Pharmacokinetics and Pharmacokinetic Variability of Heroin and its Metabolites: Review of the Literature

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Abstract: This article reviews the pharmacokinetics of heroin after intravenous, oral, intranasal, intramuscular and rectal application and after inhalation in humans, with a special focus on heroin maintenance therapy in heroin dependent patients. In heroin maintenance therapy high doses pharmaceutically prepared heroin (up to 1000 mg/day) are prescribed to chronic heroin dependents, who do not respond to conventional interventions such as methadone maintenance treatment. Possible drug-drug interactions with the hydrolysis of heroin into 6-monoacetylmorphine and morphine, the glucuronidation of morphine and interactions with drug transporting proteins are described. Since renal and hepatic impairment is common in the special population of heroin dependent patients, specific attention was paid on the impact of renal and hepatic impairment. Hepatic impairment did not seem to have a clinically relevant effect on the pharmacokinetics of heroin and its metabolites. However, some modest effects of renal impairment have been noted, and therefore control of the creatinine clearance during heroin-assisted treatment seems recommendable.

INTRODUCTION

Heroin (diacetylmorphine, (5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol diacetate (ester), diamorphine or Diagesil®) is a semi-synthetic morphine derivative and a powerful opioid analgesic. Apart from its use in pain management, the medical prescription of pharmaceutically prepared heroin is also applied in treatment of chronic heroin dependents, who do not respond to conventional interventions such as methadone and buprenorphine maintenance treatment [1,2]. Heroin-assisted treatment significantly reduced the drug seeking behaviour, and consequently led to significant improvement of physical health, mental status and social functioning of heroin dependent patients[3-5]. Heroin-assisted maintenance treatment is currently available in the UK, Switzerland and The Netherlands, for patients who suffered from severe heroin dependency for many years and where alternative treatments like methadone maintenance therapy have failed. In some other Western-European countries and Canada trials with heroin-assisted treatment are considered [6]. At the start of heroin-assisted treatment, the initial heroin dose is based on the estimated tolerance level of the individual patient. In the course of the treatment, the prescribed heroin dose is based on individual titration, taking the clinical effects and the personal response of the patients as the main dose defining indicators. In responders to heroin-assisted treatment, the prescription of heroin will be continued for several months or even years [7]. Unexpected changes in concentrations of heroin and its biological active metabolites in plasma, however, can induce withdrawal symptoms or toxic adverse events, and must therefore be avoided. Furthermore, heroin can be administered by different routes and during treatment alternative routes of administration may be used. In this article the consequences of alternative heroin administration methods for the pharmacokinetics of heroin are discussed.

Another cause of changing plasma levels of heroin is the concurrent use of other medications. Heroin addicted patients form a population at risk for many other disorders, and frequently medication other than heroin such as tuberculostatics, HIV medication, antidepressants and neuroleptics are prescribed in a heroin-assisted treatment setting. Furthermore, heroin dependent patients are often poly-drug users. The use of cocaine, alcohol and "street" benzodiazepines is common during heroin-assisted treatment trials in outpatient clinical settings.

Both the liver and kidney are involved in heroin metabolism and excretion. Hepatic impairment e.g. due to viral hepatitis and renal damage due to injection of contaminants are very common in this special population [8,9].

The aim of this manuscript is to review the pharmacokinetics of heroin and its metabolites and the influence of the route of administration, drug-interactions and the presence of liver and kidney impairment on the pharmacokinetics. The review starts with a summary of the literature on the chemical properties of heroin and the metabolic enzymes.

For other reviews concerning the pharmacokinetics of heroin we refer to Sawynok *et al.* and Kendall and Latter [10,11].

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1574-8847/06 $50.00+.00

METHOD

A Medline search was performed on articles from the period 1960 till March 2005. For review of the heroin metabolism, search terms like heroin (diacetylmorphine or diamorphine), (pharmaco)-kinetics and esterase were applied.

For the study on the influences of covariates on the metabolism of heroin and its primer metabolites we used search terms like interaction, 6-(mono)acetylmorphine, morphine, glucuronide, uridine diphosphate glucuronosyl transferase (UGT), P-glycoprotein and OATP (Organic Anion Transporting Polypeptides), age, gender, renal and hepatic.

From relevant citations, the references were reviewed on the usefulness for this article.

