Role of the Kidneys in the Metabolism of Furosemide: Its Inhibition by Probenecid[1]

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ABSTRACT

The site where furosemide is metabolized and the location where probenecid reduces furosemide metabolism remain poorly defined. The liver appears to play a minor role, and there is indirect evidence suggesting that the kidneys could be responsible for the metabolism of furosemide. To assess the role of the kidneys in the metabolism of furosemide, its intravenous kinetics have been studied in control and anephric rabbits, after the ligation of the renal pedicles. Two additional groups of rabbits, control and anephric, have received probenecid before the administration of furosemide. In the control group, the total clearance of furosemide was 18.65 ± 1.01 mL/min per kg; urinary and metabolic clearances of furosemide were 7.95 ± 0.65 and 10.70 ± 1.11 mL/min per kg, respectively. In anephric rabbits, total clearance was reduced by 85% to 2.69 ± 0.26 mL/min per kg ($P < 0.001$), secondary to the abolition of furosemide renal excretion and to the reduction in metabolic clearance from 10.70 ± 1.11 to 2.69 ± 0.26 mL/min per kg ($P < 0.001$). The pretreatment with probenecid reduced the total clearance of furosemide by 80%, to 3.62 ± 0.24 mL/min per kg ($P < 0.001$), because of a reduction of 90 and 75% in urinary and metabolic clearances, respectively. The administration of probenecid to anephric rabbits did not reduce further the metabolic clearance. It is concluded that the kidneys are responsible for 85% of furosemide total clearance, either via excretion (43%) or biotransformation (42%), and that probenecid inhibits both processes.

Key Words: *Kidney, furosemide metabolism, probenecid, nephrectomy, rabbits*

Furosemide is a potent loop diuretic used in disease states where there is retention of sodium and water. Furosemide is rapidly eliminated by renal excretion and by biotransformation, especially conjugation, to approximately the same extent (1–3). The exact site of furosemide metabolism is still uncertain (2). The role of the liver in the metabolism of furosemide is questionable because, on the one hand, in patients with hepatic cirrhosis, the metabolic clearance of furosemide is not modified (4–6). Furthermore, Verbeeck *et al.* showed that the clearance of furosemide and the proportion of conjugated furosemide excreted in urine were not significantly changed in functionally hepatectomized dogs (7). On the other hand, the biliary excretion of furosemide has been shown in both rats (8) and humans (9). Although furosemide is biotransformed in the intestine after oral administration (10), its contribution to the metabolic clearance of furosemide is unknown. Finally, the role of the intestine as an excretory organ does not appear important, because the secretion of furosemide into the intestinal lumen accounts for less than 5% of furosemide clearance (11).

In *in vitro* studies, it has been shown that the kidney can biotransform a variety of drugs (12). Conjugation, especially glucuronidation, appears to be an important metabolic pathway in the kidney (13). Because furosemide biotransformation essentially occurs through conjugation with glucuronic acid, furosemide metabolism could theoretically take place in the kidneys. Only indirect evidence supports such a hypothesis. For instance, Homeida *et al.* (14) reported that the coadministration of furosemide with probenecid reduced not only furosemide urinary clearance but also its metabolic clearance; the authors concluded that among other possibilities, *i.e.*, the reduction of furosemide glucuronidation in the liver, probenecid could have decreased furosemide metabolism in the kidneys. Smith and Benet (15) showed in kidney transplant recipients a positive correlation between furosemide glucuronide metabolite and the renal clearance of furosemide, suggesting a possible intrarenal conjugation process. The coadministration of pentopril, an angiotensin-converting enzyme inhibitor, with furosemide resulted in an increase in the percentage of furosemide excreted as glucuronide whereas the renal excretion of unchanged furosemide decreased (16). Assuming that furosemide could be conjugated in the kidneys, the authors postulated that pentopril metabolite, by blocking the secretion of furosemide at the luminal level of the proximal tubule, would enhance the intratubular concentration of furosemide and, as a consequence, the conjugation of furosemide with glucuronides.

To clarify the role of the kidneys in the biotransformation of furosemide, the disposition of this diuretic in functionally anephric and control rabbits has been

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studied *in vivo*. In a second set of experiments, to confirm the site of furosemide metabolism, as well as where the probenecid-furosemide interaction occurs, the kinetics of furosemide were assessed in control and functionally anephric rabbits pretreated with probenecid.

