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The Effect of Halothane on Morphine Disposition: Relative Contributions of the Liver and Kidney to Morphine Glucuronidation in the Dog

W. J. Merrell, M.D., L. Gordon, M.B., Ch.B., F.F.A.R.C.S.,* A. J. J. Wood, M.B., Ch.B., F.R.C.P. (Edin),† S. Shay, B.S.,‡ E. K. Jackson, Ph.D.,§ M. Wood, M.B., Ch.B., F.F.A.R.C.S.¶*

The present study determined the effect of halothane on the disposition of morphine by defining the effect of halothane anesthesia on the systemic, renal, and hepatic clearance of the parent compound, morphine, and on the generation of the primary metabolite, morphine-3-glucuronide (M3G) in the dog. Unlabeled morphine, ^{3}H-morphine, and ^{14}C-morphine were simultaneously administered into the portal vein, femoral vein, and renal artery, respectively, first during pentobarbital anesthesia and second during halothane (1.5 MAC) anesthesia; blood samples were taken for estimation of unlabeled plasma morphine and M3G concentrations by high performance liquid chromatography (HPLC). ^{3}H- and ^{14}C-morphine concentrations and corresponding M3G concentrations were determined by dual-channel liquid scintillation counting of the eluant corresponding to the appropriate peak on the HPLC. The portal clearance of morphine was not altered by halothane. However, intravenous (iv) morphine clearance (CL_s) decreased ($P < 0.05$) by 40% from 963 ± 131 to 579 ± 91 ml/min during halothane anesthesia, accompanied by an increase ($P < 0.05$) in half-life from 78 ± 8 to 106 ± 8 min. The reduction in CL_s of morphine occurred putatively on the basis of a halothane-induced decrease in hepatic blood flow, whereas morphine metabolism, reflected by morphine portal (intrinsic) clearance, was not significantly decreased by halothane. There was no significant effect of halothane on the partial metabolic clearance of morphine to M3G, and the ratio of area under the plasma concentration–time curve (AUC)–M3G to AUC unchanged morphine was not significantly altered by halothane, indicating that morphine glucuronidation is unaffected by halothane anesthesia. Because controversy surrounds the role of the kidney in morphine metabolism, the relative contribution of the kidney and liver to morphine glucuronidation was also determined. The clearance of morphine following infusion into the renal artery (1,309 ± 258 ml/min) and femoral vein (979 ± 135 ml/min) was not significantly different ($P = 0.46$). In contrast, when morphine was given *via* the portal vein, its clearance (2,185 ± 558 ml/min) was significantly ($P < 0.05$) greater than that following systemic administration, and the hepatic extraction ratio was 35 ± 11%. The extraction ratio of morphine across the kidney did not differ significantly from zero. The production of M3G as assessed by the ratio of AUC–M3G to the AUC for unchanged morphine was twofold higher ($P < 0.05$) following intraportal administration than following either systemic or renal administration. There was no significant difference between the generation of M3G after intravenous (iv) and renal artery administration. Thus, there is little glucuronidation of morphine by the kidney *in vivo*. (Key words: Analgesics: morphine. Anesthetics, inhalational: halothane. Anesthetics, intravenous: morphine. Kidney: morphine. Liver: morphine. Pharmacokinetics: metabolites; morphine; morphine-3-glucuronide.)

THE ADMINISTRATION of a wide spectrum of therapeutic agents is an essential part of perioperative patient management. It is now well recognized that inhalational anesthetics, including halothane, inhibit the metabolism of a number of drugs, the principal route of elimination of which is oxidation by the microsomal mixed function oxidase system of the liver,[1–3] and we have recently demonstrated that volatile anesthetics reduce intrinsic clearance of propranolol by about 60%.[4–6] In other situations in which drug oxidation is impaired, such as liver disease and aging, glucuronidation has been shown to be a relatively protected pathway. For example, the clearance of the benzodiazepine oxazepam, a drug that undergoes glucuronidation, is less affected by hepatic cirrhosis than that of diazepam, an agent that undergoes predominantly oxidative metabolism in the liver.[7,8] However, whether the glucuronidation pathway is a relatively protected route of metabolism during the administration of volatile anesthetics is unknown. Furthermore, because of the ubiquitous nature of the enzymes responsible for glucuronidation, the effect of halothane on glucuronidation pathways in extrahepatic tissues, such as the kidney, also requires definition.

