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A Pharmacokinetic Study of Sublingual Aerosolized Morphine in Healthy Volunteers

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Abstract

A pharmacokinetic study was undertaken to compare the pharmacokinetics of morphine after an intravenous dose with the pharmacokinetics after a sublingual dose administered from an aerosol.

Plasma levels of morphine, morphine-3-glucuronide and morphine-6-glucuronide were measured in five normal volunteers after morphine administration by the intravenous route and from a novel sublingual pressurized aerosol formulation. The mean (±s.d.) bioavailability of the sublingual aerosol morphine was 19·7 ± 6·7 %. The morphine-3-glucuronide/morphine and the morphine-6-glucuronide/morphine ratios were 5·1 ± 1·6 and 1·2 ± 0·4, respectively, for the intravenous route and 28·3 ± 11·3 and 5·2 ± 1·4, respectively, for the sublingual route. The combined total areas under the plots of systemic concentration against time (AUC) for the metabolites after the two routes was not significantly different.

When compared with published data for oral administration the results demonstrate that the sublingual aerosol morphine might provide an alternative to conventional methods of morphine delivery, and has similar pharmacokinetics to a sublingual morphine tablet. It has no particular pharmacokinetic advantages over oral morphine, except a potential for a faster onset of analgesia. Bioavailability, maximum plasma concentration, Cp_{max}, and the time at which the maximum plasma concentration is reached, T_{max}, are equivalent to those for orally administered morphine.

It has been suggested that 25% of all patients with cancer throughout the world die without adequate relief from severe pain. In an attempt to resolve this unacceptable situation, the Cancer Unit of the World Health Organization (WHO) formulated a pain-relief program in 1982 to provide guidelines for pain management and designated oral morphine as the drug of choice for the treatment of cancer pain (Swerdlow & Stjernsward 1982).

Despite the usefulness of oral morphine many patients need alternative routes of administration to enable their pain to be controlled. Coyle et al (1989) stated that in the course of pain management at least two routes of administration are necessary in the majority of patients, with 23% requiring three alternative routes. There may be a number of reasons why a patient cannot receive oral or parenteral drugs, including persistent nausea and vomiting, obstructive head and neck or gastrointestinal tumours, dysphagia, mucositis, poor venous access, and coagulation problems. Several less conventional routes have been proposed, including transdermal (Corish et al 1990), buccal (Al-Sayed-Omar et al 1987), sublingual (Hirsh 1984) and rectal (Pannuti et al 1982). Although the sublingual route has aroused some interest, few controlled studies have been performed on sublingual administration. The use of a sublingual tablet has previously been shown to have favourable kinetics compared with an oral tablet (Osborne et al 1990). A sublingual solution has also been used clinically, with beneficial effect (Hirsh 1984). Neither of these preparations, however, is easy for the patient to use.

A sublingual aerosol preparation of morphine has several additional potential advantages. Absorption might be more rapid if a dispersed product were delivered to the sublingual mucosa, thereby avoiding the added complication of dispersion necessary for tablets. In addition, the rate of onset of analgesia might be improved.

The importance of the 6-glucuronide metabolite of morphine in pain relief (Osborne et al 1992) and the possible antagonistic role of morphine-3-glucuronide have been described (Smith et al 1990). The use of morphine to metabolite ratios after different routes of administration can give an indication of the site of absorption (Osborne et al 1990). Although these ratios might be different for different routes, the extent of absorption from the administration site cannot be determined. Thus, although the morphine to metabolite ratios for sublingual morphine given as a tablet is different from that for an oral tablet that is swallowed (Osborne et al 1990), are a large proportion of the morphine absorption might still be taking place after swallowing of the morphine dissolved in saliva.

The aim of this study was to investigate the bioavailability of morphine, and the plasma levels of morphine-3-glucuronide and morphine-6-glucuronide in normal volunteers after morphine administration by the intravenous route and from a sublingual aerosol formulation. In order to achieve this it was necessary to develop a suitable aerosol formulation of morphine, capable of delivering a consistent dose of morphine sublingually to normal volunteers. The pharmacokinetics of sublingual aerosol administration of morphine was compared with intravenous administration in normal volunteers.

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Materials and Methods

Subjects

Five healthy volunteers (one male, four female), mean age 25·8 years (range 23–29 years), mean body weight 58·8 kg (range 49–78·5 kg), participated in the study after giving informed consent. The study was approved by the City and Hackney District Health Authority Ethics Committee, London, UK.

