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PLASMA LEVEL MONITORING OF THE MAJOR METABOLITES OF DIACETYLMOR PHINE (HEROIN) BY THE "CHA SING THE DRAGON" ROUTE IN SEVER E HEROIN ADDICTS

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KEYWORDS: heroin metabolites, pharmacokinetics, inhalation, polydrug use

ABSTRACT

The objective of the present study was to verify if severe physical health problems frequently encountered in heroin addicts and the concomitant use of alcohol and legal or illegal drugs other than heroin influenced the pharmacokinetics of the major metabolites of heroin.

We conducted a 90 minutes follow-up of the plasma concentrations of the pharmaceutical heroin, named diacetylmorphine (DAM), in patients recruited in a DAM assisted treatment centre. TADAM (Traitement Assiste par DiAcetylMorphine) aimed to compare the efficacy of heroin-assisted treatment (HAT) compared with methadone maintenance treatment (MMT) for heroin users considered as treatment resistant patients and who have severe physical and mental health problems.

Eleven patients were recruited. Blood samples were collected at baseline and 15, 45 and 90 minutes after DAM administration. All patients received DAM bythe "chasing the dragon" route. Plasma samples were analyzed by a previously described ultra-high pressure liquid chromatography coupled to tandem mass spectrometry (UHPLC/MS-MS) method.

A principal component analysis (PCA) was performed and 8 metabolite concentrations ratios were calculated to evaluate the influence of various factors (DAM dose, patient pathologies, concomitant use of medications, methadone, street heroin, alcohol and cocaine) on heroin metabolite pharmacokinetics. It seemed to be not affected by the DAM dose, patient pathologies and the concomitant use of medications, methadone, street heroin and alcohol. Cocaine use was the only parameter which showed differences in heroin pharmacokinetics.

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Introduction

In the European Union, between 1.3 and 1.4 million persons were considered as problematic opioid users in 2008 corresponding to 3.6-4.4 cases per 1000 population aged 15-64 years. (1). In Belgium, the use of heroin seemed to remain stable in 2005. The prevalence of heroin use was less than 1% but mortality varied from 5 to 35 per thousand person-years in opiate addicts (2). In order to reduce and possibly eliminate illicit heroin consumption and making patients more socially integrated, different substitution treatments were tried. Methadone maintenance treatment (MMT) is the first line treatment for opiate addicts in Belgium (1). However, among patients who followed MMT, many can be considered as treatment-resistant, sometimes because they don't respond positively to heroin replacement by methadone, sometimes because they present a genetic profile very different from others (3). It was suggested that for these patients, a treatment with pharmaceutical heroin could also be used as substitution treatment therapy (4). Since 1994, six countries experimented heroin-assisted treatment (HAT): Switzerland (4), the Netherlands (5), Spain (6), Germany (7), Canada (8) and the United Kingdom (9). It was shown that medical prescription of pharmaceutical heroin (diacetylmorphine or DAM) to chronic heroin addicts who have not responded favourably to MMT is effective in terms of physical and mental health, illicit heroin use and criminality and, in the same time, the feasibility and the safety of HAT were demonstrated (10-12). In Belgium, a project subsidized by the Federal Government, called TADAM (Traitement Assiste par DiAcetylMorphine), began in January 2011 in the city of Liege, where the number of heroin addicts is important (12). It is a randomised controlled study which evaluates the efficacy of MMT compared with HAT for patients who have been consuming heroin compulsively for many years, for whom MMT has failed and who present severe physical and mental health problems. When included, the patients received DAM prescribed by physicians one to three times a day in an outpatient centre where they can inject the product themselves or use the product by inhalation using the "chasing the dragon" technique: heroin is heated gently on aluminium foil with a lighter controlled by the patient. The heroin vapours generated by heating are inhaled into the lungs, using a straw in the mouth. The fumes appear to take the shape of the undulating tailof a dragon (13, 14).