Morphine undergoes extensive glucuronidation in humans to form the metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), which are then mainly excreted by the kidney in the urine. In humans 70–80% of the administered dose is recovered as M3G, approximately 10% is recovered unchanged in the urine, and a small percentage undergoes demethylation.

Although there is extensive hepatic morphine glucuronidation, hepatic devascularization reduces morphine clearance by only approximately 50% in dogs,[9] whereas the elimination of morphine and M3G has been shown

* Research Fellow, Clinical Pharmacology and Anesthesiology. Present address: Department of Anesthesiology, University of Florida, Gainesville, Florida 32610-0254.

† Professor of Medicine and Pharmacology.

‡ Research Assistant.

§ Associate Professor of Pharmacology.

¶ Professor of Anesthesiology and Associate Professor of Pharmacology.

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Address reprint requests to Dr. Wood: Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee 37232.

in one study to be relatively unaffected in patients with cirrhosis.[10] However, in other studies of patients with perhaps more severe liver disease, the elimination of morphine has been found to be decreased accompanied by an increased elimination half-life and decreased total body clearance.[11]

The relative preservation of the glucuronidation pathway in some patients with liver disease has been attributed to extrahepatic metabolism, and it has been postulated that the kidney might play a role in the metabolism of morphine. Indeed, postoperative apnea secondary to morphine administration has been suggested to be more frequent in patients with diminished renal function.[12] The role of the kidney in the glucuronidation of morphine *in vitro* and *in vivo* is unclear; morphine clearance has been shown to be reduced in patients with renal failure[13] but unchanged in others.[14–16] Microsomes from human fetal kidney contain glucuronyl transferase capable of metabolizing morphine;[17] consequently, intrarenal glucuronidation has been suggested as an important site for the metabolism of morphine. Thus, although the role of the liver in the metabolism of morphine is well defined, the role of extrahepatic sites remains controversial.

We have developed an animal preparation that allows determination of the relative contributions of both the liver and kidney to morphine disposition. By simultaneously administering unlabeled morphine into the portal vein, ^{3}H-morphine into the systemic circulation, and ^{14}C-morphine into the renal artery, it is possible to determine the amount of presystemic clearance by the liver and kidney (*i.e.*, first pass removal by liver and kidney before entering the systemic circulation) under identical physiologic conditions. The ability to determine the kinetics of the drug administered by these three routes simultaneously is critical in making comparisons between morphine extraction by the liver and kidney.

The purpose of the present study was, therefore, to investigate the effect of halothane anesthesia on the disposition of morphine, and on the glucuronidation pathway in particular, by determining the effect of halothane on the systemic, renal, and hepatic clearance of the parent compound morphine and on the generation of the primary metabolite M3G. In addition, the role of the liver and kidney in the disposition of morphine in the dog was determined by the simultaneous administration of differentially labeled morphine into the systemic, renal, and portal circulations.

Methods

Study Protocol

The study protocol was approved by the Vanderbilt University Medical School Animal Welfare Committee.

Healthy male mongrel dogs were studied. Anesthesia was induced with intravenous (iv) 30 mg/kg pentobarbital and maintained with intermittent boluses of pentobarbital totaling 1.0 $mg \cdot kg^{-1} \cdot h^{-1}$ for the duration of the study. Following tracheal intubation ventilation was controlled (FI_{O_2} = 100%) to maintain Pa_{CO_2} between 35 and 42 mmHg, which was confirmed by periodic arterial blood gas analysis. Normal saline and lactated Ringer's solution were administered intravenously (3–9 $mg \cdot kg^{-1} \cdot h^{-1}$) to maintain a urine output of at least 0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ and pancuronium bromide was administered for muscle relaxation.