RESULTS

Chemical Properties of Heroin and its Metabolites

Heroin was developed in 1874 by A.C. Wright. Heroin was first marketed in 1898 as an antitussive for patients with asthma and tuberculosis [12]. In the synthesis of heroin, morphine molecules are acetylated in an excess of acetic anhydride at higher temperatures. Initially acetylating occurs at position 3, the phenolic hydroxyl group of the morphine molecule, and consecutively at position 6, the alcoholic hydroxylgoup (see Fig. (**1**)) [13]. The morphine ingredient is a natural alkaloid harvested from the latex of Papaver somniferum poppies. Opium latex may contain many other alkaloids like papaverine, codeine, noscapine and thebaine [14,15].

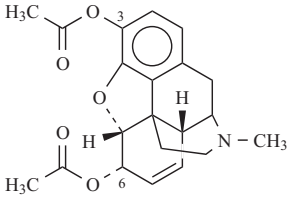

Fig. (1). Molecule structure of heroin.

The chemical addition of the ester groups renders lipophilicity [16,17]. Therefore, heroin may pass the blood-brain-barrier much faster than its precursor morphine [18,19]. This contributes to a more intense pharmacodynamic effect with a more immediate onset of heroin compared to morphine. However, opioid receptors are stereo-specific and heroin shows a lower opioid receptor affinity than its metabolites that lack conjugates at the 3-hydroxyl group, such as 6-monoacetylmorphine, morphine, and morphine-6-glucuronide (M6G) [20,21]. Therefore, heroin is often considered as a pro-drug that mainly acts by its metabolites [20,22].

The ionisation constant (pKa) of heroin is 7.6. At physiologic pH on average 40% of heroin will be in a non-ionised form and therefore accessible for membrane-transport. In comparison, morphine has a pKa of 9.4. The binding capacity of heroin to serum albumin or erythrocytes is comparable to morphine, namely 20-40% [23].

The heroin ester bonds are rapidly hydrolysed in aqueous solution or in plasma, although stability is improved at pH 3.5-5.2 and at temperatures below 4°C [24,25].

Metabolism

Metabolism of heroin is visualised in Fig. (**2**). In human plasma, heroin is rapidly hydrolysed to 6-monoacetylmorphine and finally into morphine. Thereafter, glucuronides are conjugated to the 3- and 6-positions of morphine. Morphine-3-gluronide (M3G) is the major metabolite (M6G/M3G ratio approximately 0.15) [26]. Morphine-glucuronides are hydrophylic compounds, that are mainly excreted in urine, and in minor quantities in bile. After intravenous administration, about 70% of the total heroin dose is recovered in urine, mainly as conjugated morphine (55%) [27,28]. Other metabolites that were found in minor quantities in human urine after heroin intake are normorphine-glucuronide, codeine, morphine-3-6-diglucuronide and morphine-3-ethersulphate [29-33].

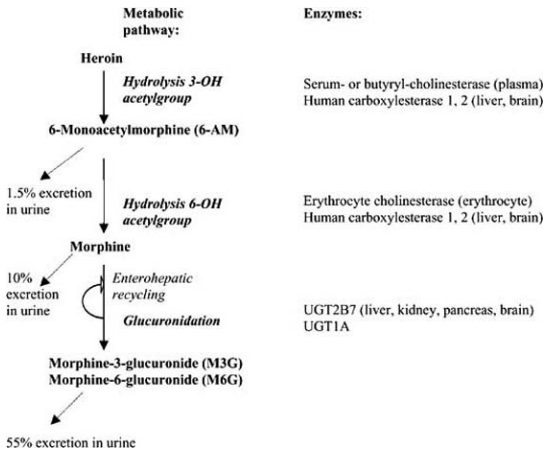

Fig. (2). Heroin metabolism.

Metabolic Enzymes

The hydrolysis of heroin and 6-monoacetylmorphine is catalysed by different types of esterases (Fig. 2) [34]. Esterases are abundantly present in the circulation and in tissues.

There is a large variability in phenotypes and genotypes of human esterases [35,36]. Heroin was not hydrolysed in serum of a carrier of the silent plasma cholinesterase variant gene *in vitro* [37]. To what extent genetic differences in expressing esterase activity account for variability in heroin metabolism *in vivo,* is not reported.

Glucuronidation is catalysed by uridine 5´-diphosphate-glucuronosyltransferases (UGT). Primarily the UGT2B7 and in minor quantities the UGT1A1 subtypes are involved in morphine metabolism [37,38]. Glucuronidation of morphine mainly occurs in the liver, but also in minor quantities in other organs like brain, kidney and intestines [39-41]. UGT 2B7 or UGT1A1 polymorphisms did not contribute significantly to the variability in the morphine/morphine glucuronides ratio [38,42]. N-demethylation of morphine

into the minor metabolite normorphine is mediated by cytochrome P450 enzymes 3A4 and 2C8 [43].