After penetration into the lungs, heroin is absorbed almost instantly. Heroin is considered as a pro-drug that acts mainly by its agonistic metabolites. In plasma, heroin is rapidly hydrolysed in 6-monoacetylmorphine (6AM) and then into morphine. These reactions are catalysed by different types of esterases in blood (plasma and erythrocytes), liver and brain. Morphine is then glucuronidated by several subtypes of uridine-5'-diphosphateglucuronosyltransferase (UGT), mainly in the liver, resulting in morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The N-demethylation of morphine into the minor metabolite normorphine is mediated by cytochrome P450 enzymes 3A4 and 2C8 (11, 15). Heroin metabolism is presented in Figure 1. M3G has no affinity for the μ-opioid receptors and has no pharmacologic activity (15), but M6G remains psychoactive.

Polydrug use including the combination of heroin with illicit drugs (cocaine and cannabis), alcohol and sometimes medicines (benzodiazepines, neuroleptics), is today very common among heroin addicts (1).Moreover, severe heroin addicts are often in poor health; they suffer from malnutrition (16) and the prevalence of hepatitis C and HIV infection is higher than in

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general population because injecting drug users share contaminated injecting materials and have a high risk sexual behaviour (prostitution) (17, 18). The aim of the present study is to verify if the pharmacokinetics of the major metabolites of heroin is influenced by severe physical health problems (hepatitis C, HIV, nephropathy, etc) frequently encountered in a general population of heroin addicts and by concomitant use of alcohol and legal or illegal drugs other than heroin. To achieve this objective, we conducted a 90 minutes follow-up of the plasma concentrations of the DAM metabolites in patients recruited in the TADAM centre receiving DAM by the "chasing the dragon" route. No restrictions concerning health, concomitant medication, alcohol and cocaine use were defined.

METHODS

DIACETYLMORPHINE

Diacetylmorphine was imported from the Netherlands, where injectable and inhalable forms of DAM were registered for opioid addiction treatment in 2006. The powder inhaled by the patients is a mix of heroin and caffeine in a ratio of 3: 1.

PATIENTS

Patient characteristics are presented in Table 1. Two female and nine male volunteers aged 29-50 years were recruited for the study. Three patients (patients 1, 7 and 8) had a haemoglobin level lower than the lower limit of reference values. Four patients (patients 1, 2, 3 and 10) had impaired hepatic function with liver amino transferases ASAT (aspartate aminotransferase) and ALAT (alanine aminotransferase) and/or serum gamma-glutamyltransferase (GGT) higher than the normal upper limit. Three patients (patients 1, 2 and 4) had a disturbed renal function: they had a creatinine clearance lower than 90 ml/min. associated with a serum creatinine concentration of 179 µmol/L for patient 1, creatinine clearance was calculated according to the Cockcroft-Gault equation.

Concerning comorbidity and comedications, patients 1 and 2 were HIV positive and received abacavir, lamivudine, lopinavir and ritonavir as antiretroviral treatment,4 patients were suffering from chronic hepatitis C; patients 1 and 3 were consuming high quantity of alcohol daily; 5 patients were receiving psychotropic drugs as chronic anxiety treatment; 3 received 30 mg methadone daily. They were also using other psychotropic drugs: cocaine on a regular basis for 5 of them and cannabis for 8 of them.

All patients received DAM 3 times a day (morning, midday and evening session) - except for patients 1 and 2 who received DAM 2 times a day (midday and evening session) - 7 days a week. DAM daily doses ranged between 600 and 900 mg. No dose changes had been made for a period of at least 15 days before entering the study.

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STUDY PROTOCOL

Participation to the study was proposed to the patients on a voluntary basis and a written informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of the University of Liege (Belgian agreement n° B707201010144).

The study took place during midday administration for 8 patients and during evening administration for 3 patients; the DAM dose ranged between 150 and 400 mg (median: 250 mg). DAM was self-administered (inhalation) under the supervision of trained nurses; the treatment duration was 20 minutes on average. Blood samples were drawn from an intravenous catheter placed in the arm at baseline (10 minutes before the treatment inhalation) and 15, 45 and 90 minutes after the DAM administration. Between the first blood sampling and the last, the maximum delay was 2 hours. Patients had to stay in the TADAM deliverance centre all the time; they were allowed to smoke tobacco cigarettes twice. The sample at 90 minutes was not drawn for patient 1 because of venous sclerosis.