After surgical exposure of both femoral arteries, bilateral femoral artery catheters and a femoral vein catheter were inserted. A midline abdominal incision was performed, and a catheter was inserted into the portal vein *via* a splenic vein radicle. Catheters were inserted into both ureters and a 22-G needle was inserted into the proximal left renal artery. The portal vein cannula, femoral vein catheter, and renal artery needle were connected to a constant rate syringe infusion pump. Femoral arterial pressure was continuously monitored and urine output from each kidney was collected hourly. After insertion of the catheters, each dog simultaneously received unlabeled morphine 0.5 mg/kg into the portal vein, 200 μCi ^{3}H-morphine (specific activity 84 mCi/mg, Amersham Searle Corporation, Arlington Heights, Illinois) into the systemic circulation *via* the femoral vein, and 200 μCi ^{14}C-labeled morphine (specific activity 153 μCi/mg, Amersham Searle Corporation, Arlington Heights, Illinois) into the left renal artery, all administered over a 5-min interval by constant rate syringe infusion pumps. Arterial blood samples were collected 8, 10, 12, 15, 20, 25, 30, 40, 50, 60, 70, 90, 105, 120, 135, 150, 165, 180, 194, 210, 240, and 270 min after drug administration. The urine produced was collected in hourly aliquots. Following the last blood sample, *i.e.*, 4.5 h after the initial morphine infusions, halothane anesthesia was then administered to achieve an end-tidal concentration of 1.5 MAC (1.3%) for the remainder of the study. Halothane concentrations were measured continuously by the Engstrom gas analyzer (EMMA) and intermittently confirmed by gas chromatography. After 90 min of halothane anesthesia, each dog again received the differentially labeled morphine infusions in an identical manner to that during pentobarbital anesthesia alone and the study protocol repeated during anesthesia with the same blood sampling procedure as before (fig. 1). Due to the well-recognized hemodynamic effects of halothane anesthesia, blood pressure decreased approximately 15 mmHg after the introduction of halothane but did not decrease below a systolic blood pressure of 80 mmHg throughout the study. Fluid boluses were administered to maintain systolic blood pressure above 90 mmHg. Rectal temperature was monitored and body temperature was

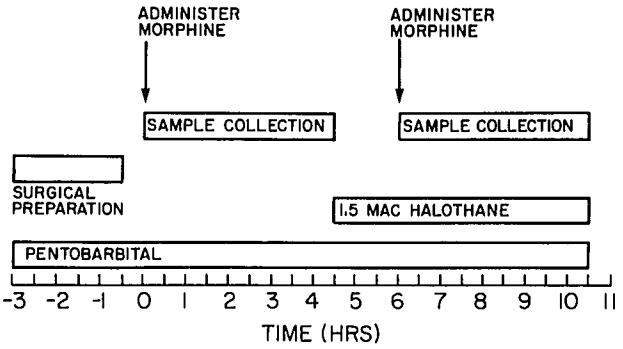

FIG. 1. Study protocol.

maintained within normal physiologic limits. The abdominal incision was approximated with loose sutures to conserve heat.

Unlabeled plasma morphine and M3G concentrations were determined by high performance liquid chromatography (HPLC),[18] and the plasma concentrations of tritiated and carbon-14 labeled morphine and M3G were determined by dual-channel liquid scintillation counting of the eluant corresponding to the appropriate peak on the HPLC. The day-to-day coefficients of variation for morphine and M3G measurements in plasma were 4.9% and 6.1%, respectively. The use of extraction and chromatographic separation ensures that only label attached to the compound of interest is measured. In six of the dogs studied urine was collected throughout both study periods for the determination of unlabeled, unchanged morphine and its metabolites by HPLC for the determination of the partial metabolic clearance of morphine as M3G.

