed the ‘dragon’s tail’ of fumes it left behind to inhale through a straw in their mouth. This process was regularly interrupted to enjoy the effect, allowing the liquid heroin to solidify between subsequent inhalations.

The alternative method for heroin inhalation involved inhaling the fumes emitted from a tablet heated on a heating device. The tablet was placed on a piece of aluminium foil that was shaped to fit in an indentation in a brass block, placed on top of a preheated heating device (30 min at 300 °C, RCT Basic, IKA Werke, Staufen, Germany). The fumes were inhaled in the same way (using a straw in the mouth) and intermittent inhalation was achieved by removing the

aluminium foil from the brass block between subsequent inhalations. However, no movement of the liquid heroin was possible.

2.2. Patients and medication

Five male patients were recruited from the patient population of the methadone maintenance treatment facility of the Municipal Health Service in Amsterdam. The inclusion criteria were similar to the criteria used in the randomised clinical trial testing the effectiveness of co-prescribed heroin in chronic treatment-resistant addicts (Van den Brink et al., 2003); in short: minimum 5 years history of DSM-IV heroin dependence, minimum age 25 years, inhalation as the predominant route of heroin administration, substantial daily or nearly daily use of illicit heroin and current treatment in a methadone maintenance program. Subjects were excluded if they had a minimum of 2 months of voluntary abstinence from heroin in the previous year. The patients were admitted to a closed clinical research unit for a period of 6 days. The use of alcohol, cannabis, cocaine and opiates besides trial medication was not allowed during this period. Care was taken to prevent concomitant use of illicit drugs during the study. The study was conducted under the provisions of the Declaration of Helsinki, as amended in Hong Kong (1989). The study was approved by the Medical Ethics Committee of the Academic Medical Centre in Amsterdam. All subjects received extensive oral and written information about the study and provided written informed consent.

Prescribed medication consisted of a daily dose of oral methadone and on day 2–6 a daily dose of pharmaceutical smokable heroin, consisting of a tablet containing 50 mg diacetylmorphine base and 100 mg caffeine anhydrate. Three of the five patients started with inhaling heroin via ‘chasing the dragon’, alternating this method with the heating device method; the other two followed the opposite schedule. In order to minimise bias from comparing a very common route of self-administration to a completely new route, participants practised both inhalation methods on the first day by inhaling a 150 mg caffeine tablet via ‘chasing the dragon’ and via the heating device.

2.3. Sampling and analysis

In general, heroin pharmacokinetics are characterised by rapid hydrolysis to 6-acetylmorphine and morphine *in vivo* (Hardman and Limbird, 1996). Therefore, diacetylmorphine and its hydrolysis products were determined in plasma samples, as well as the main metabolites of morphine: morphine-3- and -6-glucuronide. Blood samples were collected via an intravenous cannula in the underarm, taking a first sample before the start of the inhalation session and at 1, 2, 5, 7.5, 10, 15, 22.5, 30, 45, 60, 120, 240 and 480 min after the end of the inhalation session. In order to prevent degradation of diacetylmorphine, sodium fluoride was added

to the sample tubes and samples were quickly frozen at -30°C after centrifugation and collection of the plasma fraction. Concentrations of diacetylmorphine, 6-acetylmorphine, morphine, and morphine-3- and 6-glucuronide were determined using a validated high performance liquid chromatography method with tandem mass spectrometry detection (HPLC-MS/MS), that has been described elsewhere (Rook et al., 2005). Plasma samples were pre-treated by solid phase extraction through Oasis MCX sorbent columns and deuterated compounds were used as internal standards. Lower limit of quantification (LLQ) was 5 ng/mL and the upper limit of quantification (ULQ) was 500 ng/mL for all quantified analytes (equalling: $\text{LLQ}=0.011\text{--}0.018\ \mu\text{mol/L}$; $\text{ULQ}=1.1\text{--}1.8\ \mu\text{mol/L}$, depending on the analyte). Inter-assay accuracy of this method was $<5\%$ and inter-assay precision was $<11\%$ for all quantified analytes (Rook, 2003). The HPLC-MS/MS method was also suitable for detection of concomitant use of illicit drugs, by screening for the presence of codeine and 6-acetylcodeine (common constituents of street heroin), and for cocaine and its metabolites benzoylecgonine and norcocaine (Rook, 2003).

