Morphine Pharmacokinetics and Metabolism in Humans
Enterohepatic Cycling and Relative Contribution of Metabolites to Active Opioid Concentrations

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Summary
Morphine, morphine-6-glucuronide (M6G), morphine-3-glucuronide (M3G) and normorphine were analysed with high performance liquid chromatography in plasma and urine, collected over 72h after administration of single intravenous 5mg and oral 20mg doses of morphine to 7 healthy volunteers. Systemic plasma clearance of morphine was on average 21.1 ± 3.4 ml/min/kg (1.27 ± 0.20 L/h/kg), volume of distribution was 2.9 ± 0.8 L/kg and oral bioavailability was 29.2 ± 7.2%. Clearance of morphine to form M3G and M6G comprised 57.3% and 10.4%, respectively, and renal clearance comprised 10.9% of total systemic plasma clearance; hence, more than one-fifth of a dose (20.8%) remained as unidentified residual clearance. On the basis of the area under the plasma concentration-time curves determined after oral and intravenous administration, the ratios of M6G: morphine were 3.6 ± 1.2 and 0.7 ± 0.3, respectively. The corresponding figures for M3G: morphine were 29.9 ± 6.8 and 7.7 ± 1.4. Differences in metabolic ratios between the parenteral and oral routes could be attributed solely to differences in morphine concentrations as evidenced both by plasma concentrations and amounts excreted in urine. An oral: parenteral potency ratio of 1:3 may, thus, be due to differences in circulating amounts of morphine since the proportions of an administered dose found as M6G and M3G after administration by both routes were equal.

A major finding was a slowly declining terminal phase of morphine and metabolites that was evident both in plasma and in urinary excretion versus time curves, where the half-lives of morphine, M3G and M6G were 15.1 ± 6.5h, 11.2 ± 2.7h and 12.9 ± 4.5h, respectively. The terminal half-life of normorphine was 23.9 ± 10.1h after oral administration. Comparison of oral with intravenous excretion curves showed that a greater part of morphine and metabolites were excreted during the slowly declining phase after the oral dose than the intravenous dose, which is highly suggestive of enterohepatic cycling. The renal clearance of M6G and morphine was seen to exceed creatinine clearance, possibly due to an active secretion process.

Morphine is considered to be an intermediate to high clearance drug subject to pronounced pre-systemic elimination (Såwe et al. 1981, 1985). The liver is the major site of metabolism of morphine but evidence of extrahepatic glucuronidation has been reported (Bodenham et al. 1989; Jacqz et al. 1986; Mazoit et al. 1990; Såwe et al. 1985; Sloan et al. 1991). The metabolism of morphine has mainly been studied in humans by analysing the urinary excretion pattern of the parent compound and main metabolites (Yeh 1975; Yeh et al. 1977), while more detailed studies of the plasma pharmacokinetics of the metabolites after clinical doses are scarce (Hanna et al. 1991; Osborne et al. 1990).
The main metabolite morphine-3-glucuronide (M3G) does not have any analgesic effect but has been shown to exhibit functional opioid antagonistic properties in animal models (Gong et al. 1991; Smith et al. 1990). The 2 minor metabolites morphine-6-glucuronide (M6G) and normorphine are both active (Lasagna & Kornfeldt 1958; Shimomura et al. 1971) and since the first description of the analgesic effect of M6G in the rat (Shimomura et al. 1971) reports of excessive opioid effects and associated high concentrations of M6G in patients with renal failure (Hasselstrom et al. 1989; Osborne et al. 1986) have led to a renewed interest in further study of the mechanism of action of this polar metabolite. M6G has also been administered to patients with cancer (Hanna et al. 1990; Osborne et al. 1988) and volunteers (Peat et al. 1991) where the analgesic properties and ability to cause respiratory effects were investigated.

Different figures of the amount of metabolites formed in humans after therapeutic doses of morphine have appeared in the literature. Depending on route of administration, renal function and analytical methods, relative amounts of M6G : morphine ranging from 1 : 1 to 11 : 1 have been reported (McQuay et al. 1990; Osborne et al. 1990; Säwe 1986b; Säwe et al. 1983, 1985), excluding severe renal failure where the concentrations of M6G can be much higher (Säwe & Odarcederlof 1987). On the basis of these figures a debate on the oral : parenteral potency ratio has been initiated (Hanks et al. 1987; Hanks & Wand 1989).

Recent studies of the pharmacokinetics of morphine have revealed new findings of the pattern of morphine and metabolite plasma concentrations which sometimes differ from what is expected on the basis of literature data (Säwe 1986a). For example, comparing single dose pharmacokinetics of morphine and metabolites with those obtained during presumed steady-state, the area under the concentration-time curve (AUC) in the latter situation was on average more than 30% greater than that obtained after single doses using conventional ways of calculation (Hasselström et al. 1991). In our previous investigations (Hasselström et al. 1991) we also noted several patients with detectable morphine and metabolite concentrations in urine and plasma past the theoretical limits, if extrapolating from known pharmacokinetic parameters. One explanation for these phenomena would be the presence of enterohepatic cycling of morphine and/or metabolites. If this is the case, different sampling strategies and mathematical handling of the data could result in large interstudy differences in pharmacokinetic parameters and partly explain the more than 15-fold variation in morphine plasma clearance values published (Olkola et al. 1988; Säwe 1986a).

The aim of the study has been to describe the metabolic pattern of morphine as well as to collect basic information of the pharmacokinetics of morphine, its major glucuronidated metabolites and its demethylated metabolite normorphine in humans after both oral and intravenous administration. The protocol was planned with an extended observation period of 72h taking a possible enterohepatic cycling process into account.

**Subjects and Methods**

Seven healthy volunteers, 3 smokers and 4 nonsmokers, with normal renal and hepatic function as judged by physical and chemical investigations without any past or present gastrointestinal pathology participated in the study (table I). The protocol was reviewed and approved by the Ethics Committee at the Karolinska Institute, Huddinge University Hospital. The volunteers were all colleagues and well known to the investigators.

Morphine hydrochloride was administered after an overnight fast as single intravenous and oral doses at least 72h apart. The 5mg intravenous dose (corresponding to 3.8mg base) was given as a 1min bolus and the 20mg (15.2mg base) oral dose as a tablet (ACO Drugs, Sweden) together with 150ml of water. Plasma samples were drawn from an indwelling antecubital catheter into heparinised vacuum tubes at 0, 2.5, 5, 15, 20, 30 and 40 min, and 1, 2, 3, 4, 5, 6, 7, 9, 11, 24, 32 and 48 h after the intravenous dose and 0, 10, 20, 30 and 40 min, and 1, 1.5, 2, 3, 4, 5, 6, 7, 9, 11, 24, 32 and 48 h after the oral dose. The volunteers remained in a recum-