To evaluate the reproducibility of the parameters of morphine disposition during pentobarbital anesthesia alone and to assess the effect of time on morphine disposition in this animal preparation, a pilot study was undertaken in which an additional four dogs were given morphine (0.5 mg/kg) over 5 min *via* the portal vein catheter and arterial blood samples were collected as previously described. Six hours after the initial morphine infusion, morphine was readministered in an identical fashion and blood samples were collected at the same time points. Following extraction from plasma, plasma morphine and M3G concentrations were again determined by HPLC.

Pharmacokinetic Calculations

The area under the plasma concentration–time curve (AUC), calculated by the log-trapezoidal method (and extrapolated to infinity from the last data point using the terminal rate constant) was determined for morphine and its metabolite for each route. From these data, the clearance following systemic (CL_s), portal (CL_p), and renal artery administration (CL_r) were calculated as

$$CL = \frac{Dose}{AUC}$$

where Dose is the dose administered by each route and AUC is the appropriate AUC for that route of administration extrapolated to infinity. (The extrapolated portion contributed 11.9 ± 2.7%.) The concentrations of unlabeled morphine and M3G were corrected to take into account the contribution made by the labeled material to the total concentrations.

The terminal rate constant (Kel) was calculated by least squares regression analysis of the terminal portion of the plasma concentration–time curve. Half-life ($t_{1/2}\beta$) was calculated as:

$$t_{1/2}\beta = 0.693/Kel$$

Volume of distribution ($V_d\beta$) was calculated as:

$$V_d\beta = CL_s/Kel$$

Bioavailability (Fp) following portal administration was calculated as:

$$Fp = CL_s/CL_p$$

and the hepatic extraction ratio was calculated as 1 − Fp.

The partial metabolic clearance of morphine to M3G was calculated during pentobarbital and halothane anesthesia; partial metabolic clearance was defined as the product of the fraction of drug excreted as the metabolite (M3G) and the total clearance of the parent drug morphine. Thus, pharmacokinetic data for morphine administered intraportally, intrarenally, and intravenously were compared during pentobarbital and during halothane anesthesia. During the second drug administration, the AUC was corrected for any residual contribution made to that AUC by the first drug administration. The residual contribution to the total second area contributed 6.9 ± 2.5%.

Statistical Analysis

The results are presented as mean ± SEM and were analyzed by Student's *t* test for paired data or Wilcoxon sum-rank test for paired values as appropriate, with $P < 0.05$ being taken as the minimum level of significance.

Results

The disposition of morphine and its primary metabolite M3G was determined during pentobarbital anesthesia and then again during halothane–pentobarbital anesthesia. In the pilot study of four dogs to determine reproducibility between the two studies of morphine disposition when pentobarbital alone was administered, the mean clearance of morphine when administered into the portal vein did not differ from the first (1,442 ± 135) to the second administration (1,170 ± 173) 6 h later.

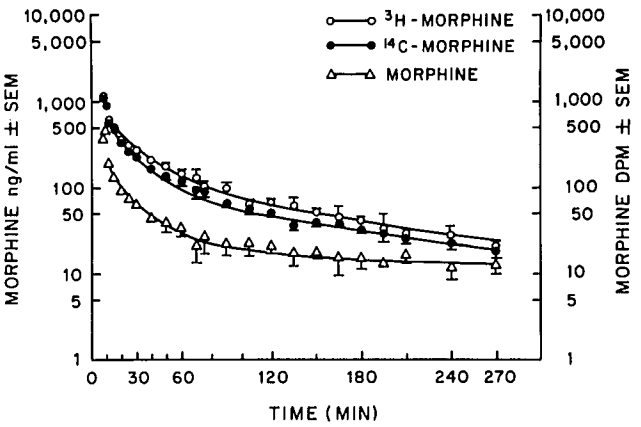

FIG. 2. Plasma morphine concentrations (ng/ml), ^{14}C (dpm/ml), and ^{3}H morphine concentrations (dpm/ml) following simultaneous administration into the portal vein, renal artery, and femoral vein, respectively, (mean ± SEM) during pentobarbital anesthesia.

