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The systemic bioavailability of buprenorphine by various routes of administration

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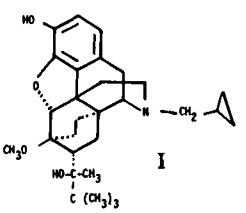
The systemic bioavailability of buprenorphine has been studied in female rats following single doses (200 μg kg^{-1}) administered by one of six different routes. Relative to the 100% bioavailability from the intraarterial route the mean bioavailabilities were intravenous, 98%; intrarectal, 54%; intrahepatoportal, 49%; sublingual, 13%; and intraduodenal, 9·7%. Area under the curve analysis of buprenorphine concentrations in blood showed the relative fractions of drug extracted (first pass) by gut, liver and lung to be 0·80, 0·50 and 0·02 respectively, In situ absorption studies showed that the poor availability of intraduodenally administered buprenorphine is not due to slow or incomplete absorption.

The systemic bioavailability and therefore the potency of drugs is often influenced by their route of administration. Such a situation exists especially when the drug is subject to metabolic clearance before it reaches the systemic circulation and accounts for the low oral availability of drugs such as terbutaline (Conway et al 1973), morphine (Brunk & Delle 1974) and propranolol (Walle et al 1979). The principal organs involved in such presystemic elimination are the gut, liver and lung with the relative anatomical locations of these tissues governing drug bioavailability by different routes. For oral administration, the organs represent to the drug three separate metabolizing systems arranged in series. Such organs may be bypassed, however, by an appropriate choice of drug route, for example rectal administration anatomically circumvents the gut, and, as shown by studies with lidocaine (De Boer et al 1979), represents a valuable drug delivery route when metabolism in the gut would otherwise limit drug availability. It follows also that the buccal or sublingual routes of administration may also reduce first-pass effects.

Buprenorphine (I) is a new phenolic opiate analgesic which after parenteral administration shows up to twice the duration of action and approximately 30 times the analgesic potency of morphine (Kay 1978). In contrast to morphine the drug has a low physical dependence liability in man (Jasinski et al 1978) and may prove a valuable therapy in the treatment of heroin dependence (Mello & Mendelson 1980). In common with other phenolic opiates buprenorphine shows low oral potency and the work of Rance & Shillingford (1977) has suggested first pass metabolism as a causative factor. In the present studies we compare the relative bioavailability of buprenorphine in the rat for six different routes of administration and deduce also the relative metabolic contributions of gut, liver and lung to the observed first-pass effects. The absorption of buprenorphine from the gut has also been investigated.



I

MATERIALS AND METHODS

[15–16 (n)-^{3}H]Buprenorphine hydrochloride (spec. act. 3·6 mC i mg^{-1}) was synthesized by the method of Lewis et al (1974). All drug solutions were prepared in 0·9% (w/v) NaCl (saline) in concentrations appropriate to doses of 200 μg kg^{-1} and nominal dose volumes of 1 ml kg^{-1} (intra arterial, intravenous and intrahepatoportal routes), 10 ml kg^{-1} (intraduodenal) and 0·1 ml kg^{-1} (sublingual and rectal routes). Polyethylene tubing was obtained from Portex Plastics Ltd., Hythe, Kent, U.K.

Surgical procedures

Adult female Sprague-Dawley rats (175–200 g) were anaesthetized with sodium pentobarbitone (Sagatal, May & Baker) (60 mg kg^{-1} i.p.) and the common

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bile-duct cannulated towards the liver using pp 25 polyethylene tubing. To maintain patency of the airways the trachea was exposed and fitted with a polyethylene cannula. The left carotid artery was clamped and cannulated towards the heart with a pp 50 polyethylene cannula connected to a luer fitting 3 way stopcock by means of a 23 gauge hypodermic needle. On removal of the artery clamp, a control blood sample (0·2 ml) was taken before flushing the arterial cannula with 0·2 ml of heparinized isotonic saline (25 units ml^{-1}).

Dosing of the intravenous group was made by injection into the left femoral vein whereas for the intraarterial group the injection was made via an indwelling cannula (pp 10) passed into the dorsal aorta close to the heart.