Pharmacokinetics of Heroin

Results of pharmacokinetic studies on intravenously administered heroin are summarised in Table **1a** [31,44-46]. Pharmacokinetic parameters of heroin and its metabolites following intramuscular administration [47,48], intranasal snorting [47,49] or by inhalation of vapours of heated heroin [46,50] are summarised in Table **1b**.

Heroin blood levels declined very rapidly and mono-exponentially after intravenous drug administration and became undetectable after 10-40 min, with a lower limit of quantification of the bioanalytical methods between 5-50 ng/mL. Estimates of the volume of distribution of heroin varied between 60-100 L. The half-life was on average 1.3-7.8 min. The estimates of the mean heroin clearances of 128-1939 L/hr exceeded by far the hepatic and renal blood flow (on average 80 L/hr and 60 L/hr, respectively in a standard 70 kg human), indicating that heroin is metabolised primarily in peripheral tissue and in the circulation. The high clearance of heroin from plasma is mainly due to the rapid elimination by esterases, spontaneous hydrolysis of heroin in the basic environment of body fluid and the extensive distribution.

In a study with high intravenous heroin doses by Rentsch *et al.*, heroin and its major metabolites were measured in arterial and venous blood [45]. Initially, the arterial plasma concentrations of heroin and 6-monoacetylmorphine were considerably higher than venous plasma values, although equilibrium between the arterial and venous compartments was already achieved within 4-6 minutes.

Heroin was not recovered in urine except for one study, where 0.13% of the heroin dose was recovered unchanged in urine after long-term continuous intravenous administration [28]. This finding implicates that heroin is virtually fully converted into its metabolites before renal excretion.

Pharmacokinetics of Metabolites: 6-Monoacetylmorphine

The maximal concentrations of 6-monoacetylmorphine, the first hydrolysis product of heroin, were already reached 0.7-2.7 min after intravenous heroin administration (see Tables **1a** and **1b**). 6-Monoacetylmorphine is very lipophilic and may have higher receptor affinity than its precursor heroin [20]. It is considered to be responsible for all the acute effects following heroin administration [22].

6-Monoacetylmorphine levels declined somewhat slower than heroin levels. Estimates of half-life and clearance ranged from 5.4 to 52 min and from 564 to 607 L/hr, respectively (Tables **1a**,**1b**). After heroin injection, 6-monoacetylmorphine was detected in plasma for 1-3 hours. About 1.3% of the total intravenous heroin dose was recovered as 6-monoacetylmorphine in urine [28]. 6-Monoacetylmorphine was detectable for 1.2-4.3 hrs in urine after intravenous injection or inhalation of 2.6-20 mg heroin [51].

Table 1a. Overview of Pharmacokinetic Parameters of Heroin, its Metabolites 6-Monoacetylmorphine (6-AM) and Morphine (MOR) (Mean ± SD or Range). In these Studies, Heroin was Administered Intravenously by Injection of a Bolus or by 3 hrs Infusion

	Reference	Inturrisi [44]	Jenkins [50]	Rentsch [45]	Rook [46]	Gyr [31]	Girardin [48]
	Application	3hrs infusion	Bolus injection	Bolus injection	Bolus injection	Bolus injection	Bolus injection
	Subjects (n)	3	2	8	10	2	8
	Subject category	I	II	III	III	III	III
Heroin	Dose (mg)	20-60	3-20	40-210	133-450	200	146±48
	Vd (L)	-	66 ± 32	70±29	96±13	60-63	37±16
	Cl (L/hr)	128±9	685 ± 289	822±252	930±40	1194-1920	696±168
	$t^1/_2$ (min)	3.0±1.3	3.6 ± 1.4	3.3±1.2	3.8±1.1	1.3-2.2	3.0 ± 1.0
	C_{max} (ng/mL)	-	-	-	3119±60	1530-2270	3960±1369
	t_{max} (min)	-	-	-	-	-	-
	AUC (µgr/l*hr)	57-114	56.5 ± 35.1	-	329±40	5.2-8.8	185±62
6-AM	Cl/Fm (L/hr)	-	-	564±210	607±20	-	-
	$t^1/_2$ (min)	-	9.3±8.9	-	22±3	46-52	3.0±1.0
	C_{max} (ng/mL)	-	-	-	1731±190	4620-3400	5742±1837
	t_{max} (min)	-	-	2.7±2.4	-	0.7-1.5	0.3±0.1
	AUC (µg/l*hr)	-	-	-	482±20	26.3-27.2	257±12
	$t^1/_2$ (min)	-	109±107.5	-	177±10	182-287	-
MOR	C_{max} (ng/mL)	-	-	-	829±84	340-810	-
	t_{max} (min)	-	-	6.4±5.8	7.8±2	3.6-3.9	-
	AUC (µgr/l*hr)	-	-	-	2594±105	64.3-84.7	-

Subject category: I cancer patients, **II** regular heroin users after 3 days abstinence, **III** heroin dependents in heroin-assisted treatment.