Plasma morphine concentrations following administration by all three routes during pentobarbital anesthesia alone declined in a biexponential fashion in nine dogs (weight 23.2 ± 1.7 kg, mean ± SEM), as shown in figure 2. The AUC corrected for dose was lower following intraportal injection than systemic injection ($P < 0.05$), and the AUC for the systemic and intrarenally administered isotopes did not differ significantly from one another. The portal clearance of unlabeled morphine (2,185 ± 558 ml/min) was more than twofold greater than systemic clearance (979 ± 135 ml/min, $P < 0.05$) (table 1), so that the systemic availability (F) following portal injection was 65 ± 11%, resulting in an hepatic extraction ratio of 35 ± 11%. There was no significant difference between the clearance of morphine administered by the iv or renal route, implying that little presystemic extraction occurred in the kidney. The extraction ratio of morphine across the kidney did not differ significantly from zero.

The production of M3G from morphine administered by the systemic, hepatic (portal) and renal route was assessed as the ratio of AUC–M3G that of the AUC of unchanged morphine. The ratio of AUC–M3G to AUC morphine was twofold to threefold higher following intraportal administration ($P < 0.05$) than following either systemic or renal administration (table 1). There was no significant difference between the generation of M3G after iv (systemic) and intrarenal artery administration, in keeping with the lack of difference in the morphine clearance by the two routes, implying that morphine glucuronidation to the metabolite M3G occurs primarily in the liver.

TABLE 2. Effect of Halothane (1.5 MAC) Anesthesia on Morphine Pharmacokinetics in Dogs

	Pentobarbital Anesthesia	Halothane Anesthesia
Systemic $V_d\beta$ (l)	113 ± 16	87 ± 10
Systemic $t_{1/2}\beta$ (min)	78 ± 8	106 ± 8*
Systemic CL (ml/min)	963 ± 131	579 ± 91*
Hepatic CL (ml/min)	1,975 ± 611	1,499 ± 184
Renal CL (ml/min)	1,175 ± 271	822 ± 276
Hepatic extraction ratio	0.28 ± 0.11	0.54 ± 0.07*

Values are mean ± SEM.
* $P < 0.05$, *versus* pentobarbital anesthesia.

The pharmacokinetics of morphine in nine dogs during pentobarbital and then halothane anesthesia are compared in table 2 (weight 22.3 ± 4.4 kg, mean ± SD). The clearance of morphine following portal and renal administration was not significantly altered by halothane anesthesia (table 2). However, when administered intravenously, morphine clearance decreased by approximately 40% from 963 ± 131 to 579 ± 91 ml/min during halothane anesthesia ($P < 0.05$). Halothane anesthesia increased the half-life following iv administration by approximately 36% from 78 ± 8 to 106 ± 8 min ($P < 0.05$).

To determine the effect of halothane on the metabolism of morphine to the metabolite M3G, the partial metabolic clearance of morphine to this metabolite was calculated (table 3). There was no significant effect of halothane on the partial metabolic clearance of morphine to M3G, indicating that halothane did not inhibit M-3-glucuronidation, nor did halothane alter the fraction of drug metabolized to the metabolite M3G (table 3). The lack of effect of halothane on the generation of metabolite following iv and intrarenal morphine administration is shown in figure 3. The ratio of the AUC for plasma M3G to unchanged morphine in plasma was not altered significantly by halothane. However, as previously discussed, the generation of M3G following intraportal administra-