In the sublingual group the oesophagus of each animal was ligated to prevent swallowing of the drug and the animals dosed and maintained, in a face-down position. Intrahepatic portal vein and intraduodenal drug administrations were made by direct injection into the superior mesenteric vein and duodenum respectively.

Sample collection and assay

Blood samples (0·3 ml) were collected from the arterial cannula at suitable time intervals after dosing, the cannula being flushed with a solution (25 units ml^{-1}) of heparinized saline (0·3 ml) after each sample. Bile was collected into weighed containers each changed at 0·5, 1·0, 1·5, 2, 3 and 4 h after dosing. The radioactivity in each bile sample was measured by counting duplicate aliquots (10 μl) in 1 ml distilled water and 10 ml ES 299 scintillation cocktail (Packard Instruments Ltd). Whole blood samples were prepared for assay of non-labile radioactivity (after drying over P_2O_5 for 3 days) by combustion in O_2 using a Packard 306 sample oxidizer. Samples were assayed for radioactivity using an Intertechnique SL4221 liquid scintillation spectrometer and d min^{-1} values obtained using an on-line linear interpolation quench curve program.

Unchanged [^{3}H]buprenorphine in whole blood was determined by a differential extraction procedure. A measured aliquot of whole blood (100–200 μl) was added to a glass extraction tube containing 100 μg non-radioactive buprenorphine carrier in 0·5 ml of 100 mM glycine/NaOH buffer pH 9·8. The samples were then extracted with diethyl ether (3 × 2·0 ml) and the organic extracts made up to 10 ml with diethyl ether. Aliquots (3 ml) of each extract were evaporated to dryness and then counted in 1 ml distilled water and 10 ml ES 299. The extraction efficiency for [^{3}H]buprenorphine was determined in triplicate by extracting control bloods each containing an added quantity of labelled drug. The nature of the radioactivity in the extracts was checked for selected samples of each group of animals, after evaporation of the remaining organic extracts to low volume. The residues were chromatographed on silica t.l.c. plates (Merck silica gel 60 F_{254}) using a solvent system comprising ethyl acetate–methanol–NH_4OH (sp.gr. 0·88), 75:25:1 (v/v). Authentic samples of non-radiolabelled buprenorphine were co-chromatographed with the extracts. Silica on the developed chromatograms was scraped into scintillation vials as 1 cm bands then suspended in 2 ml distilled water and 5 ml ES 299 for analysis as counts min^{-1} by liquid scintillation counting. Concentrations of buprenorphine in blood were obtained from the concentration of radioactivity in the extracts and corrected where necessary for both extraction efficiency and the relative proportion of buprenorphine in the extracts. Area under the curve values were calculated by trapezoidal analysis of the data.

In situ absorption studies

The absorption of [^{3}H]buprenorphine from the small intestine was measured using the in situ technique of Doluisio et al (1969). Male Sprague-Dawley rats (190–270 g) cannulated for bile collection were each dosed intraduodenally with 12 ml (200 μg) of a [^{3}H]buprenorphine solution prepared in 0·073 M sodium phosphate buffer, pH 6·5. The disappearance of radioactivity from the lumen was followed by measurement of suitable aliquots of the lumen contents at various times over the 90 min following dosing. The relative proportion of buprenorphine in the lumen contents was determined by direct t.l.c. on silica plates as described earlier and from which it was then possible to calculate the actual percentage of buprenorphine still remaining in the gut lumen at any time.

On termination of the experiment, the small intestine was removed, emptied, and then homogenized in 5 volumes of distilled water. Aliquots of the homogenates were combusted and assayed for radioactivity as described earlier. Samples of the gut homogenate were also treated with an equal volume of methanol, centrifuged and the supernatant composition assayed by t.l.c. as described above. Bile was collected over the 90 min after dosing and total radioactivity determined by scintillation counting.

RESULTS

Examination by t.l.c. of the ether extracts of all blood samples showed buprenorphine to be the major component (>70%) and that this varied little between time of sample and dose route. The mean extraction efficiency of buprenorphine from control blood was shown to be 85%.