Sublingual aerosol preparation

Aluminium aerosol canisters (20 mL) fitted with 100-μL metering valves (Neotechnic Engineering, UK) were filled (Pamasol 2016, Pamasol, Switzerland) with a suspension of morphine sulphate (Hillcross Pharmaceuticals, Burnley, UK) in a blend of trichlorofluoromethane and dichlorodifluoromethane propellants (ICI, UK). The mean (±s.d.) dose of morphine sulphate delivered was 0·96 (±0·01) mg per actuation as determined using a modified twin impinger technique (British Pharmacopoeia 1993), with deposited drug measured by UV analysis at 285 nm.

Treatment

Fasted subjects, instructed to take no fluids in the two hours before each study, received an intravenous dose of morphine sulphate and a sublingual dose of morphine sulphate in randomized order, given on two study days at least seven days apart. Approximately 15 min before the dose was administered, the subjects were given 200 mL water to drink; to ensure adequate hydration and therefore reasonable conditions for absorption of the sublingual dose. The subjects also received 100 mL water at 2 h and 3 h post-dose.

For the sublingual dose, morphine (9·6 mg; 10 × 0·96-mg puffs) was sprayed under the tongue of each subject over a period of about 90 s beginning at time 0. Intravenous morphine sulphate was given as a slow bolus over 2 to 3 min beginning at time 0, in the contralateral arm to the indwelling sample cannula. The intravenous dose (0·075 mg kg^{-1}; equivalent to approximately 5 mg for a 70 kg subject) was given in 5 mL 0·9% w/v sodium chloride.

Sampling

Blood samples (8 mL) were collected from an indwelling venous cannula at 0, 5, 10, 15, 30 and 45 min and 1, 1·5, 2, 2·5, 3, 3·5, 4, 5, 6, 8, 10 and 12 h after morphine dosing. Blood samples were separated by centrifugation, 2000 revolutions min^{-1} for 10 min, and the plasma samples stored at −40°C before analysis.

Assay

Samples were assayed for morphine, morphine-3-glucuronide and morphine-6-glucuronide using a modification (Joel et al 1988) of the HPLC method developed by Svensson et al (1982). The limits for detection for this method were 1 ng mL^{-1} for morphine and morphine-6-glucuronide, and 10 ng mL^{-1} for morphine-3-glucuronide.

Pharmacokinetic calculations

Individual pharmacokinetic parameters were calculated using an interactive computer program (STRIPE; Johnston & Woolard 1983). To enable comparison between the different studies, values were normalized to those that would be expected for subjects who weighed 70 kg and who received a 10-mg dose of morphine.

Statistical analysis

Individual comparisons between pharmacokinetic parameters were performed using Student's paired *t*-test. Individual comparisons amongst data that were not normally distributed were performed using the Wilcoxon or the Mann-Whitney *U*-test. Normality was tested before analysis.

Results and Discussion

Although the number of subjects in this study was small, an idea of the pharmacokinetic properties of the sublingual aerosol formulation can be established. Statistically significant differences are unlikely to be shown with five subjects unless the differences are large; clinical significance is, however, more readily demonstrated.

Pharmacokinetic parameters for morphine, morphine-3-glucuronide and morphine-6-glucuronide, calculated using STRIPE, are given in Tables 1, 2 and 3, respectively, for both routes of administration.

Mean plasma concentrations of morphine and its metabolites after the intravenous dose are shown in Fig. 1. Morphine was present in measurable quantities in the plasma for 4 to 6 h after intravenous administration.

Table 1. Mean (±s.d.) morphine pharmacokinetic results, corrected to 10 mg dose and 70 kg weight.

	Intravenous	Sublingual
Number of volunteers	5	5
Lag-time (h)		0·12 ± 0·07
Absorption half-life (h)		0·22 ± 0·10
Terminal elimination half-life (h)	1·8 ± 0·27	2·6 ± 2·35
Area under plasma-time curve (AUC; ng mL^{-1} h)	107·3 ± 17·0	21·1 ± 7·0
Clearance (mL min^{-1})	1347·4 ± 418·1	
Volume of distribution (area) (L)	217·4 ± 86·6	
Maximum plasma concentration (ng mL^{-1})	97·6 ± 32·5	8·0 ± 1·9
Time to maximum plasma concentration (h)		0·80 ± 0·11
Bioavailability (%)		19·7 ± 6·7
Morphine-3-glucuronide/morphine AUC ratio	5·1 ± 1·6	28·3 ± 11·3*
Morphine-6-glucuronide/morphine AUC ratio	1·2 ± 0·4	5·2 ± 1·4**

*$P < 0·01$, **$P < 0·005$ compared with intravenous.

Table 2. Mean (± s.d.) morphine-3-glucuronide pharmacokinetic results, corrected to 10 mg dose and 70 kg weight.