TABLE 1. Disposition of Differentially Labeled Morphine Simultaneously Administered into the Systemic, Renal, and Portal Circulations in Dogs during Pentobarbital Anesthesia

	CL (ml/min)	$t_{1/2}\beta$ (min)	$V_d\beta$ (l)	AUC–M3G: AUC–Morphine
Systemic ^{3}H-morphine	979 ± 135	77 ± 8.0	15 ± 17	10 ± 0.9
Hepatic (portal) unlabeled morphine	2,185 ± 558*	129 ± 34	—	22 ± 8†
Renal ^{14}C-morphine	1,309 ± 258	90 ± 6	—	9 ± 0.7

Values are mean ± SEM.
* $P < 0.05$, *versus* systemic administration.
† $P < 0.05$, *versus* systemic and renal administration.

TABLE 3. Effect of Halothane Anesthesia on M3G in Dogs

	Pentobarbital	Halothane
Total morphine clearance (ml/min)	1,880 ± 631	1,406 ± 212
Partial metabolic clearance as M3G* (ml/min)	944 ± 258	611 ± 128
Percent of dose excreted as unchanged drug	9.5 ± 3.1	8.6 ± 2.4
Percent of dose excreted as M3G	56.9 ± 11.1	41.6 ± 7.9

Values are mean ± SEM. There were no statistically significant differences.

* Partial metabolic clearance

$$= \frac{\text{Amount of drug excreted as metabolite}}{\text{Total dose}} \times \text{Total morphine clearance}$$

tion was twofold to threefold higher ($P < 0.05$) than that following either iv or renal administration, which were similar (fig. 3).

Discussion

To evaluate the relative roles of the kidney and liver in the metabolism of morphine, we developed a technique that allows the simultaneous determination of the clearance of morphine and its major metabolite M3G following simultaneous administration into the systemic, hepatic, and renal circulations. When injected into the portal vein, all of the drug must pass through the liver before entering the systemic circulation, after which it is handled identically to that injected systemically. The difference in clearance between the two routes reflects the extent of drug removal by the liver during the first passage of morphine through the liver and allows calculation of the extraction ratio across the liver. Similar arguments can be applied to drug injected into the renal artery for measurement of drug extraction across the kidney.

The results of this study demonstrate that clearance of morphine following portal injection is more than twice that following systemic administration, whereas, in contrast, the clearances of morphine following systemic and renal administration are not significantly different from each other, implying that extraction of unchanged morphine by the kidney is minimal. In addition, there was no significant difference between generation of the metabolite M3G after iv or renal injection, but the ratio of M3G to morphine was twofold greater following administration *via* the hepatic route than following either systemic or renal administration. Thus, although significant presystemic glucuronidation of morphine occurs in the liver when this drug is given intraportally, there is no evidence that administration of the drug directly into the renal artery resulted in the generation of more M3G than when morphine was administered into a peripheral vein. This implies that there is little glucuronidation of morphine by the kidney *in vivo*. We therefore conclude that the liver is a major site of morphine metabolism and that the kidney is not a major contributor to morphine metabolism in the dog.

Recently, a number of case reports have appeared describing unexpected respiratory depression associated with the use of morphine in patients with impaired renal function,[13,19,20] and there has been speculation regarding the effects of renal failure on morphine elimination; some studies have suggested a reduction in morphine clearance in patients with renal disease and others have failed to confirm this finding.[13–16] Although the explanation for these disparate findings is not clear, part of the difference may lie in the nonspecificity of the radioimmunoassay used in some of the studies, which may not be able to distinguish between morphine and its metabolites. In patients with renal impairment failure to excrete morphine glucuronides, the polar metabolites of morphine, will result in their accumulation in the blood, and there is evidence that the elimination of M3G is prolonged in patients with renal disease.[14,15,21] Back conversion of the glucuronide to the parent drug might result in higher levels of unchanged morphine in patients with renal failure, which