Blood concentrations of buprenorphine varied widely according to the route of administration, the intraarterial route providing the greatest availability and the intraduodenal the lowest (See Fig. 1). The relative bioavailability of buprenorphine by the different routes employed was determined for the 4 h period after dosing by calculation of the area under the curve (AUC) values up to 4 h after dosing for each dose route. Taking the intraarterial route to represent complete (100%) bioavailability the relative availability of buprenorphine by the other routes was intravenous (98%), rectal (54%), intrahepatoportal (49%), sublingual (13%) and intraduodenal (9·7%) (see Table 1).

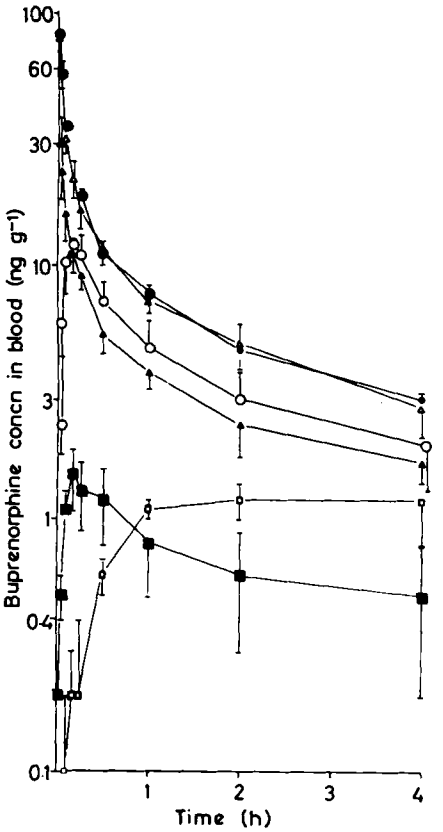

FIG. 1. Blood concentrations of buprenorphine in female rats following administration (200 μg kg^{-1}) by various routes. ●, intraarterial; △, intravenous; ○, rectal; ▲, intrahepatoportal; □, sublingual; ■, intraduodenal. Points represent mean values of 4 animals ± s.e.m.

Table 1. Relative bioavailabilities of buprenorphine for various routes over the 0–4 h after dosing.

Route	Area under blood concentration time curve (AUC_{0-4h}, ng ml^{-1} min)	Relative systemic* availability (%) over the 0–4 h period
Intraarterial	1852 ± 189	100*
Intravenous	1807 ± 242	98 ± 13
Intrarectal	1000 ± 267	54 ± 14
Intrahepatoportal	900 ± 161	49 ± 9
Sublingual†	249 ± 39	13 ± 2
Intraduodenal	180 ± 71	9·7 ± 4

* Intraarterial route assigned to represent complete availability.

† The slow absorption profile for this route means any comparison of availability with other routes would be a considerable underestimate.

Values represent the means of 4 animals ± s.e.m.

From the pharmacokinetic considerations described by Cassidy & Houston (1980) it can be shown that the individual fractions (f) of drug escaping clearance by the gut (f_G), liver (f_H) or lung (f_L) are given by the expressions

$$f_G = \frac{AUC\ (i.d.)}{AUC\ (h.p.v.)} \qquad f_H = \frac{AUC\ (h.p.v.)}{AUC\ (i.v.)}$$

$$f_L = \frac{AUC\ (i.v.)}{AUC\ (i.a.)}$$

where AUC is the area under the curve to infinite time for the intraduodenal (i.d.), hepatic portal vein (h.p.v.), intravenous (i.v.) and intraarterial (i.a.) routes. By reference to Fig. 1 it was clear that the 0–4 h after dosing was insufficient in duration to permit an accurate determination of a terminal rate constant for the concentration curves and therefore $AUC_{0-\infty}$ values. However, since blood concentrations at 4 h after dosing were low and the curves (with the exception of sublingual) showed similar shaped profiles, f_G, f_H and f_L were calculated from AUC_{0-4h} ratios. From these values the approximate first-pass clearance of buprenorphine by gut, liver

and lung was calculated to be 80, 50 and 2% respectively (Table 2).

Table 2. First-pass elimination of buprenorphine by gut, liver and lung.