MATERIALS AND METHODS

Experimental Model

Male New Zealand rabbits (Ferme Cunicole, Les Lapins Léonard, Mirabel, Canada) weighing 2.2 to 2.8 kg were individually housed in ventilated metabolic cages and maintained on Purina (Ralston-Purina, St. Louis, MO) pellets and water *ad libitum*. An acclimatization of at least 7 days was allowed for the animals before any experimental work was undertaken. All of the experiments were conducted in accord with the Canadian Council on Animal Care guidelines for care and use of laboratory animals.

Rabbits were fasted for at least 12 h before surgery. A lateral vein of an ear was cannulated with a Butterfly-25 (Venisystem; Abbot Ireland, Sligo, Ireland) for the infusion of a 0.9% NaCl and 5% glucose (50/50) solution, to which 0.05 mEq/mL of sodium bicarbonate was added, at a rate of 50 mL/h to compensate for losses of water and blood sampling. Urinary losses after the administration of furosemide were also replaced with a solution of 0.9% NaCl. The lateral vein of the opposite ear was also cannulated with a Butterfly-25 for furosemide and probenecid administration. Rabbits were anesthetized with 30 mg/kg sodium pentobarbital iv, the trachea was exposed, and an endotracheal tube (CDMV; ST-Hyacinthe, Québec, Canada) was inserted between the fourth and fifth tracheal rings, caudally to the thyroid cartilage, for artificial ventilation (21 mL/cycle, 48 cycles/min) (Harvard Apparatus, Boston, MA). The right femoral artery was dissected, and a polyethylene tube (P-60, Intramedic, Becton, Dickinson and Co., Parsippany, NJ) was inserted into the abdominal aorta, above the renal arteries, for blood sampling and arterial blood pressure measurement. Finally, a vesical catheter (Bardex Foley 8 Ch/Fr, Mississauga, Ontario, Canada) was installed to collect urine.

Once the rabbits were anesthetized, the abdomen was opened by a midline incision to clear surrounding tissues to have access to the kidneys. Functional anephria was produced by the ligation of both renal pedicles. The surgical procedure was completed in less than 20 min.

Arterial pH, PaO_2, and $PaCO_2$ were measured in arterial blood samples withdrawn throughout the experiment with an automated and computerized 1312 pH/oxygen analyzer (Instrumentation Laboratory, Lexington, MA). Throughout the experiment, arterial blood pressure was monitored via a three-way stopcock (Seamless, Division of Professional Medical Products, Inc., Ocala, Florida) connected to a pressure transducer (E and M Instruments, Houston, TX) and a physiograph (E and M Instruments).

Experimental Protocol

Four groups of six anesthetized rabbits each were used. Rabbits of the first group (control animals) received 2.5 mg/kg iv of furosemide (Lasix; Sabex, Montréal, Québec, Canada). Rabbits of the second group were functionally anephric and received 2.5 mg/kg iv of furosemide. The rabbits of the third group received 50 mg/kg iv of probenecid (Sigma Chemical Company, St. Louis, MO) 2 h and 30 min before the administration of furosemide (2.5 mg/kg iv). The rabbits of the fourth group were functionally anephric and received probenecid and furosemide as specified for the third group. The dose of furosemide was based on the fact that the kinetics of furosemide injected intravenously are first order up to doses of 10 mg/kg (17).

In all cases, immediately after the sham laparotomy or the functional nephrectomy, furosemide was injected in 1 min. The same protocol was used in the four groups. Blood samples (2 mL) were withdrawn at 0, 3, 6, 10, 15, 20, 25, 30, 45, and 60 min. Additional blood samples were withdrawn at 90, 120, and 150 min in the rabbits of Groups 2, 3, and 4. Urine was collected for 60 min from the rabbits of Group 1 and for 150 min from the rabbits of Group 3. Plasma and urine were stored in tubes protected from light at −20°C until furosemide was assayed. Furosemide in plasma and urine was assayed by high-performance liquid chromatography as described elsewhere (18).

The plasma protein binding of furosemide was assessed by ultrafiltration at the end of each experiment, because any change in furosemide plasma protein binding secondary to the experimental procedure should be more pronounced at this time. Plasma (1.5 mL) spiked with 75 μg of furosemide (Sigma Chemical Company) was incubated for 20 min in a shaking bath at 37°C. After the incubation, 250 μL of plasma was used to determine the total concentration of furosemide. The remaining plasma was centrifuged at 3,500 rpm in Centrifree System devices (Amicon; W.R. Grace & Co.-Conn., Beverly, MA) for 30 min at 25°C. The concentration of unbound furosemide was assayed in 250 μL of the resulting ultrafiltrate.