SAMPLES ANALYSIS

Blood was collected in two 4 ml polypropylene tubes, containing 2.25 mg/ml sodium fluoride. Sodium fluoride inhibits the plasma esterase activity and contributes to stabilise analyte concentration (19). Blood samples were centrifuged immediately and plasma fractions were stored at -20°C prior to analysis which was performed the following day. The quantification of opiates and opioids in plasma was done according to a previously described method (20). Briefly, 50 µL of deuterated internal standards were added to 500 µL of plasma which were next acidified with 0.15N HCI. Oasis MCX (30 mg, 1ml) cartridges purchased from Waters (Zellik, Belgium) were used for solid phase extraction (SPE). The conditioning was performed with methanol, water, and 1OmM citric acid and the acidified sample was loaded onto the column. Then, the cartridges were washed with 2% formic acid and dried. The elution was done with ammonia in methanol (5/95: VN). The eluate was evaporated to dryness and reconstituted with a mixture of 5 mM ammonium formate pH3 and methanol adjusted to pH3 with formic acid (90/lO:VN). Ten µL were injected on the ultra-high pressure liquid chromatograph (UHPLC) Acquity coupled to a tandem mass spectrometer Quattro Premier (Waters, Zellik, Belgium). The chromatographic separation was performed on an Acquity High Strength Silica HSS-T3 column (100x 2.1 mm, 1.8 µm, Waters). The mobile phase consisted in 5mM ammonium formate in water (pH3) and methanol adjusted to pH3 with formic acid delivered according to a gradient mode. The tandem mass spectrometer operated in the positive electrospray mode at 1.0 kV. Two multiple reaction monitoring (MRM) sequences were studied by analyte. Illicit heroin consumption markers (6-acetylcodeine, papaverine, noscapine, meconine and 7-desmethylmeconine) were also analysed with this technique.

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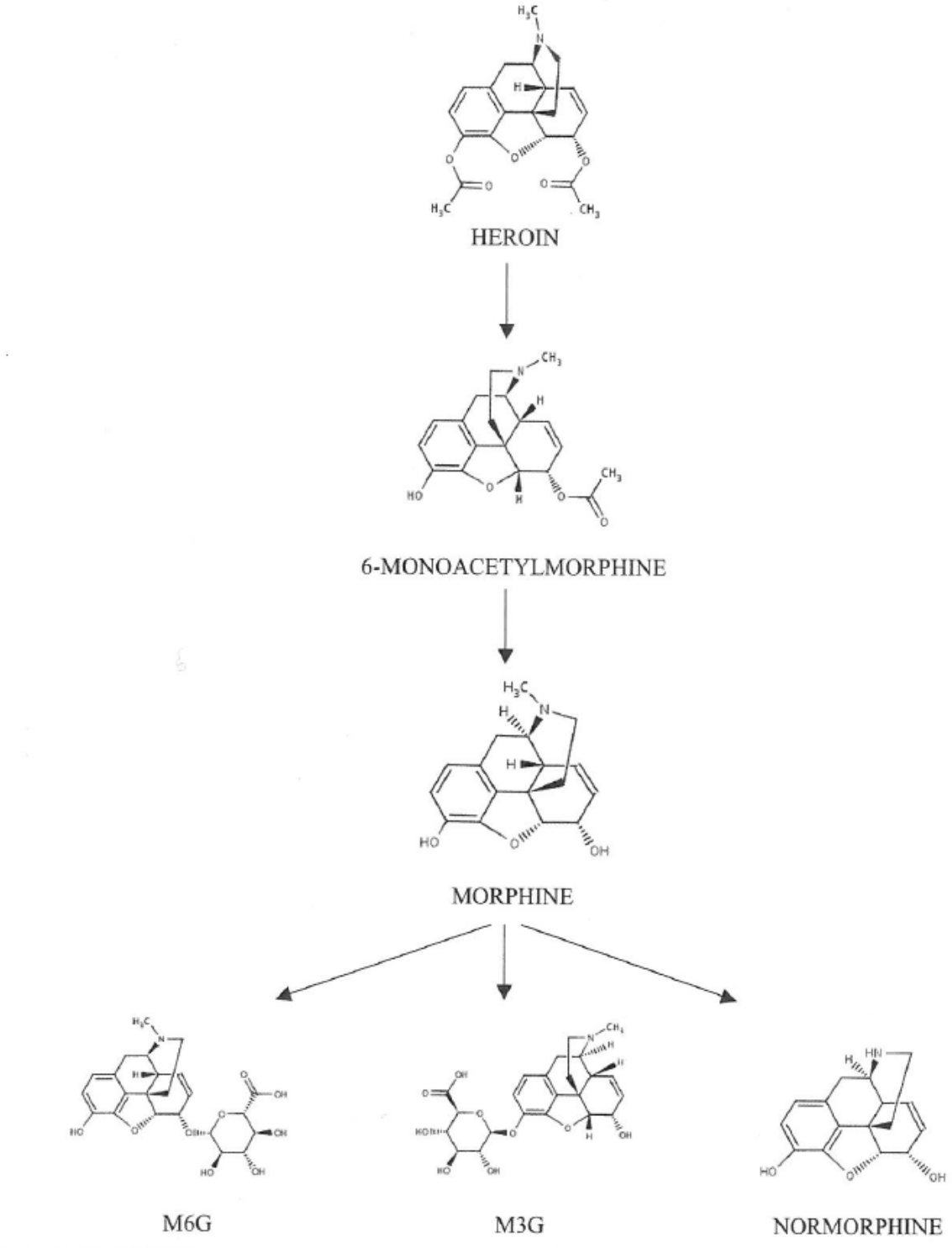