Tissue	Fraction crossing tissue (f)	Mean first-pass effect (%)
Gut	$f_G = \frac{AUC\ (i.d.)}{AUC\ (h.p.v.)} = 0{\cdot}20 \pm 0{\cdot}08$	80
Liver	$f_H = \frac{AUC\ (h.p.v.)}{AUC\ (i.v.)} = 0{\cdot}50 \pm 0{\cdot}08$	50
Lung	$f_L = \frac{AUC\ (i.v.)}{AUC\ (i.a.)} = 0{\cdot}98 \pm 0{\cdot}13$	2

AUC represents the area under the concentration time curve up to 4 h after dosing by the intraduodenal (i.d.), intrahepatoportal (h.p.v.), intravenous (i.v.) or intraarterial (i.a.) routes.

Values for f_G, f_H, and f_L represent mean values ± s.e.m.

Administration of buprenorphine to rats was followed by a rapid excretion of drug-related material in the bile (See Fig. 2). However, biliary excretion after sublingual administration was relatively slow, presumably being dependent upon rate of mobilization of the drug from the sublingual and buccal cavities. The extent of biliary excretion over the 4 h varied with route of administration, being greatest after intrahepatoportal (mean 91%) and newest after intraduodenal (mean 46%) and sublingual (mean 22%) administration. (Fig. 2).

Buprenorphine appeared to be well absorbed from the small intestine as shown by the in situ absorption studies (see Fig. 3). For the first 30 min the radioactivity in the lumen was almost exclusively unchanged buprenorphine, but after this time conjugated drug began to appear as shown by t.l.c.-radioassay of the lumen contents. The percentage of buprenorphine remaining in the lumen was therefore obtained by suitable correction of the total radioactivity data. Loss of buprenorphine from the lumen appeared to follow a biexponential decline (Fig. 3) with an initial phase showing a disappearance half-life of approximately 7 min and lasting until some

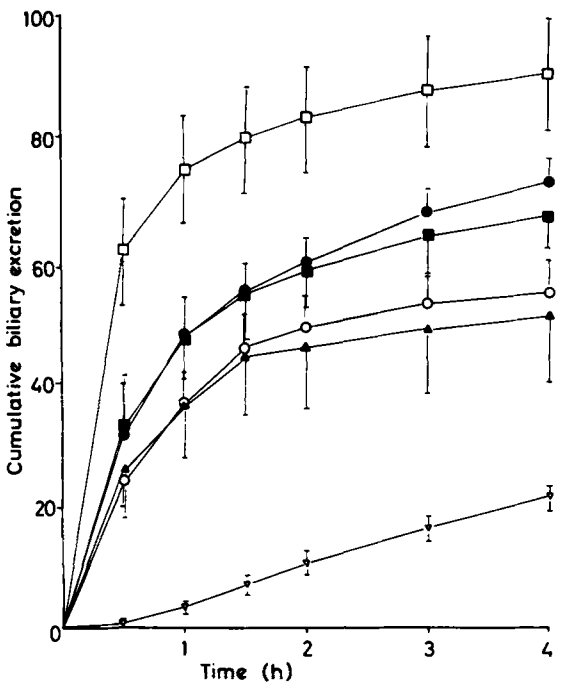

FIG. 2. Cumulative biliary excretion of radioactivity by female rats following administration of [^{3}H] buprenorphine 200 μg kg^{-1} by various routes. Points represent the means of 4 animals ± s.e.m. □, intrahepatoportal; ●, intravenous; ■, intraarterial; ○, intrarectal; ▲, intraduodenal; ▽, sublingual.