Data Analysis

Furosemide kinetic parameters were estimated assuming noncompartmental kinetics. The area under the curve of furosemide concentrations in plasma as a function of time ($AUC_{0-\infty}$) was estimated by means of the trapezoidal method. Total clearance (Cl_t), terminal half-life ($T_{1/2}$), and apparent volume of distribution (Vd) of furosemide were calculated as described by Gibaldi and Perrier (19). The urinary clearance of furosemide (Cl_u) was calculated by use of the following equation: $Cl_u = Xu_{0-t}/AUC_{0-t}$. Where Xu_{0-t} is the amount of furosemide excreted unchanged in the urine during the experiment. Furosemide metabolic clearance (Cl_m) was estimated by subtracting Cl_u from Cl_t. The metabolic clearance of furosemide is the sum of the metabolism of furosemide in the kidneys, *i.e.*, renal metabolic clearance (Cl_{rm}), and the metabolism of furosemide in organs other than the kidneys, *i.e.*, extrarenal metabolic clearance (Cl_{erm}). The Cl_{erm} corresponds to furosemide total clearance in functionally anephric rabbits. Cl_{rm} was calculated by subtracting Cl_{erm} in functionally anephric rabbits from Cl_m in control rabbits.

The results are expressed as mean ± SE. Differences between groups were assessed by the use of unpaired *t* test and ANOVA test. The threshold of significance was $P < 0.05$.

RESULTS

Hemodynamic Monitoring

Mean arterial pressure, after anesthesia and surgical manipulations, was not affected by the functional exclusion of the kidneys, *i.e.*, 66 ± 1 *versus* 62 ± 2 mm Hg in control and functionally anephric rabbits. During the experiments, blood pressure remained constant with no significant decrease, and at the end of the experiments, mean blood pressure was similar in

both groups (56 ± 3 *versus* 55 ± 1 mm Hg in anephric and control rabbits, respectively)

Furosemide Pharmacokinetics in Control and Functionally Anephric Rabbits

In functionally anephric rabbits, the mean concentrations of furosemide in plasma were consistently greater than those measured in control rabbits because of a slower rate of decline (Figure 1). As a consequence, the $AUC_{0-\infty}$ of furosemide in functionally anephric rabbits was seven times greater ($P < 0.001$) than in control animals (Table 1).

In the control group, the total clearance of furosemide was 18.65 ± 1.01 mL/min per kg, of which 43% was urinary and 57% was metabolic clearance (Table 1; Figure 2). In functionally anephric rabbits, the total clearance of furosemide was reduced by 85% ($P < 0.001$), secondary to both the abolition of furosemide renal excretion and the reduction in the metabolic clearance ($P < 0.001$) (Table 1). In functionally anephric rabbits, the furosemide volume of distribution was smaller than in control animals. Furosemide was highly bound to plasma proteins, because only 6% of furosemide concentrations in plasma were found unbound (Table 1). Functional nephrectomy did not modify the fraction of unbound furosemide.

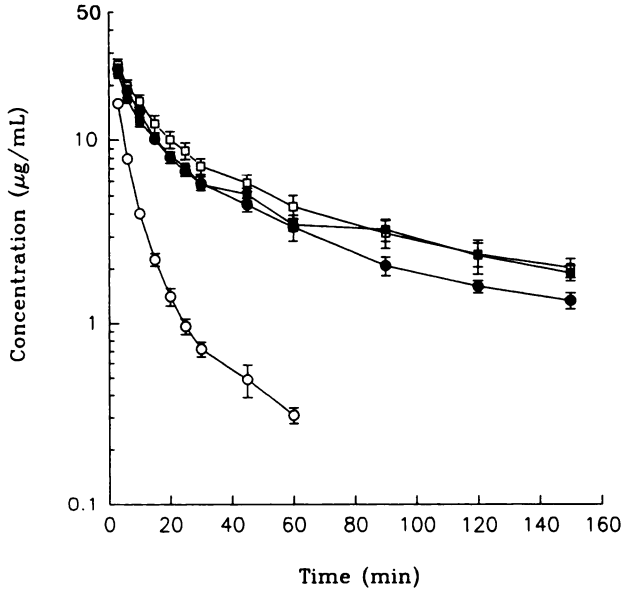

Figure 1. Mean concentrations of furosemide in plasma as a function of time after the iv administration of 2.5 mg/kg to control rabbits without (open circles) and with (closed circles) probenecid pretreatment and to functionally anephric rabbits without (open squares) and with (closed squares) probenecid pretreatment. Vertical bars are SE.