Figure 1. *Heroin metabolism.*

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Table 1 Patient characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Reference interval
Sex	M	F	M	F	M	M	M	M	M	M	M	-
Age (years)	47	50	45	44	41	35	34	35	29	41	49	-
Length (m)	1.78	1.60	1.80	1.63	1.76	1.75	1.78	1.76	1.74	1.81	1.78	-
Weight (kg)	62	68	61	58	68	67	65	68	70	83	91	-
Body mass index (kg/m^2)	**19.6**	26.6	**18.8**	21.8	22.0	21.9	20.5	22.0	23.1	25.3	28.7	20-25
Hb (g/dL)	**13.2**	14.9	14.6	14.4	14.6	15.9	**13.1**	**12.5**	13.3	15.0	14.5	M : 13.3-17.2 F : 11.7-15.0
ALAT (U/L)	**42**	**41**	**50**	15	10	10	n.a.	10	14	38	20	6-40
ASAT (U/L)	25	**43**	**79**	18	21	18	n.a.	13	20	32	27	14-40
GGT (U/L)	**175**	**145**	**56**	17	20	19	45	10	8	**65**	15	5-50
Creatinine (µmol/L)	**178.6**	75.7	66.0	80.1	73.0	81.8	71.3	66.9	83.6	75.7	60.7	M : 65-120 F : 50-100
Creatinine clearance (ml/min.)	**40**	**84**	110	**72**	115	107	121	133	116	136	170	M : 100-140 F : 90-130
HIV	**Positive**	**Positive**	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	-
Hepatitis C	**Positive**	**Positive**	**Positive**	Negative	Negative	Negative	Negative	Negative	**Positive**	Negative	Negative	-
DAM daily dose (mg)	750	600	650	700	700	900	750	650	900	700	675	-
DAM dose (mg)	400	300	250	200	200	300	250	150	300	200	175	-
Methadone treatment	**Yes**	**Yes**	No	No	No	No	No	No	**Yes**	No	No	
Cocaine use	No	No	No	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**	No	No	
Cannabis use	Yes	**Yes**	**Yes**	No	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	No	No	
Alcohol abuse	**Yes**	No	**Yes**	No	No	No	No	No	No	No	No	
HIV treatment Medication	Kivexa® Kaletra®	Kivexa® Kaletra®	No	No	No	No	No	No	No	No	No	
Psychotropic drugs	Trazodone Clonazepam Prothipendyl	Trazodone Clonazepam Prothipendyl	Clonazepam	Clonazepam	Clonazepam	No	No	No	No	Trazodone	No	

Hb = haemoglobin ; ALAT = alanine aminotransferase ; ASAT = aspartate aminotransferase ; GGT = gamma-glutamyltransferase ; HIV = Human Immunodeficiency Virus.
n.a. = not available.