Pharmacokinetic parameters: AUC= area under the curve, **Cl**= clearance, $\mathbf{C_{max}}$= maximal concentration, $\mathbf{t^1/_2}$ =half-life $\mathbf{t_{max}}$= time-point C_{max}, **Vd**= distribution volume, **Fm**=fractions metabolized.

Table 1b. Pharmacokinetic Parameters of Heroin and Metabolites 6-Monoacetylmorphine (6-AM) and Morphine (MOR) (Mean ± SD or Range). Heroin was Administred Intra-Muscular (im), Intranasal (in) and by Inhalation of Heroin Vapours After Heating

	Reference	Skopp [47]		Cone [49]	Girardin [48]		Jenkins [50]	Rook [46]
	Application	Im	In	In	Im	Im	Inhalation	Inhalation
	Subjects (n)	2	6	6	6	8	2	12
	Subject category	II	II	II	II	III	II	III
Heroin	Dose (mg)	6	6-12	6-12	6-12	233±51	2.6-10.5	133-450
	Vd/F (L)	-	-	-	-	-	120±94	147±16
	Cl/F (L/hr)	-	-	-	-	-	1255±1183	1939±30
	$t^1/_2$ (min)	5.4	5.4±0.6	4.2±1.2	7.8±4.2	-	3.3±1.8	3.2±1.2
	C_{max} (ng/mL)	45.7	0-44.3	-	-	3293±888	-	685±29
	t_{max} (min)	4.8	4.8-15	<5	<5	4±2	-	2
	AUC (µg/L*hr)	0-6	3.7-6.5	24.5	34.5	962±265	-	174±54
	F (%)	-	-		-	346 ± 146	100±94	52.3±10
6-AM	Cl/F*Fm (L/hr)	-	-	-	-	-	-	1826±59
	$t^1/_2$ (min)	-	-	-	-	-	5.4±1.7	26±5
	C_{max} (ng/mL)	-	-	-	-	1115±426	-	289±37
	t_{max} (min)	-	-	-	-	6±2	-	-
	AUC (µgr/l*hr)	-	-	-	-	453±88	-	177±30
MOR	$t^1/_2$ (min)	-	-	-	-	-	18.8±14.3	184±15
	C_{max} (ng/mL)	-	-	-	-	487±229	-	271±30
	t_{max} (min)	-	-	-	-	17±6	-	8.0±5
	AUC (µgr/l*hr)	-	-	-	-	1455±730	-	1043±200

Subject category: I cancer patients, **II** regular heroin users after 3 days abstinence, **III** heroin dependents in heroin-assisted treatment

Pharmacokinetic parameters: AUC= area under the curve, **Cl**= clearance, $\mathbf{C_{max}}$= maximal concentration, **F** = bioavailability, $\mathbf{t^1/_2}$ = half-life, $\mathbf{t_{max}}$= time-point C_{max}, **Vd**= distribution volume, **Fm** = fraction metabolized.

Pharmacokinetics of Metabolites: Morphine and Morphine -Glucuronides

The formation of morphine after heroin administration occurred very rapidly, and maximal concentrations could be measured between 3.6-8.0 min after heroin administration (Tables **1a**,**1b**). The half-life of morphine as a metabolite generally varied between 100-280 min, which is comparable with data from pharmacokinetic studies after morphine administration. This indicates that the formation of morphine from its precursor heroin is not the rate-limiting step in metabolism of morphine after heroin administration.

However, the half-life of morphine was extremely short in the study of Jenkins (18.8 min) [50]. Probably under-estimation occurred since morphine plasma levels near lowest limit of quantification were obtained after a single dose of 10.5 mg heroin by inhalation.

Data on the M3G or M6G kinetics after heroin administration are scarce, mostly because in earlier times it was assumed that the morphine-glucuronides were not relevant for the pharmacodynamic action of heroin. M6G is however a powerful opioid that after intrathecal administration directly into the cerebrospinal fluid, significantly exceeded the pharmacodynamic action of intrathecal administered morphine [52]. However, M6G passes the blood-brain barrier with more difficulty than morphine, and only after significant accumulation of M6G in plasma a pharmacodynamic effect is to be expected [53,54]. M3G lacks intrinsic opioid activity. Based on animal experiments with M3G administration in the brain ventricles, it has been suggested that clinical adverse events like myoclonus and seizures after long-term morphine treatment might be related to M3G accumulation [55]. Epileptic insults and motoric restlessness are often seen in heroin therapy, but whether M3G accumulation contributes to this phenomenon has not yet been established yet.