	Intravenous	Sublingual
Number of volunteers	5	5
Lag-time (h)	0·04 ± 0·03	0·33 ± 0·11
Absorption half-life (h)	0·07 ± 0·06	0·39 ± 0·09
Terminal elimination half-life (h)	2·88 ± 0·24	1·88 ± 0·30*
Area under plasma-time curve (AUC; ng mL^{-1} h)	533·7 ± 114·6	544·5 ± 127·2
Maximum plasma concentration (ng mL^{-1})	117·6 ± 29·6	139·6 ± 32·7
Time to maximum plasma concentration (h)	0·47 ± 0·38	1·40 ± 0·42

*$P < 0·001$ compared with intravenous.

Table 3. Mean (± s.d.) morphine-6-glucuronide pharmacokinetic results, corrected to 10 mg dose and 70 kg weight.

	Intravenous	Sublingual
Number of volunteers	5	5
Lag-time (h)	0·07 ± 0·03	0·37 ± 0·08
Absorption half-life (h)	0·18 ± 0·03	0·43 ± 0·16
Terminal elimination half-life (h)	2·40 ± 0·44	1·79 ± 0·40*
Area under plasma-time curve (AUC; ng mL^{-1} h)	121·7 ± 41·1	102·4 ± 21·3
Maximum plasma concentration (ng mL^{-1})	28·2 ± 7·7	29·5 ± 8·1
Time to maximum plasma concentration (h)	0·90 ± 0·14	1·45 ± 0·45

*$P = 0·062$ compared with intravenous.

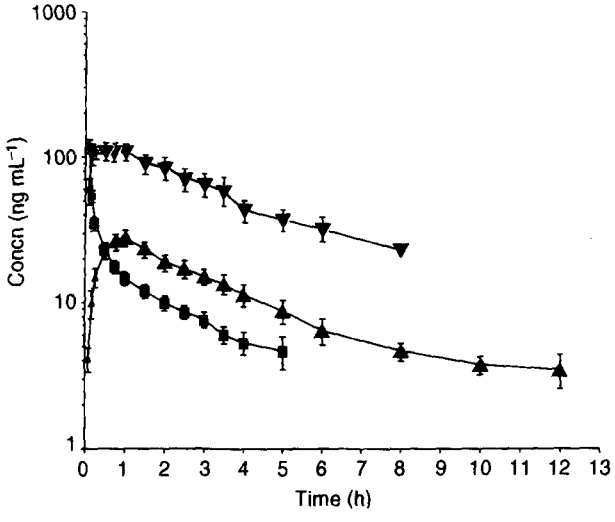

FIG. 1. Mean corrected plasma concentration (± s.e.) of morphine (■), morphine-3-glucuronide (▼) and morphine-6-glucuronide (▲) after administration of intravenous morphine.

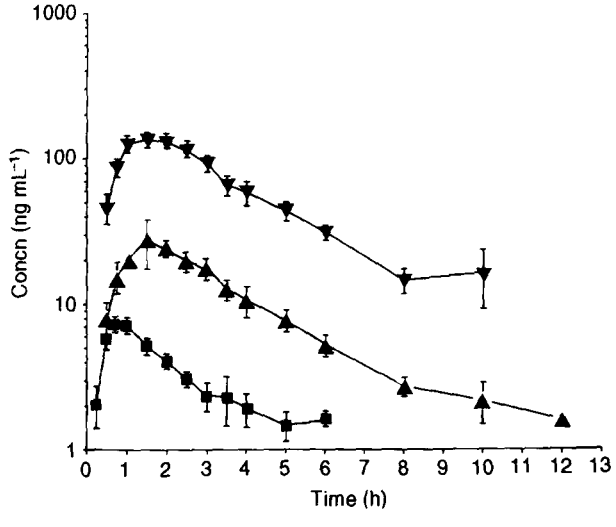

FIG. 2. Mean corrected plasma concentration (± s.e.) of morphine (■), morphine-3-glucuronide (▼) and morphine-6-glucuronide (▲) after administration of sublingual morphine.

Clearance of morphine from the plasma was rapid with detectable quantities of the metabolites occurring within 5 to 10 min. Mean plasma levels of morphine-3-glucuronide were higher than those of morphine within 5 to 10 min, whereas mean morphine-6-glucuronide levels exceeded those of morphine from 30 to 45 min onwards. The major metabolite of morphine, morphine-3-glucuronide has a larger AUC than morphine-6-glucuronide. The pharmacokinetic parameters for the intravenous dose from this study (Table 1) are comparable with those reported in the study by Osborne et al (1990).