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RESULTS

EXPLORATORY DATA ANALYSIS

To understand the behaviour of the DAM metabolites and the correlation between various factors, a principal component analysis (PCA) on the correlation matrix was performed. The factors studied with the PCA where the logarithm of the concentrations of the DAM metabolites 6AM, morphine, M3G, M6G, the dose of DAM administered and time of blood sampling. The first two principal components (PCs) explained 37.5% and 24.5% of the variability, respectively. Figure 2 shows the scores plot and the loadings plot of these two PCs. When looking at the scores plot in Figure 2, we can observe that these two PCs discriminate the patients in two groups: those who have consumed cocaine and those who have not. This group generation is mainly due to the 2nd PC and the loadings that are mostly responsible of this behaviour are morphine, M3G and M6G concentrations.

Finally, the dose of DAM administered is strongly positively correlated with M3G and M6G concentrations and not correlated with 6AM concentration.

PHARMACOKINETICS OF DAM METABOLITES

The plasma concentrations-time curves of 6AM, morphine, M3G, M6G and normorphine are presented in Figure 3.

Three patients (patients 1, 2 and 3) were found positive for 6AM in plasma samples collected prior to DAM administration. The highest concentration of 6AM was detected 15 minutes after the end of the inhalation, its median value was equal to 68 µg/L and ranged from 15 to 156 µg/L; the concentration decreased rapidly until 21 and 9 µg/L after 45 and 90 minutes respectively. The calculated 6AM plasma half-life was 22.6±9.2 minutes on average.

Morphine was present in all collected samples. The residual median concentration of morphine at baseline was 68 µg/ L, ranging from 33 to 252 µg/L; morphine reached its highest level 15 minutes after DAM administration with a median concentration of 158 µg/L. The morphine concentration decreased after 45 minutes for 8 patients. The morphine median concentrations were 138 and 117 µg/ L after 45 and 90 minutes respectively. The morphine plasma half-life was calculated at 140.6±67.8 minutes on average.

M6G was found positive in all collected samples. The M6G plasma concentration at baseline was 191 µg/L, ranging from 73 to 684 µg/L. The highest concentration of M6G was reached in samples taken at 45 and 90 minutes. The M6G median concentrations were 275,295 and 251 µg/L after 15, 45 and 90 minutes respectively.

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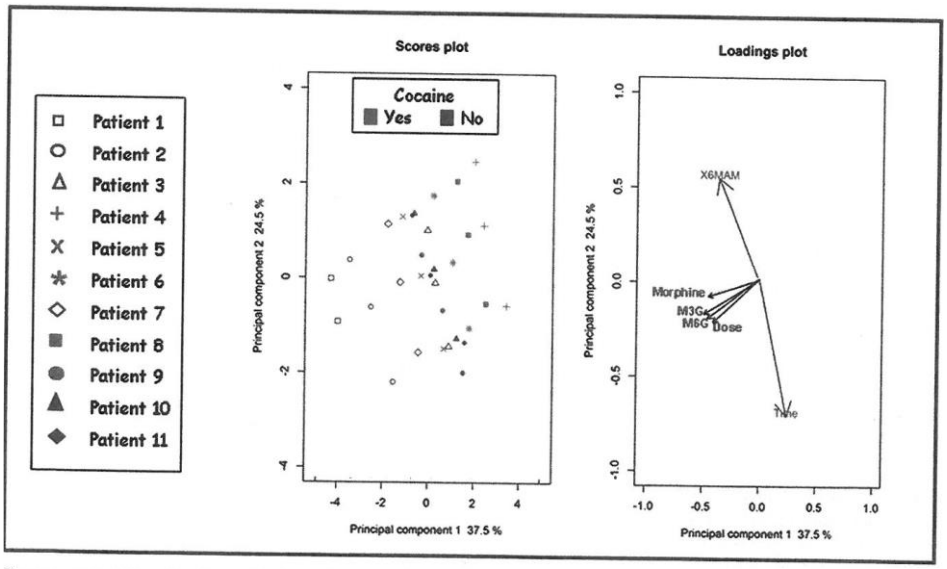