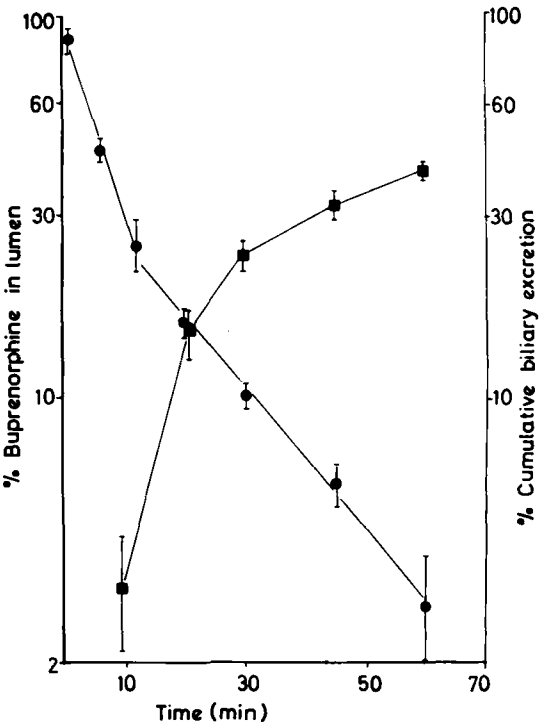

FIG. 3. In situ absorption and subsequent biliary excretion of [^{3}H]buprenorphine in female rats. Insitu absorption curve (●) represents the disappearance of buprenorphine from the lumen. The biliary excretion curve (■) represents the cumulative excretion of total radioactivity in bile. All points represent the means of 4 animals ± s.e.m.

75% of the drug had been lost. A second phase accounting for the loss of remaining drug showed a half-life of some 15 min (Fig. 3). The disappearance of buprenorphine from the gut lumen was considered indicative of absorption of the drug since a considerable proportion of the original dose of radioactivity appeared in the bile of the same animals (Fig. 3). Furthermore, assay of radioactivity in the gut wall after 10 min or 90 min of the in situ preparation showed a total content of only 20–28% and 9–10% respectively of the original dose. Of the radioactivity recovered from the gut wall at these times, t.l.c. showed that a mean of 53% (10 min) and 73% (90 min) was present as conjugated buprenorphine, and is evidence of first-pass metabolic effects on buprenorphine in this tissue.

DISCUSSION

It is evident from the present studies that the systemic availability of buprenorphine is dependent upon the route of administration. For the 4 h after dosing, intravenous administration provided complete availability (98%) relative to the intraarterial route. Delivery by the hepatic portal vein (49%) or rectal (54%) routes was good, but characteristically for a phenolic opiate, intraduodenal availability (9·7%) was low. Comparison with sublingual availability (13% over 4 h) is inappropriate since the blood profile was different from the above routes and appeared to be still in an absorption phase 4 h after dosing. Route dependence on the bioavailability of buprenorphine does not appear to be a consequence of variable absorption since the extent of biliary excretion over the 4 h was not proportional to drug availability. Furthermore, in situ absorption studies confirmed that buprenorphine is quickly and efficiently absorbed from the small intestine.

Variability between delivery routes may often be a consequence of particular physicochemical properties such that for example absorption from the gut is poor or that drug mobilization from a subcutaneous injection site is incomplete. In the case of buprenorphine it is apparent that first-pass metabolism effects are the major influence. Pre-systemic elimination of drugs is becoming better understood, the number of documented examples is now considerable (Rowland 1977) and the pharmacokinetic consequences have been considered (Rowland 1972; Gibaldi & Feldman 1969). The first-pass effect on buprenorphine by gut and liver probably accounts for the inter-individual variation observed in the present studies. Since their first-pass effect is considerable (Table 2) small inter-animal variations result in relatively large variations in the resulting systemic availability. Generally, first-pass mechanisms apply to the tissues gut, liver and lung, and any combination of metabolism by such tissues may be regarded as a first-pass effect.

High metabolic clearance has been observed for drugs such as lidocaine (Boyes et al 1970), propranolol (Shand et al 1970) and salicylamine (Barr 1970).

Of the more common drug delivery routes, oral administration is generally the most influenced by first-pass elimination and this is because the gut and liver effectively represent metabolizing systems arranged in series. Although metabolic activity in gut has been known for many years (Hartiala 1973), the full metabolic capabilities of the tissue have until recently being underestimated. It is becoming apparent, however, that for some drugs this tissue is of greater importance than the liver. Conway et al (1973) for example, showed that intrahepatoportal or intraperitoneal administration of terbutaline to rats provided a 6 or 7 fold increase in availability compared with the oral route, and Ilett et al (1980) have reported an extensive first-pass conjugation of isoprenaline in the dog intestine. It is apparent also that phenolic opiates are extensively metabolized by gut tissue. In vitro studies have shown that buprenorphine and other phenolic opiate agonists or antagonists undergo conjugation in rat gut and that the extent of conjugation is related to lipophilicity (Rance & Shillingford 1977). These findings are supported by our observations that the first-pass inactivation of buprenorphine during passage across the rat gut is of the order of 80%. Morphine has also been shown to be extracted first-pass by rat gut and that the contribution of the gut was double that of the liver (Iwamoto & Klaasen 1976). For phenol alone, a 94% first-pass extraction by rat gut has been shown to primarily account for an oral availability in this species of only 3% (Cassidy & Houston 1980). Extraction of drugs by the gut can be minor compared with that of the liver, however, as demonstrated by an increase in the oral bioavailability of lidocaine from 15 to 81% in dogs after surgical implantation of a portacaval shunt (Gugler et al 1975).