After heroin administration, the terminal half-lives of morphine-glucuronides (M3G/M6G) ranged from 2.0 to 6.4 h. T_{max} varied from 0.7 to 5.1 h [45,46,49], which is comparable to the results from morphine pharmacokinetic studies [56]. Half-life of the morphine-glucuronides did not depend on the route of heroin administration [31,46].

The long circulation time of morphine and the glucuronides is probably maintained by enterohepatic cycling [57]. After excretion in bile, morphine-glucuronides are hydrolysed into morphine in the digestive tract by β-glucuronidase enzymes of the colon flora. The regained morphine molecules are available again for re-absorption into the circulation. The contribution of enterohepatic cycling to the total bioavailability of morphine is probably considerable. The bioavailability of oral M6G declined with 65% when the enterohepatic cycle was interfered by blocking of the β-glucuronidase activity of the colon flora in rodents [58]. For further details about pharmacokinetics of morphine and morphine-glucuronides after morphine administration, we refer to other review articles [26,56].

PHARMACOKINETIC VARIABILITY

Routes of Administration

The pharmacodynamic effects of heroin depend on the pharmacokinetic profile of heroin and its metabolites followin g different routes of administration. The immediate effect of intravenous heroin is often described by heroin dependents as a "flash", a warm and intensively pleasant sensation [59]. The intensity of the flash is thought to be related to C_{max} of heroin and 6-monoacetylmorphine and the heroin absorption rate into the circulation from the application site (t_{max}). The flash is followed by an euphoric, benumbed state, which may be more related to morphine and M6G plasma levels [31,46].

Considerable peak plasma concentrations of heroin and a fast absorption rate were established after intranasal application (snorting) or inhalation in the lungs (Table **1b**). The t_{max} varied between 2-15 min after inhalation or intranasal administration. Because of its lipophilicity and low ionisation grade at physiological pH, heroin is rapidly absorbed through the mucous membranes. The intranasal mucosa and the lung are well-perfused organs, which contributes to a high absorption rate for lipophilic compounds. Moreover, the alveolar-capillary bed of the lung forms a very large area for absorption (approximately $100m^2$ in healthy male adults) and the first pass effect by the liver is avoided in these routes of administration. Maximal heroin concentrations were established within 2-5 min after intranasal heroin use or inhalation. Plasma concentration-time profiles demonstrated a second morphine peak in some heroin snorters, indicating that a part of the heroin dose was swallowed and later absorbed from the gastro-intestinal tract [47,49]. Half-lives of heroin after intranasal administration or inhalation were comparable to intravenous data.

In a heroin-assisted trial for the treatment of heroin-addiction in The Netherlands, pharmaceutically prepared heroin base was administered by smoking the agent from aluminium foil (chasing the dragon). In this technique, the heroin smoker keeps a lighter underneath a piece of aluminium foil filled with heroin base and the sublimated heroin fumes are inhaled by a straw in the mouth [60]. The bioavailability of smoking heroin by this procedure was estimated between 38-53% [27,46,61]. In contrast, when cigarettes containing both tobacco and heroin were smoked, a low recovery of 14% was found [27]. Probably disintegration of heroin had occurred because of the temperatures above 173°C (the melting point of heroin base) that were achieved during taking a pull from the heroin-cigarette [27]. The higher bioavailability of heroin after smoking from aluminium foil was probably achieved because the heating process could be better controlled by manipulating the lighter. Although plasma peaks of heroin were 2-4 times lower after smoking from aluminium foil than after equivalent intravenous doses, the flash effect was achieved in both administration groups [46,61].

After intramuscular administration, significantly lower heroin peak plasma concentrations were reached than after intravenous injection. However, heroin circulated longer after intramuscular than after intravenous injection, because of a sustained release of heroin into the circulation. This resulted in AUC levels that were 3-4 times higher than AUCs following intravenous injection of similar heroin dosages (Table **1b**). However, this may very well be explained by the inherent difficulties in accurately estimating the AUC of heroin after intravenous bolus administration [48]. Remarkably, heroin was not rapidly metabolised in the muscular tissue.