Figure 2. *Scores plot and loadings plot of the two first principal components of the Principal Component Analysis of themetabolites 6AM (X6MAM), morphine, M3G, M6G, the dose of DAM administered (Dose) and the time of blood sampling (Time).*

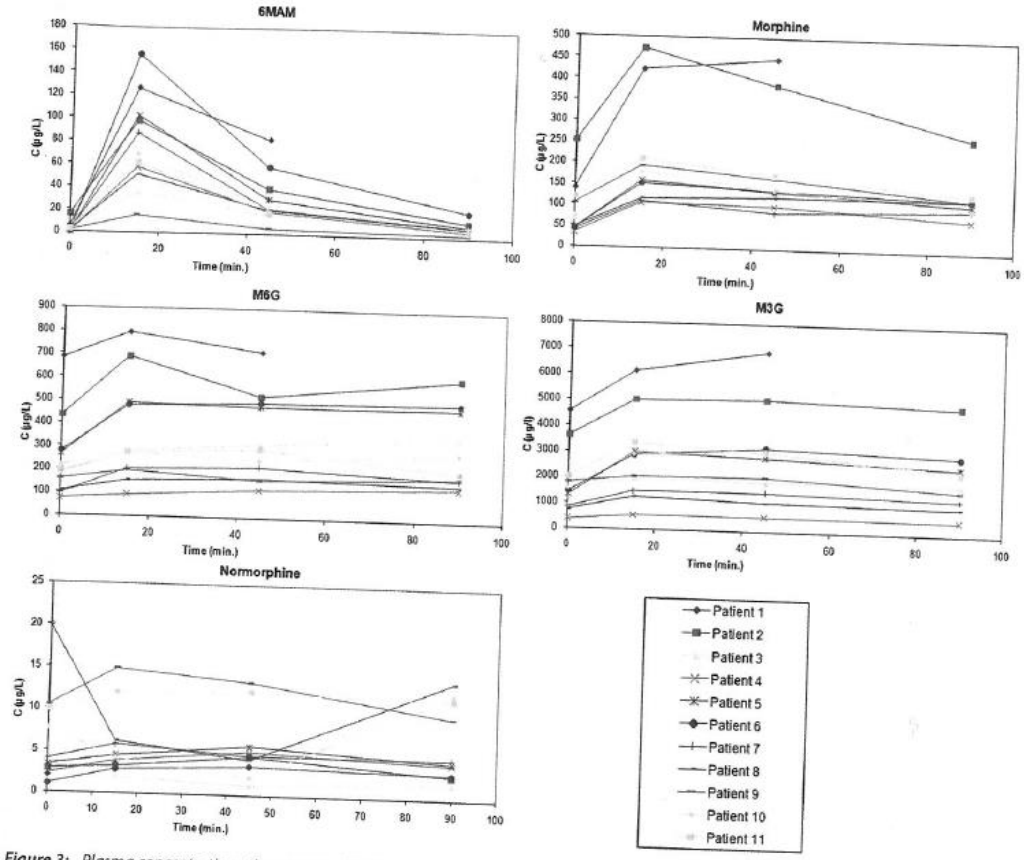

Figure 3: *Plasma concentrations-time curves of 6AM, morphine, M3G, M6G and normorphine.*

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INFLUENCE OF BIOLOGICAL AND CLINICAL PARAMETERS ON DAM METABOLITE PHARMACOKINETICS

The influence of biological andclinical parameters on DAM metabolite pharmacokinetics was evaluated on the basis of the study of 8 metabolite concentrations ratios calculated at each sampling time. The ratios between the different metabolites were chosen taking into account their chronology of appearance: DAM was first deacetylated in 6AM and in morphine which was then converted to M6G and M3G by glucuronidation. The 8 studied ratios are presented in Table 3.It was shown that almost all ratios were stable during the 90 minutes followup except for ratios which have 6AM as denominator: "MOR/6AM '; "(MOR + M3G)/6AM'; "(MOR + M6G)/6AM" and "(MOR +M6G+M3G)/6AM''.

Patients were grouped according to several criteria: low BMI (lower than 20), haemoglobin low level (lower than 13.3 g/dl), impaired renal function (creatinine clearance lower than 90 ml/min.), disturbed hepatic function (GGT and/or ASAT and ALAT higher than the upper limit of normal), HIV and hepatitis C seropositivity, alcohol abuse, cocaine, methadone and psychotropic drug use.