Pharmacokinetic parameters for all compounds were calculated by non-compartmental analysis, using WinNonlin software (Professional Ed., Version 4.1, 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 a semi-log scale). The elimination constant was also used to calculate the elimination half-life ($T_{1/2}$) for all analytes. When plasma concentrations were above the LLQ at the baseline measurement (C_0), AUC was corrected by subtracting C_0/k_e .

Maximal plasma concentrations (C_{max}) and the time these concentrations were measured (T_{max}) were derived from experimental data. Inter- and intra-patient variabilities for the two administration methods were calculated by dividing the standard deviations in C_{max} and AUC values by the corresponding means. Differences in pharmacokinetic parameters between the two inhalation methods were tested using the Wilcoxon Matched Pairs, Signed Ranks test.

3. Results

3.1. Patients

Five male heroin addicts were included in the study, four of them were Caucasian, one subject was Asian. The mean age was 36.2 years (range 30–48) and the mean body weight was 65 kg (range 51–89 kg). All subjects used methadone once daily; mean dose 78 mg (range 45–100 mg). No evidence for co-use of illicit drugs during the study was found: none of the plasma samples contained 6-acetylcodeine, codeine, cocaine, norcocaine, or benzoylecgonine. No plasma samples were obtained for patient B on days 2 and 6 (first and last day of diacetylmorphine administration). A total of 23 plasma concentration–time curves were available for analysis: 13 after ‘chasing the dragon’, 10 after inhaling via heating device. In one sample series (patient E, day 5, inhaling via heating device), no diacetylmorphine was detectable; in another (patient D, day 1, inhaling via heating device) diacetylmorphine was only detected at $t=1$ min. In both cases only the concentrations of diacetylmorphine metabolites were included in the pharmacokinetic and statistical analyses.

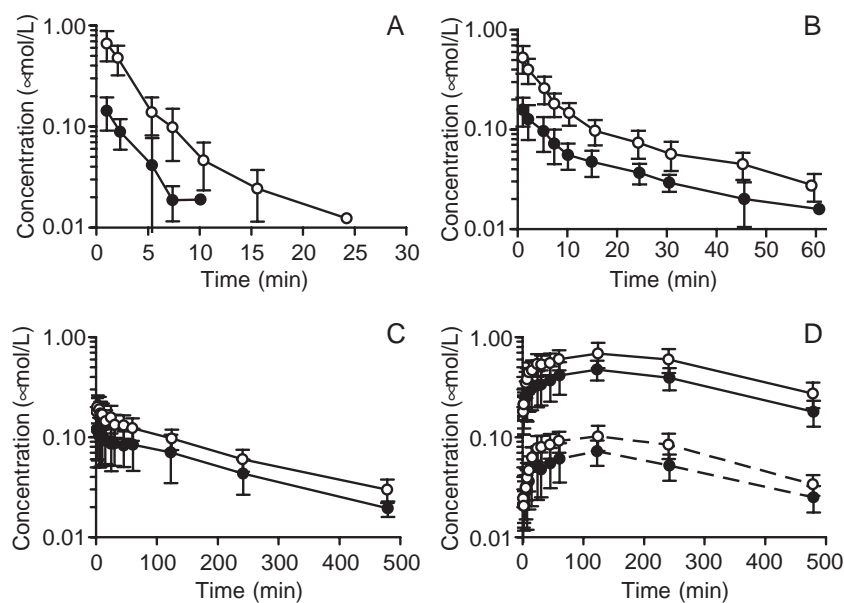


Fig. 1. Mean plasma concentration–time curves of diacetylmorphine (A), 6-acetylmorphine (B), morphine (C), morphine-3-glucuronide (D: solid lines) and morphine-6-glucuronide (D: dashed lines) after smoking 50 mg heroin tablets using the method of ‘chasing the dragon’ (open bullets) or using the heating device (closed bullets). Error bars indicate the 95% confidence interval.