Rectal drug administration is preferred in some countries to the oral route and used in others when necessary as in patients with uncontrolled vomiting. Providing drug absorption from the rectum is efficient, rectal administration provides for improved delivery when oral drugs would otherwise suffer extensive pre-systemic extraction by the gut

and/or liver. Certainly the value of the rectal route has been exemplified with drugs such as diazepam (Magnussen et al 1979) and lidocaine (De Boer et al 1979). The present results with buprenorphine also show the value of the rectal route in the rat as indicated by a five-fold increase in bioavailability over the oral route. However, the fact that rectal delivery was still less than that by the intravenous route could indicate a first-pass effect in the rectum wall. Such metabolism is a possibility since glucuronyl transferase activity is known to extend to lower regions of the gut (Dawson & Bridges 1979). Translating rectal studies in animals to clinical potential is not a simple process because the relative proportions of blood drained systemically compared with hepatically probably varies between different species and man. In rats, the evidence from studies with lidocaine and propranolol suggests blood return from the rectum to be mainly systemic. In man, however, the superior haemorrhoidal vein links via the inferior mesenteric vein to the portal vein, although the inferior and middle haemorrhoidal veins connect directly to the inferior vena cava. Studies in man using lidocaine suggest the non-hepatic blood return from the rectum to be around 50–60% (De Boer et al 1979). Since in the rat, the liver does not appear the prime clearance organ for buprenorphine there may not be a marked difference between man and rat in the systemic availability of buprenorphine administered by the rectal route.

A most valuable non-invasive route of drug administration, which is also considered to bypass the gut and liver, is sublingual or buccal delivery (for review see Gibaldi & Kanig 1965). For drugs with suitable partition profiles, sublingual administration can, in contrast to the oral route, provide relatively rapid and efficient drug delivery as exemplified by the use of glyceryl trinitrate in the treatment of angina pectoris and isoprenaline in bronchial asthma (Altman et al 1960). In the present work some evidence for the usefulness of the sublingual route for buprenorphine was seen. Although the bioavailability of the sublingually administered drug was only marginally greater than when given intraduodenally, it was clear from the plateau of blood levels during the 1–4 h after dosing that drug was still entering the systematic circulation long after that by other routes. Furthermore, in contrast to other routes, biliary excretion of drug-related material (only 20% after 4 h) was still occurring in an almost linear manner 4 h after sublingual dosing. In the anaesthetized animal model, blood flow and hence absorption from the sublingual cavity would not be expected to be as efficient as in a conscious man. It is predicted therefore that the overall availability of buprenorphine by the sublingual route is high and this has been confirmed in a recent clinical investigation (Bullingham et al 1981). Such bioavailability studies correlated with the efficacy of sublingual buprenorphine in clinical studies (Edge et al 1979; Robbie 1979) and may be ascribed to the greater lipophilicity of the drug compared to morphine (Rance & Shillingford 1977), which by comparison is poorly and irregularly absorbed by this route (Edge et al 1979).

There are important biological consequences which may result from the first-pass metabolism of drugs. After parenteral administration, buprenorphine is extensively biliary excreted and an intestinal deconjugation and subsequent enterohepatic cycling of the drug occurs (Brewster et al 1981). However, this is slow and is not regarded to be of clinical significance because of first-pass inactivation during reabsorption. This may prove to be of greater importance after oral administration since the amount of drug recycled may be appreciable compared with the systemic availability by this route. Presystemic metabolism of buprenorphine occurs via conjugation at the 3-phenol group (Brewster et al 1981) and does not appear to produce an active metabolite. The route dependence of the efficacy of buprenorphine is thus regarded as a consequence of inactivation rather than activation of the parent drug.

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