The mean values for the ratios and for 6AM and morphine half-lives were compared using a t-student test and a Mann-Whitney test.

For patients with hepatic disease (patients 1, 2, 3, 9 and 1O), when compared with other patients, no difference was found for the 8 tested ratios and for 6AM and morphine half-lives. Therefore, a disturbed hepatic function or chronic hepatitis C did not affect DAM pharmacokinetics.

For patients suffering from impaired renal function (patients 1, 2 and 4), when compared with other patients, no difference was found between the 8 calculated ratios and between 6AM and morphine half-lives. Impairment of renal function did not significantly modify heroin transformation into metabolites.

Similarly, low haemoglobin levels (patients 1,7 and 8) did not influence heroin metabolism since no difference between metabolite concentrations ratios and 6AM and morphine half-lives was observed.

For the 2 patients (patients 1 and 2) infected by HIV and treated by abacavir, lamivudine, lopinavir and ritonavir, calculated ratios were not significantly different compared to seronegative patients.

The same methodology was applied to patients consuming alcohol daily, patients treated with methadone and with psychotropic drugs showing that concomitant use of alcohol, methadone and psychotropic drugs did not change DAM metabolism.

For the group of cocaine users, several differences were found for the calculated ratios as suggested previously by the scores plot of Figure 2. After 15 minutes, the ratios "MOR/6AM'; "(MOR + M3G)/6AM" and "(MOR + M6G)/6AM" were found respectively 2.0, 2.5 and 2.2 times lower in cocaine users compared to other patients. After 45 minutes, the 2 ratios "(MOR + M3G)/6AM" and "(MOR +M6G + M3G)/6AM" were found respectively 2.2 and 2.0 times lower in cocaine users. After 90 minutes, no ratio was found different in cocaine users. Mann-Whitney test for those ratios is presented in Table 4.

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Finally, patient 2 was found positive for the markers of street heroin consumption (acetylcodeine, papaverine, noscapine, meconine and 7-desmethy lmeconine) but metabolite concentrations ratios were not modified.

Table 2 Metabolite concentrations expressed in µg/L in samples collected at baseline and 15, 45 and 90 minutes after DAM administration

Time (minutes)	Baseline		+ 15		+ 45		+ 90	
Metabolites	Median	Range	Median	Range	Median	Range	Median	Range
6AM	ND	ND-16	68	15-156	21	5-82	9	2-22
Morphine	68	33-252	158	106-473	138	87-450	117	75-266
M3G	1471	367-4548	2882	542-6140	2841	555-6923	2106	526-4905
M6G	191	73-684	275	93-795	295	120-714	251	139-608
Normorphine	4	ND-16	5	2-14	5	2-13	5	2-13

ND = Not detected.

Table 3 Heroin metabolite concentrations ratios. Values are expressed as median (range)

Time (min.)	M3G/M6G	M3G/MOR	M6G/MOR	(M3G+M6G)/ MOR	MOR/6AM	(MOR+M3G)/ 6AM	(MOR+M6G)/ 6AM	(MOR+M6G+M3G)/ 6AM	(6AM+MOR+M6G)/ M3G
Baseline	6.92 (4.95-11.34)	20.15 (11.14-33.56)	2.38 (1.54-6.49)	22.53 (13.37-40.05)	n.a.	n.a.	n.a.	n.a.	0.19 (0.15-0.29)
+ 15	7.27 (5.79-12.16)	14.51 (5.13-18.93)	1.52 (0.89-3.15)	16.39 (6.02-22.08)	2.62 (0.98-12.58)	45.29 (11.36-145.56)	6.60 (3.49-25.43)	49.27 (13.00-158.42)	0.25 (0.16-0.47)
+ 45	6.85 (4.61-12.86)	15.37 (5.41-23.24)	1.69 (0.97-3.59)	17.03 (6.58-26.83)	5.88 (2.37-34.77)	98.92 (33.90-468.00)	16.97 (10.90-68.46)	114.85 (40.11-501.69)	0.22 (0.13-0.44)
+ 90	7.03 (3.78-11.06)	17,31 (7.03-23.94)	2.07 (1.25-4.30)	19.69 (8.89-27.99)	13.27 (5.69-51.21)	245.11 (115.56-746.21)	47.27 (28.73-129.33)	288.44 (142.33-824.33)	0.22 (0.15-0.42)