TABLE 1. Pharmacokinetic parameters of furosemide in control and functionally anephric rabbits[a]

Parameter	Control ($N = 6$)	Anephric ($N = 6$)
$AUC_{0-\infty}$ (μg · min/mL)	136 ± 7	926 ± 72[b]
Cl_t (mL/min per kg)	18.7 ± 1.0	2.7 ± 0.3[b]
Cl_u (mL/min per kg)	8.0 ± 0.7	0.0
Cl_m (mL/min per kg)	10.7 ± 1.1	2.7 ± 0.3[b]
Vd (mL/kg)	243 ± 18	186 ± 18[b]
fu (%)	5.9 ± 2.6	7.3 ± 0.9
$T_{1/2}$ (min)	12.5 ± 1.3	54.2 ± 3.3[b]

[a] Values are means ± SE. $AUC_{0-\infty}$ is the area under furosemide concentrations in plasma curve-time from time 0 to ∞; Cl_t, Cl_u, and Cl_m are furosemide total, urinary, and metabolic clearances, respectively; Vd is furosemide apparent volume of distribution; fu is furosemide plasma unbound fraction; $T_{1/2}$ is furosemide terminal half-life.
[b] $P < 0.001$ compared with control rabbits.

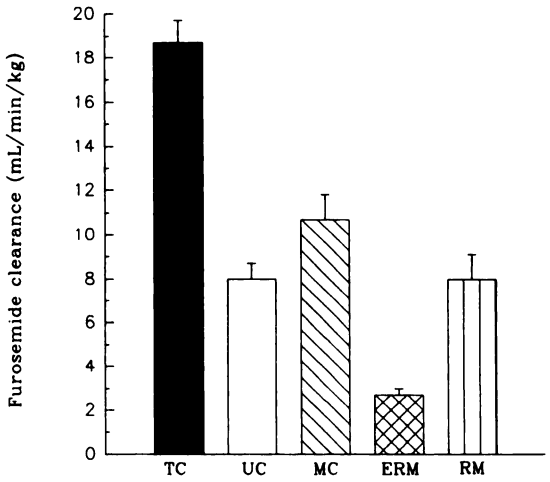

Figure 2. Furosemide clearances in control and in functionally anephric rabbits. TC, UC, and MC are total, urinary, and metabolic clearances in control rabbits, respectively; ERM is extrarenal clearance in functionally anephric rabbits, and RM is the calculated renal metabolic clearance.

Furosemide Pharmacokinetics After Pretreatment With Probenecid in Control and Functionally Anephric Rabbits

The pretreatment of rabbits with probenecid reduced the slope of the decline of furosemide concentrations in plasma as much as did functional nephrectomy (Figure 1). Compared with control rabbits, probenecid decreased the total clearance of furosemide by 80% ($P < 0.001$), because of a reduction of 90 and 75% in the urinary and the metabolic clearances of furosemide, respectively (Table 2). The administration of probenecid to functionally anephric rabbits elicited no effect on extrarenal metabolic clearance (Table 2). Compared with control rabbits (Table 1), pretreatment with probenecid did not modify the furosemide apparent volume of distribution in rabbits with and without functional nephrectomy (Table 2).

TABLE 2. Pharmacokinetic parameters of furosemide after pretreatment with probenecid in control and functionally anephric rabbits[a]

Parameter	Control (N = 6)	Anephric (N = 6)
$AUC_{0-\infty}$ (μg · min/mL)	706 ± 47	919 ± 67[b]
Cl_t (mL/min per kg)	3.6 ± 0.2	2.8 ± 0.2[b]
Cl_u (mL/min per kg)	0.6 ± 0.2	0.0
Cl_m (mL/min per kg)	3.0 ± 0.3	2.8 ± 0.2
Vd (mL/kg)	208 ± 12	219 ± 19
fu (%)	4.9 ± 0.5	8.4 ± 1.2
$T_{1/2}$ (min)	46.3 ± 2.0	65.8 ± 8.4[b]

[a] Values are means ± SE. $AUC_{0-\infty}$ is the area under furosemide concentrations in plasma curve-time from time 0 to ∞; Cl_t, Cl_u, and Cl_m are furosemide total, urinary, and metabolic clearances, respectively; Vd is furosemide apparent volume of distribution; fu is furosemide plasma unbound fraction; $T_{1/2}$ is furosemide terminal half-life.
[b] $P < 0.05$ compared with control rabbits.

Pretreatment with probenecid did not affect the binding of furosemide to plasma proteins in control or in functionally anephric rabbits.