Table 1

Analyte	AUC (min · μmol/L)		C_{\max} (μmol/L)		$T_{1/2}$ (min)	
<i>'Chasing the dragon'</i>						
Diacetylmorphine	2.99	(2.11)	0.61	(0.36)	n.d.	
6-Acetylmorphine	6.31	(3.32)	0.53	(0.28)	n.d.	
Morphine	37.71	(15.23)	0.21	(0.12)	143.0	(67.9)
Morphine-3-glucuronide	347.5	(156.3)	0.74	(0.36)	280.1	(81.7)
Morphine-6-glucuronide	50.77	(25.52)	0.11	(0.05)	269.9	(123.4)
<i>Heating device</i>						
Diacetylmorphine	0.56	(0.24)	0.12	(0.06)	n.d.	
6-Acetylmorphine	1.96	(1.27)	0.16	(0.08)	n.d.	
Morphine	22.82	(13.44)	0.13	(0.09)	127.0	(36.7)
Morphine-3-glucuronide	214.1	(91.3)	0.50	(0.20)	252.0	(47.6)
Morphine-6-glucuronide	29.15	(12.91)	0.08	(0.04)	216.2	(35.0)

Mean values are given, with standard deviations in parentheses; n.d.=value could not be determined accurately.

3.2. Pharmacokinetics

Mean plasma concentration–time curves for diacetylmorphine, 6-acetylmorphine, morphine and morphine-3- and -6-glucuronide resulting from the two inhalation methods are given in Fig. 1. Distinct differences between the two inhalation methods could be observed in these plots: concentration–time curves appeared to be lower for diacetylmorphine and 6-acetylmorphine and variation in mor-

phine and morphine glucuronide concentrations appeared to be larger in the first hour after inhaling via the heating device. The first observation was reflected in the pharmacokinetic data (Table 1), which indeed showed 80 and 73% lower AUC values ($p=0.043$) after using the heating device for diacetylmorphine and 6-acetylmorphine, respectively. Although the differences were less obvious in the concentration–time curves, AUCs for morphine and the glucuronides were also significantly lower (38–42%, $p=0.043$).

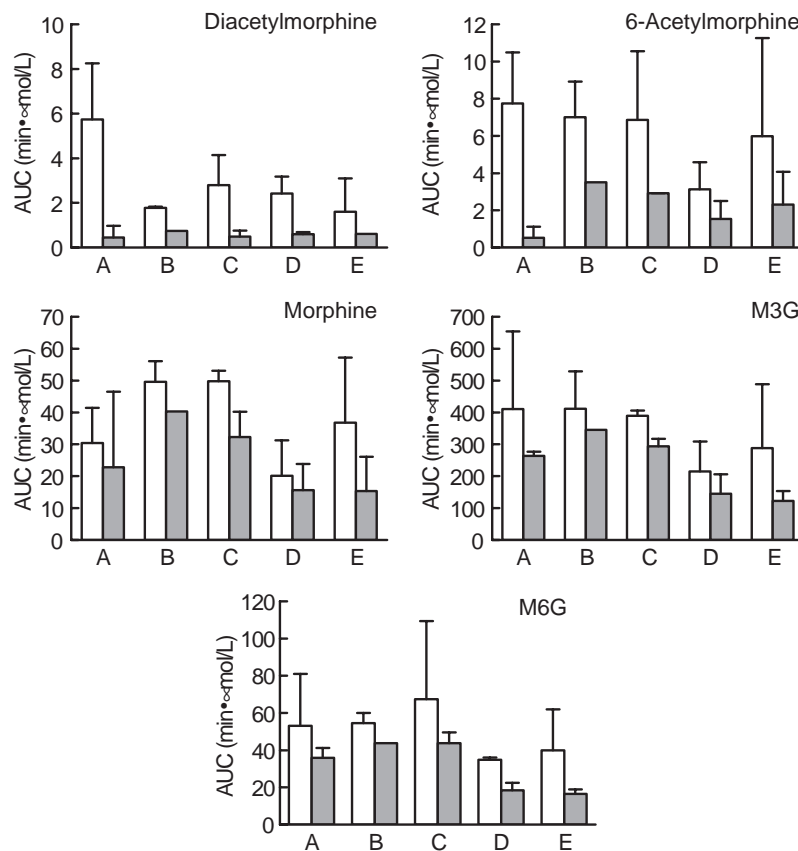


Fig. 2. Exposure to diacetylmorphine, 6-acetylmorphine, morphine and the morphine glucuronides, for all five patients (A–E) after smoking 50 mg heroin tablets: white bars represent area under the curve (AUC) after 'chasing the dragon', grey bars after using the heating device. Error bars indicate the standard deviation.