When heroin was administered orally or rectally, no heroin or 6-monoacetylmorphine could be detected in plasma [31,44,48]. Consequently no "flash" was achieved after oral administration, although a sustained period of mild euphoria was reported. Probably hydrolysis of heroin into morphine occurred under the alkaline conditions of the duodenum and colon before absorption. Moreover, heroin could be subject of the first pass effect by esterases in the liver. The intravenous/oral AUC ratio of the metabolite morphine varied between the 50 and 67 % in different studies, which is comparable with oral morphine administration [31,48]. The first pass mechanism by the liver is avoided to a high extent after application of a heroin suppository, resulting in a lower M3G/morphine ratio after rectal administration (1.5-2.9) than after oral administration of heroin (4.6-12.3) [31,62]. Scores on euphoria were significantly higher after rectal application than after an equal oral heroin dose [31].

Role of P-Glycoprotein and Organic Anion Transporting Polypeptides

P-glycoprotein (P-gp) is an efflux pump that protects the body against xenobiotic compounds [63]. Absorption from the gastro-intestinal tract and entrance to the brain through the blood-brain-barrier (BBB) are limited by P-gp substrates, while the excretion into urine is promoted. In several *in vitro* studies, it has been demonstrated that both morphine and morphine-glucuronides are P-gp substrates [64-68]. The transfer capacity of P-gp for morphine and morphine glucuronides was however relatively small compared to other compounds (e.g. paclitaxel) and opioids (e.g. loperamide) in *in vitro* studies [64,69,70]. Whether heroin itself is subject to P-gp mediated transport remains to be studied. Remarkably, chronic exposure of morphine increased P-gp density in rat brains, which may contribute to the development of tolerance [71,72].

Another class of protective efflux transporters in brain, liver and kidney is formed by the Organic Anion Transporting Polypeptides (OATPs). Morphine, M3G and to lesser extent M6G are subject of OATPs mediated transport, as is shown in several experiments with the specific OATPs inhibitor probenecid [73-75]. For interactions between P-gp blockers and inducers see section "*Interactions with transporting enzymes"* of this article.

Drug-Drug Interactions

In Table **2**, drug-drug interactions demonstrated or suggested for heroin and its metabolites are summarised.

Interactions with Hydrolysis

Many heroin addicts use heroin and cocaine concomitantly ("speed-balling" or "speed basing"). Both heroin and cocaine are metabolised by carboxylesterases and *in vitro* competitive inhibition of heroin metabolism by cocaine has been

Table 2. Drug interactions with Heroin and its Metabolites

Co-medication	Interaction	Type of Study, Results		Clinical Relevance	Reference
Hydrolysis of heroin and 6-monoacetylmorphine (6-AM)					
Cocaine	Inhibition	*In vitro*	Competitive inhibition	Unknown	[77]
Ethanol	Inhibition	*Post-mortem*	In presence of ethanol 6-AM levels ↑	Enhanced risk for overdose	[82]
Glucuronidation to morphine 3-glucuronide (M3G) and morphine-6-glucuronide (M6G)					
Acetaminophen (paracetamol)	Induction	*In vivo*	Observational study morphine treated patients	Unknown	[88]
Benzodiazepines	Inhibition	*In vitro* *In vivo*	Competitive inhibition M3G formation relatively more inhibited by oxazepam. Trend for ↓ M3G/morphine serum ratio in morphine treated patients	Unknown Unknown	[84-88,119]
Chloramphenicol	Inhibition	*In vitro* *In vivo*	Competitive inhibition Rodents, extreme doses chloramphenicol, AUC morphine ↑	Unknown	[89,90]
Ethanol	Inhibition	*In vitro*	Dose dependent	Unknown	[83]
Ranitidine	Inhibition	*In vitro* *In vivo*	M6G forming relatively spared Healthy volunteers	Opioid effect ↑	[94,120]
Amitriptyline, nortriptyline, fluoxetine	Inhibition	*In vitro*	Competitive + non-competitive	Unknown	[91]
Zidovudine	Inhibition	*In vitro*		Clinical morphine sparing effect	[92]
Transporting enzymes (morphine substrates)					
Quinidine	P-gp blocker	*In vivo*	Healthy volunteers, oral morphine: AUC morphine ↑	iv morphine: insign. PK/PD interaction effect	[100,101]
Valspodar	P-gp blocker	*In vivo*	Healthy volunteers, iv morphine: AUC M3G ↑	Insign. PD effects	[102]
Rifampin	P-gp induction	*In vitro* *In vivo*	Healthy volunteers Double-blind crossing over Bioavailability oral morphine ↓	Analgesic effect ↓	[72,103]
Probenecid	OATP blocker	*In vitro* *In vivo*	Rodents, antinociception ↑	Unknown	[75,104]

OATP= organic anion tranporters, **P-gp**= P-glycoprotein, **AUC**= area under the curve.

demonstrated [76]. Whether this interaction is relevant *in vivo* has not yet been established.