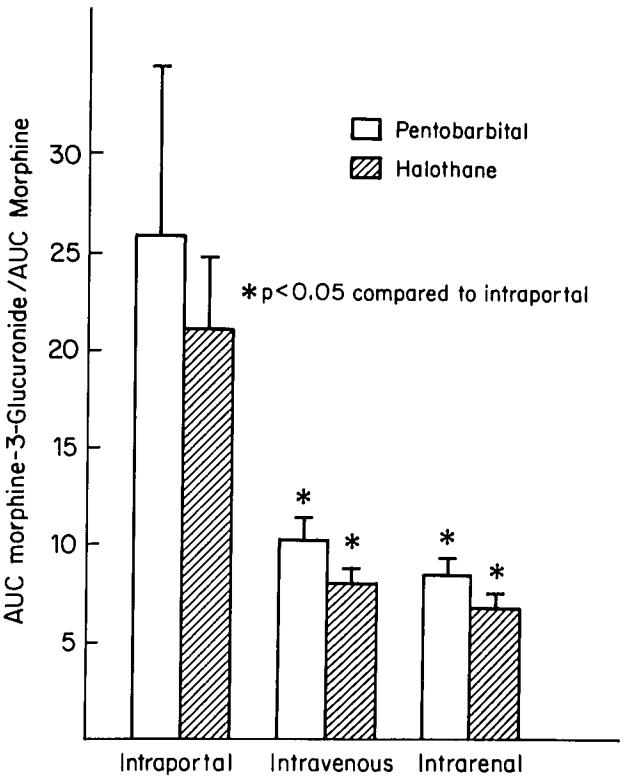

FIG. 3. Ratio of plasma AUC of morphine-3-glucuronide to AUC of unchanged morphine during pentobarbital and halothane anesthesia for the three routes, portal, iv, and renal.

has been suggested as a possible explanation for the altered morphine concentrations found in some studies.[22] Although the present study does not address the issue of back conversion to morphine from the glucuronide, the HPLC method used in this study separates parent drug from its metabolites and is therefore not subject to the problems of nonspecificity seen in some of the previous studies that used radioimmunoassay techniques.

Although the metabolite M3G has been shown to possess no analgesic activity and is unlikely to be responsible for morphine-induced respiratory depression in patients with impaired renal function, M6G has powerful opioid effects,[23] penetrates the blood–brain barrier unchanged,[24] and has high affinity for the opioid receptor.[25,26] Thus, it is possible that although morphine does not accumulate in renal failure, the increased clinical effects may be due to accumulation of the pharmacologically active M6G.[12,27–29]

Halothane anesthesia has been shown to have profound effects on drug disposition, and the elimination of a wide variety of drugs is reduced during halothane anesthesia.[2–4] The present study demonstrates that halothane alters the disposition of morphine but through a different mechanism from that previously described for drugs biotransformed by oxidative enzymes. Morphine clearance following portal administration was not significantly altered during halothane anesthesia, but the systemic clearance of morphine was reduced by about 40%. Portal or oral drug clearance is independent of liver blood flow and is only dependent on the intrinsic metabolizing ability of the liver. However, when a drug, such as morphine with a moderately high extraction ratio, is given intravenously, clearance by the liver is dependent upon both liver blood flow and the intrinsic capacity of the hepatic enzymes to metabolize morphine. Because halothane is a well-recognized cardiovascular depressant and is known to decrease hepatic blood flow, it is possible that the reduction in systemic clearance of morphine is due to a decrease in hepatic blood flow during halothane anesthesia, whereas morphine metabolism, reflected by morphine portal clearance, was not significantly decreased. We found that systemic clearance was decreased during halothane anesthesia compared with pentobarbital anesthesia. Because the blood pressure was decreased in the dogs during halothane anesthesia and portal clearance was not affected by halothane anesthesia, the reduction in systemic clearance of morphine must have been due to a reduction in hepatic blood flow during halothane anesthesia.