The same pattern was observed in diacetylmorphine and 6-acetylmorphine C_{\max} (80% and 70% lower) as compared to morphine and its metabolites (27–38% lower). No significant differences were found in the $T_{1/2}$ values of the analytes between the two inhalation methods (Table 1).

The second observation from the concentration–time plots, concerning the differences in variation observed in the morphine and morphine–glucuronide concentrations in the first hour, was not reflected as variability in the AUCs of these analytes. Both smoking methods show similar inter-patient variability (ranging from 26% to 58% for ‘chasing the dragon’ and from 15% to 57% for the heating device, depicted in Fig. 2) and intra-patient variability (7–93% and 8–115%; depicted by the error bars in Fig. 2) in AUCs of diacetylmorphine and its metabolites. However, the inter-patient variation in C_{\max} of morphine and morphine-3- and 6-glucuronide were higher (56%, 42%, 53%) after using the heating device compared to ‘chasing the dragon’ (47%, 30%, and 34%, respectively), while intra-patient variabilities were similar. The differences were however not statistically significant (F -test, $p=0.51$ – 0.94).

Diacetylmorphine and 6-acetylmorphine T_{\max} was consistently equal to the first time point, 1 min after the end of the inhalation session, for both inhalation methods. The time to morphine peak concentrations was 2 min and morphine-3- and -6-glucuronide T_{\max} occurred about 2 h after the end of the inhalation session with both methods.

Baseline concentrations were below LLQ in all curves for diacetylmorphine, 6-acetylmorphine and morphine. Morphine-3-glucuronide baseline concentrations were above the LLQ in 18 (out of 23) curves: mean 0.065 $\mu\text{mol/L}$ (range 0.027–0.130 $\mu\text{mol/L}$). Morphine-6-glucuronide baseline concentrations were above LLQ in 5 curves: mean 0.014 $\mu\text{mol/L}$ (range 0.010–0.016 $\mu\text{mol/L}$). In these cases, AUC values were corrected as described in the Experimental procedures section.

4. Discussion

The alternative inhalation device was developed as part of the preparation for the Dutch Heroin Trial (Van den Brink et al., 2003). It was considered important to provide a safe, controllable and standardised method for administration of smokable heroin to the patients in the experimental condition of the inhalation trial. Since temperature is known to be important in degradation as well as recovery of volatilised heroin (Cook and Brine, 1985; Cook, 1991; Huizer, 1987), controlling the volatilisation temperature was considered essential; hence the simple solution of the heating device with a preheated brass sample holder. It might be argued that both smoking methods are potentially dangerous, as smoking heroin has been associated with progressive spongiform leukoencephalopathy (Keogh et al., 2003; Kriegstein et al., 1997, 1999; Wolters et al., 1982). However, to date no toxin has been identified

as the cause for this condition. Diacetylmorphine is not the most likely cause, considering that all cases published until now have occurred in users ‘chasing’ street heroin, which is known to be a very variable mixture of substances. The presence of diacetylmorphine in their street heroin is most likely one of the few similarities between users who develop spongiform leukoencephalopathy and those who do not.

The simple, temperature-controlled, standardised alternative for ‘chasing the dragon’ turned out to be less efficient, possibly because other important aspects of smoking heroin were not controlled. Many heroin addicts have developed tricks and habits in their chasing technique that serve to minimise the loss of heroin vapour through charring, combustion, and fumes escaping the straw. The heating device method did not allow optimal use of these ‘tricks of the trade’, which could have resulted in sub-optimal inhalation efficiency. An important difference between the inhalation methods was the absence of movement of the liquefied heroin on the heating device. This hampered efficient inhalation of volatilised heroin, since the fumes did not appear as a neat ‘dragon’s tail’, but rather as a broad smoke column or cloud. Furthermore, movement of liquid heroin might contribute to controlling the temperature of the drug, preventing overheating and subsequent decomposition. The volatilisation rate of the tablet could also differ between inhalation methods; during the study, patients complained of a slow volatilisation rate when inhaling using the heating device, reportedly even resulting in incomplete volatilisation of the tablet within the 10 min inhalation period (Hendriks et al., 2001). All of these aspects could have contributed to the low exposures to diacetylmorphine and metabolites after inhaling via the heating device. Moreover, it is likely that they also caused variation in the plasma concentrations of diacetylmorphine and 6-acetylmorphine during the inhalation session. The short half-lives of these substances, combined with the absence of samples taken during the inhalation session could have resulted in underestimation of AUC and C_{\max} values for diacetylmorphine and 6-acetylmorphine in this study. This means that the actual difference in efficiency between the inhalation methods might be reflected more accurately by the AUCs of morphine and its glucuronides.