It has been found, however, that concomitant use of alcohol enhances the risk for a heroin overdose [77-79]. Ethanol inhibited the hydrolysis of cocaine by carboxylesterases *in vitro* [80]. Whether the hydrolysis of heroin is also inhibited in the presence of ethanol remains to be studied. In plasma samples of heroin overdose victims a relationship was found between ethanol levels and 6-monoacetylmorphine concentrations, probably indicating that hydrolysis of 6-monoacetylmorphine into morphine had been delayed by alcohol use [81].

Interactions with Glucuronidation

Ethanol inhibited the glucuronidation of morphine dose dependently *in vitro* [82]. In several *in vitro* and *in vivo* studies, competitive inhibition of the glucuronidation of morphine by UGT2B7 enzyme occurred when benzodiazepines [83-87], chloramphenicol [88,89], tricyclic antidepressants [90] and the nucleoside reverse transcriptase inhibitor zidovudine [91] were added. The net pharmacodynamic effect of interference of the glucuronidation of morphine is however hard to predict. The formation of the inactive or even antagonistic, metabolite M3G was relatively more inhibited by oxazepam than the formation of the

agonistic conjugate M6G [83,87]. Morphine conjugate M6G circulates longer and is thought to be a more potent μ-opioid receptor agonist than its precursor morphine [52]. When after inhibition of the glucuronidation the morphine plasma concentrations would increase, the expected increase of opioid effect could be opposed by the lower quantities of the biologically more active metabolite M6G [92]. After inhibition of the glucuronidation of morphine by oxazepam and ranitidine [93], the formation of M6G was relatively spared compared to the formation into M3G. Ranitidine indeed enhanced the opioid effects of morphine *in vivo* [93].

In post-operative patients, lower opioid doses are required for adequate analgesia at concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) [94]. NSAIDs are also cleared by glucuronidation although in contrast to morphine, primarily by UGT 1A3 [95], and in minor quantities by UGT2B7 iso-enzymes [96]. The opioid sparing effect of NSAIDs is therefore probably not related to pharmacokinetic interaction but rather to a pharmacodynamic interactive effect. However, administration of NSAIDs diminished the creatinine clearance in post-operative patients with 22mL/min (95% CI 7-37), a process that could have contributed to the morphine sparing effect of NSAIDs [97,98].

Interactions with Transporting Enzymes

When morphine was administered orally in humans, co-administration of the P-gp blocker quinidine significantly increased the absorption and plasma concentrations of oral morphine [99]. However, when morphine was administered intravenously in human volunteers, the effects of P-gp blockers quinidine and valdospar on the pharmacokinetics and pharmacodynamics of morphine was limited [100,101]. If quinidine and valdospar are both equally effective inhibitors of P-gp in the BBB and digestive tract, it might be concluded that P-gp efflux did not appear to have a significant effect on access of morphine to the central nervous system. In a study by Fromm *et al.*, co-administration of P-gp inducer rifampin, significantly reduced the analgesic effects of oral morphine [102]. However, based on this study it could not be concluded whether the reduced pharmacodynamic effects of oral morphine were due to P-gp induction in the digestive tract, or to P-gp induction in the blood brain barrier.

The involvement of Organic Anion Transporters (OATPs) in morphine distribution is only recently discovered and other clinical relevant interactions with OATPs activity, except for probenecid [103], have not been described thus far.

Hepatic Impairment

Liver enzymes are involved in heroin hydrolysis and glucuronidation of the heroin metabolite morphine. However, esterases are also abundantly present in blood and other organs and it is therefore not very likely that hepatic impairment would influence hydrolysis of heroin.

The liver is the major organ involved in the glucuronidation of morphine. However, morphine metabolism was relatively normal in patients with severe liver cirrhosis, possibly because glucuronidation was taken over by other organs [104,105]. In general, oxidative pathways are more impaired than glucuronidation in liver diseases [68]. It is hypothesized that glucuronidation is maintained in diseased liver, because of the leakage of microsomal UGT from damaged hepatocytes [106]. The bioavailability of oral heroin would probably be enhanced in patients with serious liver disease. This occurred following oral morphine administration in patients with serious liver cirrhosis, probably because of the loss of the first pass effect [107].