Mean plasma concentrations of morphine and its metabolites after the sublingual dose are shown in Fig. 2. Metabolism of morphine to morphine-3-glucuronide and morphine-6-glucuronide was rapid after sublingual administration, with plasma levels of both morphine-3-glucuronide and morphine-6-glucuronide higher than those of morphine for the duration of the study.

The mean (± s.d.) bioavailability of the aerosol formulation of morphine in this study was 19·7 ± 6·7% (Table 1). This compares with previously reported values of 19·6 ± 8·3% for an oral tablet and 21·9 ± 6·0% for a sublingual tablet (Osborne et al 1990).

The lag-time (i.e. the first time morphine was detected in the plasma) was calculated as $0{\cdot}12 \pm 0{\cdot}07$ h for the sublingual dose (Table 1). An oral tablet has been shown to have a mean lag-time of $0{\cdot}3 \pm 0{\cdot}12$ h (Osborne et al 1990), and a sublingual tablet a mean lag-time of $0{\cdot}72 \pm 0{\cdot}56$ h, both of which must disperse and dissolve before absorption can take place. The mean time to peak concentration (T_{max}) for the sublingual aerosol was $0{\cdot}80 \pm 0{\cdot}11$ h, a value similar to that found by Osborne et al (1990) ($0{\cdot}8 \pm 0{\cdot}35$ h) for the oral tablet. The sublingual tablet had a T_{max} of $1{\cdot}75 \pm 1{\cdot}3$ h. Mean maximum plasma concentrations ($C_p$max) were also comparable: $8{\cdot}0 \pm 1{\cdot}9$, $8{\cdot}0 \pm 2{\cdot}9$ and $7{\cdot}4 \pm 1{\cdot}7$ ng mL^{-1} for sublingual aerosol, oral tablet and sublingual tablet, respectively. This suggests that although sublingual morphine begins to be absorbed earlier, its absorption rate is lower, reaching peak concentration at the same time as oral morphine.

The AUCs for morphine-3-glucuronide and morphine-6-glucuronide after each route, were not significantly different (Tables 2 and 3, respectively), indicating that all the administered sublingual dose was absorbed. From these data, however, it is not possible to determine whether the principal site of absorption was from the sublingual mucosa or from lower down the gastrointestinal tract after the sublingual dose had been swallowed. The morphine-3-glucuronide to morphine and morphine-6-glucuronide to morphine AUC ratios after sublingual administration were not consistent with those found by Osborne et al (1990) for the oral route, and are closer to those found for sublingual administration. Although the AUC for morphine-3-glucuronide and morphine-6-glucuronide was not significantly different between the two routes, because of a considerably lower morphine AUC after sublingual dosing, the ratios of morphine-3-glucuronide to morphine AUC and morphine-6-glucuronide to morphine AUC change significantly between the intravenous and the sublingual dose. The 5·5-fold increase in morphine-3-glucuronide to morphine AUC ratio and the 4·3-fold increase in the morphine-6-glucuronide to morphine AUC ratio between the sublingual and the intravenous route in this study compare with 7·1 and 6·9, respectively, for the oral route and 4·6 and 4·4, respectively, for the sublingual route (Osborne et al 1990). This demonstration that there are pharmacokinetic differences between sublingual aerosol morphine and oral morphine suggests that at least some of the dose was absorbed locally.

The elimination rate and the elimination half-life for morphine were the same for both routes; this was not true, however, for the elimination of morphine-3-glucuronide and morphine-6-glucuronide. The elimination half-lives for morphine-3-glucuronide (Table 2) and morphine-6-glucuronide (Table 3) were significantly longer ($P < 0{\cdot}001$ and $P = 0{\cdot}062$, respectively) for the intravenous route. This might be because elimination was not the only process occurring during the apparent elimination phase. Although the same total amount of metabolites are produced by both routes, the levels of the parent compound remain higher for several hours after intravenous administration, resulting in the prolongation of the elimination phase because of continued production of significant amounts of morphine-3-glucuronide and morphine-6-glucuronide from the parent compound. The slope of the elimination phase, therefore, comprises not merely elimination, but also continued production of the metabolites from morphine.

While this study has not demonstrated an advantage of the sublingual aerosol formulation of morphine over the oral route, nor its analgesic activity, the pharmacokinetic data acquired in this study suggest that this easily administered formulation might be a useful alternative in the clinical setting. At present the choice of routes for the administration of opioids to patients, both adults and children, is often limited to oral or parenteral. An alternative to parenteral administration, when oral dosing is not possible, would be a major advance in this field.

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