Considering the pharmacokinetics and pharmacodynamics of diacetylmorphine, it is reasonable to assume that peak concentrations of diacetylmorphine and 6-acetylmorphine are responsible for the initial ‘flash’ effect and exposure to morphine and its metabolites for the more prolonged euphoria (Gyr et al., 2000). Therefore, our findings of significantly higher peak concentrations of diacetylmorphine and 6-acetylmorphine after ‘chasing the dragon’ could explain the trend towards improved subjective drug effects after ‘chasing the dragon’ compared to the heating device observed in the pharmacodynamic comparison study (Hendriks et al., 2001). However, since no plasma samples were obtained during the 10 min inhalation session, due to the intensive assessment schedule

for the pharmacodynamic parameters (Hendriks et al., 2001), it is not possible to link the actual diacetylmorphine and 6-acetylmorphine concentrations to the corresponding pharmacodynamic effects.

Interestingly, Hendriks et al. reported no difference in bioavailability between the two inhalation methods, based on the total excretion of morphine (conjugated and free morphine) in 24-h urine samples (Hendriks et al., 2001), while our plasma data indicate that the heating device yields $\pm 40\%$ lower AUCs for morphine and its glucuronides than ‘chasing the dragon’. It would be expected that these differences in plasma concentrations would be reflected (with some delay) in urine concentrations. It is possible that the combination of the alternated use of the inhalation methods and the long circulation time of morphine and its glucuronides has generated a carry-over effect, obscuring the difference between the smoking methods in the 24-h urine samples. The finding that baseline morphine-3-glucuronide concentrations were above LLQ on 18 out of 23 patient days supports this proposition. The determination of the bioavailability of inhaled heroin via measurements of total morphine (morphine+conjugated morphine) in urine must be considered a rough estimate, since it has been found that after intravenous administration of heroin, only 68% of the heroin dose was recovered as total morphine in urine (Mo and Way, 1966). In this study, an accurate determination of the absolute bioavailability using the plasma concentrations of diacetylmorphine and its metabolites was not possible, as no intra-patient comparison with intravenous administration was available.

Differences in inhalation technique, as well as (pharmacokinetic) patient characteristics contribute to the inter-patient variability in AUC (Fig. 2). The fact that intra-patient variability (error bars in Fig. 2) was similar to the inter-patient variability might indicate variability in inhalation efficiency. The observation that even experienced heroin chasers sometimes burn their eyebrows from accidental combustion of their heroin illustrates the existence of such inter-occasion variability.

No time effects were observed in the AUCs of any of the analytes, indicating that there was no apparent learning effect, neither for using the alternative inhalation method nor for inhaling a tablet rather than street heroin (powder or granules). Moreover, AUC values in our study were comparable (after dose correction) to those found by Rook et al. in a pharmacokinetic study among Dutch heroin addicts inhaling 200–300 mg of pharmaceutical heroin powder via ‘chasing the dragon’ (Rook, 2003). This was true for all analytes except for diacetylmorphine, of which the AUC was 65% higher in the high-dose study. This could have been a result of sampling during the inhalation session, which was not possible in our study. The half-lives of morphine and morphine glucuronides were also comparable to literature (Rook, 2003) and no differences were found in $T_{1/2}$ values between the inhalation methods in our study; no difference was expected, since in both

methods heroin is administered via inhalation and it has been shown that $T_{1/2}$ does not depend on route of administration (Rook, 2003).

In conclusion, ‘chasing the dragon’ was found to be a more efficient method for inhalation of diacetylmorphine/caffeine tablets than use of a heating device. Exposure to diacetylmorphine and its metabolites was found to be significantly higher, as well as peak concentrations of diacetylmorphine and 6-acetylmorphine. These differences could be explained by the technique that experienced heroin ‘chasers’ have developed to avoid degradation and loss of heroin fumes that cannot be applied when using the heating device. This may lead to degradation due to overheating of the sample and to decreased inhalation efficiency. In summary, we conclude that ‘chasing the dragon’ is a more effective method for inhaling heroin than the heating device used in this study.

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