Liver diseases can cause low albumin serum concentrations. The binding of heroin and morphine to albumin is however moderate. In several studies the variability in serum morphine concentrations was indeed not related to albumin levels [87,104].

Therefore, it can be concluded that hepatic impairment probably has no major consequences for the pharmacokinetics of heroin.

Renal Impairment

The kidneys are primarily involved in the excretion of morphine and morphine glucuronides following heroin administration [27,28]. In a clinical study, the renal clearance of unbound morphine exceeded the renal clearance of creatinine, a measure of the glomerular filtration rate [108]. In isolated perfused rat kidneys, morphine is subject to glomerular filtration, active secretion in proximal tubules and probably partly re-absorption, resulting in a net tubular secretion [109,110]. The tubular secretion process was not saturable within a large range of morphine concentrations (0.2-200 μM) in a rodent model [111]. The morphine-glucuronides were partly reabsorbed in the kidney, active excretion of the morphine-glucuronides in urine did not occur [110]. In several studies among patients with renal impairment, it was confirmed that the total exposure to morphine glucuronides and to lesser extent morphine was significantly increased in blood or CSF [108,112-114]. However, variations in creatinine clearance only minimally accounted for the variability of morphine-glucuronide conjugates levels in patients with minor renal dysfunction or in healthy volunteers [54,87]. In conclusion, accumulation of morphine glucuronides can be considerable in patients with serious renal impairment, but seem not clinical relevant in milder cases. Although pathologic-anatomical abnormalities of the kidney are commonly found post-mortem in intravenous users of contaminated street heroin, renal impairment would probably be relatively mild in most heroin dependents [8,9,115-117]. Control of creatinine clearance during heroin-assisted treatment is however advised.

DISCUSSION AND CONCLUSION

There is an international growing interest in the prescription of high doses pharmaceutically prepared heroin as a maintenance treatment in heroin addicted patients. The aim of heroin-assisted therapy is prevention of the drug seeking behaviour outside the clinics. Adequate prevention of withdrawal symptoms as well as the providing of euphoric effects may contribute to continuation and success of heroin maintenance therapy. Of all administration methods, heroin inhalation and intranasal administration resembled most the intravenous pharmacokinetic profile, and thereby the intense euphoric feelings following intravenous heroin, the so called “flash”. Oral, rectal and intramuscular administrations are

probably more suitable to prevent withdrawal symptoms and craving.

Long-term heroin prescription is not very common and information about the consequences of the introduction of co-medication, the use of other substances and the impact of renal or hepatic impairment on heroin metabolism is scattered and relatively sparse. The aim of this article was therefore to review the pharmacokinetics of heroin and to discuss factors that are involved in variability in heroin pharmacokinetics. Most pharmacokinetic interactions data originate from *in vitro* or animal studies and studies on morphine administration in healthy volunteers. Inhibition of glucuronidation of the heroin metabolite morphine by ranitidine and zidovudine resulted in clinical relevant effects. Co-administration of inhibitors and inducers of transporter enzym P-glycoprotein are probably only clinical relevant when heroin is administered orally. When morphine was administered intravenously, these P-glycoprotein modulators did not result in clinical relevant interactions. In renal impaired patients, accumulation of morphine and morphine-glucuronides occurred. Control of creatinine clearance during heroin-assisted treatment is therefore advisible. In hepatic impairment, heroin and morphine metabolism was relatively spared. Consumption of other licit and illicit substances besides heroin is very common in addicted patients. Heroin prescribing physicians should be aware that alcohol, cocaine and benzodiazepines can cause both pharmacodynamic and pharmacokinetic interactions and thereby a prolonged effect of heroin.

When plasma concentrations of heroin and/or its metabolites slowly change e.g. due to an interaction or slowly developing renal dysfunction, pharmacodynamic adaptation may occur and the effects may not be detected. However, an acute decline of renal clearance may induce serious overdose symptoms. Furthermore, a sharp increase in clearance or P-gp activity (e.g. by the introduction of rifampin) may induce abstinence symptoms, and thereby an increasing drug-seeking behaviour.

Pharmacokinetic interactions that resulted in adverse events or withdrawal symptoms during heroin treatment, were not reported in the literature. Overdoses are often thought to be due to the use of illicit opiates beside the prescribed heroin dosage, and therefore relevant pharmacokinetic interactions may have been overlooked in the clinical practice of heroin-assisted treatment. More awareness of the possibility of pharmacokinetic interactions in heroin-assisted therapy may prevent overdose events, withdrawal symptoms and therapy failure in the future.

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Received: 13 May, 2005 Revised: 27 June, 2005 Accepted: 18 July, 2005