DISCUSSION

This study demonstrates that the biotransformation of furosemide takes place primarily in the kidneys and that probenecid inhibits both renal metabolism and excretion, with no apparent effect on extrarenal clearance. It is unlikely that the low extrarenal clearance of furosemide may be secondary to the experimental protocol. The contribution of the hepatic metabolism, as well as the biliary excretion of furosemide, to the total clearance of furosemide appears to be small (4–7,11,20,21). Therefore, changes in the hepatic metabolism or the biliary excretion of furosemide secondary to the ligation of renal pedicles should not have important repercussions on the kinetics of the diuretic. Supporting such hypothesis, it has been shown that bile flow, as well as the biliary excretion of furosemide, was not modified after the ligation of the renal pedicles of rats (8).

The liver plays a major role in drug metabolism because of the presence of significant amounts of Phase I and Phase II isoenzymes. Enzymes involved in the metabolism of xenobiotics are also present in the kidneys, particularly those implicated in conjugation reactions, such as uridine diphosphate-glucuronyltransferases (UDPGT), glutathione S-transferases, and N-sulphotransferases (12). Some of these enzymes, particularly UDPGT, have a high activity in the kidney, predominantly in the proximal tubule (22). In *in vitro* studies, using either isolated perfused tubules or perfused kidneys, it has been demonstrated that the kidneys have the ability to biotransform drugs such as paracetamol, morphine, and sulindac (23–25). However, few *in vivo* studies have been performed to compare the ability of the kidneys to metabolize xenobiotics with that of other organs, especially the liver (26).

The results of this study in rabbits show that 43% of a dose of furosemide is excreted unchanged in urine, and 57% is metabolized. Bilateral functional nephrectomy reduced the total clearance of furosemide by 85%, indicating that only 15% of the total clearance is extrarenal. Of the renal clearance, 43% corresponds to urinary clearance and 42% corresponds to metabolic clearance. That is, the kidneys are responsible for nearly 85% of the total clearance of furosemide. *In vivo*, the intestine contributes to the biotransformation of oral furosemide, and *in vitro*, both the intestine and the liver are able to metabolize furosemide (27). Therefore, we postulate that the extrarenal clearance of furosemide occurs in the liver and/or in the intestine. Supporting that the liver may contribute to the systemic elimination of furosemide is the fact that in functionally hepatectomized dogs, the clearance of furosemide decreased by about 20% (7).

The glomerular filtration of furosemide is limited by its binding to plasma proteins (*i.e.*, >90%) (2). Thus, renal furosemide excretion is primarily carried out by proximal tubular secretion, via the organic anion transport system. The tubular secretion of furosemide can be inhibited by the concomitant administration of probenecid (14,28). In this study, high doses of probenecid decreased the tubular secretion of furosemide by 90%.

In vitro, probenecid has the ability to inhibit the glucuronidation of acetaminophen and lorazepam in either rat, mouse, or human liver microsomes (29,30). It has been suggested that *in vivo*, probenecid reduces the metabolic clearance of furosemide, either in the kidney or in extrarenal sites (14,28). In this study, probenecid pretreatment reduced the metabolic clearance of furosemide by 75%, with essentially no effect on the extrarenal metabolic clearance of furosemide. As a matter of fact, the administration of high doses of probenecid produced the same effect on furosemide biotransformation as bilateral nephrectomy. We may speculate that as a consequence of the inhibition of the organic anion transport pathway by probenecid, the entry of furosemide into the proximal tubule is blocked, impeding thus its intracellular metabolism as well as its secretion into the tubular lumen.

Probenecid did not influence the access of furosemide into extrarenal organs, because pretreatment with probenecid did not affect the extrarenal metabolic clearance of the diuretic. Probenecid is secreted into the bile and as a consequence can depress the biliary secretion of other organic anion compounds such as rifampin (31). With the experimental protocol presented here, we have not assessed whether the biliary excretion of conjugated furosemide was affected.

In functionally anephric rabbits, the furosemide volume of distribution decreased by 24%, supporting that furosemide distributes into the kidneys. Although not statistically significant, probenecid pretreatment also induced a small decrease in the furosemide volume of distribution. In rats, the kidney

tissue to plasma concentration ratio of furosemide is around 4 (8), suggesting that the diuretic does accumulate into this organ. In humans, probenecid reduces the furosemide volume of distribution by 50% (14). These observations suggest that independent of the species, the kidneys are an important site for furosemide distribution.

In conclusion, the results of this study indicate that in the rabbit, the kidneys are responsible for most of the biotransformation of furosemide. Probenecid reduces both the excretion and the metabolism of furosemide in the kidneys and does not affect the extrarenal biotransformation of the diuretic.

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