We have previously shown that halothane reduces the clearance of propranolol, a drug, the principal route of metabolism of which is by oxidation.[4] To determine the effects of halothane on the glucuronidation pathway *per se*, we measured the partial metabolic clearance to the glucuronidated metabolite of morphine, in which the fraction of the dose that appears as a particular metabolite reflects the fraction of the total dose being metabolized by that pathway.[30] Thus, the product of total drug clearance and the fraction of the dose excreted as a metabolite can be used as a measure of the clearance accounted for by that pathway of metabolism. Because enzymes capable of glucuronidating morphine are present in sites outside the liver, such as the kidney, we also examined the effects of halothane anesthesia on morphine glucuronidation, when given *via* the intraportal, iv, and intrarenal routes.

We found that halothane anesthesia produced no change in the intrinsic clearance of morphine, nor did halothane inhibit the metabolism of morphine to the glucuronidated metabolite M3G when given by any of the three routes. In addition, halothane anesthesia did not inhibit the partial metabolic clearance of morphine by the glucuronidation pathway and it had no effect on the fraction of morphine excreted in the urine as unchanged drug or as the metabolite M3G. Thus, there appears to be no inhibition of the M-3-glucuronidation pathway by halothane, and the kidney does not play an important role in morphine glucuronidation either as a primary site of metabolism or by shunting of glucuronidation from the liver to renal tissue during halothane anesthesia. Earlier workers investigating the effects of inhalational anesthetics on rat liver microsomal glucuronyl transferase activity *in vitro* showed that the formation of uridine diphosphoglucuronic acid (UDPGA) was depressed by diethyl ether but not by halothane.[31] More recently, the depressant effect of diethyl ether on UDPGA concentrations in the liver has been confirmed and a smaller effect of halothane on UDPGA levels demonstrated *in vitro*.[32] However, our study clearly demonstrates that *in vivo* morphine glucuronidation is unaffected by halothane anesthesia.

Morphine undergoes extensive glucuronidation both in humans and dogs. During enflurane–nitrous oxide anesthesia in surgical patients, morphine elimination has been demonstrated to be triexponential with a systemic terminal elimination half-life of 104 min, whereas the terminal elimination half-life of conjugated morphine was slower (169 min).[33] In the anesthetized dog (enflurane), the systemic terminal elimination half-life has been shown to be about 75 min,[29] whereas in the present study we report values ranging from 78 min during pentobarbital anesthesia to 106 min during halothane anesthesia. Clearance values were 23 $ml \cdot min^{-1} \cdot kg^{1}$ and 57 $ml \cdot min^{-1} \cdot kg^{1}$ in enflurane-anesthetized surgical patients[33] and dogs,[29] respectively. Thus, although interspecies differences in drug metabolism always exist, the dog is an appropriate laboratory model in which to study the possible effects of halothane anesthesia on morphine metabolism.

In summary, we conclude that the liver is the major site of morphine metabolism and presystemic metabolism by the liver is an important contributor to the low bio-

availability of morphine following oral administration. We were further able to demonstrate that even though the enzyme UDP-glucuronyl transferase is present in renal tissue, the kidney is not a major site of morphine metabolism *in vivo* or the generation of metabolites, although it may play a major role in the excretion of the polar morphine metabolites. In addition, we have shown that the effects of halothane on drug metabolism and disposition may be relatively pathway-specific and multifactorial, with glucuronidation being a more protected pathway than oxidation. Thus, it appears that halothane inhibits the metabolism of drugs undergoing oxidation but not those that are glucuronidated. In addition to the direct effects on drug metabolism, systemic clearance is also reduced probably because of the effects of halothane on liver blood flow independent of its effect on drug metabolism. Thus, in clinical practice, if these findings are confirmed in humans, halothane anesthesia is likely to have relatively unimportant effects on morphine metabolism.

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