n.a. = not available

DISCUSSION

The aim of the present study was to evaluate the evolution of heroin metabolite concentrations immediately after heroin consumption in severe heroin addicts without ineligibilities concerning health, comedication, alcohol and cocaine use. To our knowledge, only one study is available on heroin metabolite pharmacokinetics by the "chasing the dragon" technique in a general population of heroin addicts (21). Moreover, the pharmacokinetics of the "chasing the dragon" consumption mode has been investigated in only few studies (21, 22) while it is the most appreciated by occidental European heroin addicts since few years (1). Heroin metabolite concentrations levels were similar to levels found in other studies (21). The design of our study did not allow us to calculate the plasma half-life for M6G and M3G since their concentrations were not decreasing enough after 90 minutes which was the time of the last collected sample. 6AM and morphine plasma half-lives were similar to those found inthe Rook's studies (21, 22). Almost all studied heroin metabolite concentrations ratios were stable - except for those which have 6AM as denominator - for all patients during the 90 minutes study whatever the DAM dose, the patient pathologies and the concomitant use of medications, methadone, street hemin and alcohol. Ratios with 6AM as denominator were found significantly lower in cocaine users and PCA showed two distinct groups depending on the consumption of cocaine. This can be explained by the fact that cocaine and heroin metabolism are catalysed by the same liver carboxylesterases (23); Rook et al. found that the terminal half-life of 6AM was prolonged by

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13% in cocaine addicts (21).As shown on the scores plot of Figure 2, the cocaine users had generally higher blood concentration of 6AM and lower blood concentration of morphine, M3G and M6G than non-cocaine consumers.

The ratio between psychoactive compounds (6AM, morphine, M6G) and the non-psychoactive metabolite (M3G) was stable; patients had therefore a constant quantity of circulating pharmacologically active substances during at least 4 hours, the elapsed time between morning and midday or between midday and evening administrations.

The only metabolite concentrations ratio calculated in other studies was the M3G/M6G ratio which was equal to 7.0 on average in our study and was similar to the mean ratio of 5.8 found by E. Rook on 9 pharmaceutical heroin inhalers (21). It seems that antiretroviral therapy did not affect the pharmacokinetics of DAM, as it is the case for methadone (24), this could be expected since cytochrome P450 enzymes are not very involved in heroin metabolism. In the same order of ideas, we did not note influence of alcohol on heroin pharmacokinetics as it was suggested in another study (25).

Table 4 Mann-Whitney test for MOR/6AM, (MOR+M3G)/6AM and (MOR+M6G)/6AM ratios 15 minutes after DAM treatment, for (MOR+M3G)/6AM and (MOR+M6G+M3G)/6AM ratios 45 minutes after DAM treatment

	Cocaine users	No cocaine users
15 minutes after DAM treatment		
MOR/6AM		
	n = 4	n = 7
Median Range	1.70 1.25-2.29	3.38 0.98-12.58
p	0.0424	
(MOR+M3G)/6AM		
	n = 4	n = 7
Median Range	22.68 11.36-30.84	56.10 19.45-145.56
p	0.0121	
(MOR+M6G)/6AM		
	n = 4	n = 7
Median Range	4.47 3.49-6.35	9.63 4.05-25.43
p	0.0121	
45 minutes after DAM treatment		
(MOR+M3G)/6AM		
	n = 4	n = 7
Median Range	63.37 33.90-98.92	138.97 57.55-468.00
p	0.0424	
(MOR+M6G+M3G)/6AM		
	n=4	n=7
Median Range	75.50 40.11-114.85	150.53 66.08-501.69
p	0.0424	

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Conclusion

The pharmacokinetics of heroin metabol ites seemed to be not affected by the DAM dose,patient pathologies and the concomitant use of medications, methadone, street heroin and alcohol. Cocaine use was the only parameter wich showed differences in heroin pharmacokinetics.

Acknowledgments

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CONFLICT OF INTEREST: None.

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