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Clinical Consequences of the Biphasic Elimination Kinetics for the Diuretic Effect of Furosemide and its Acyl Glucuronide in Humans

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Abstract

This review discusses the possibility of whether furosemide acyl glucuronide, a metabolite of furosemide, contributes to the clinical effect of diuresis.

First an analytical method (e.g. HPLC) must be available to measure both parent drug and furosemide acyl glucuronide. Then, with correctly treated plasma and urine samples (light protected, pH 5) from volunteers and furosemide-treated patients, the kinetic curves of both furosemide as well as its acyl glucuronide can be measured. The acyl glucuronide is formed in part by the kidney tubules and it is possible that the compound is pharmacologically active through inhibition of the $Na^+/2Cl^-/K^+$ co-transport system; up to now the mechanism of action has been solely attributed to furosemide.

The total body clearance of furosemide occurs by hepatic and renal glucuronidation (50%) and by renal excretion (50%). Enterohepatic cycling of furosemide acyl glucuronide, followed by hydrolysis, results in a second and slow elimination phase with a half-life of 20–30 h. This slow elimination phase coincides with a pharmacodynamic rebound phase of urine retention. After each dosage of furosemide, there is first a short stimulation of urine flow (4 h), which is followed by a 3-day recovery period of the body.

The following clinical implications arise from study of the elimination kinetics of furosemide. Repetitive dosing must result in accumulation of the recovery period. Accumulation of furosemide and its acyl glucuronide in patients with end-stage renal failure results from infinite hepatic cycling. Impaired kidney function may result in impaired glucuronidation and diuresis. While kidney impairment normally requires a dose reduction for those compounds which are mainly eliminated by renal excretion, for diuretics, a dose increment is required in order to maintain a required level of diuresis.

The full clinical impact of the accumulation of furosemide and its acyl glucuronide in patients with end-stage renal failure has to be determined.

Furosemide (frusemide; 4-chloro-*N*-(2-furylmethyl)-5-sulphamoylanthranilic acid, pKa 3·9) inhibits the active reabsorption of chloride ions in the thick ascending limb of the loop of Henle by binding to one of the Cl^- binding sites of the $Na^+/2Cl^-/K^+$ co-transport system (Burg et al 1973; Burg 1976; Jacobson & Kokko 1976; Branch et al 1977; Seeley & Dirks 1977; Greger & Schlatter 1983; Heidenreich et al 1983; Ponto & Schoenwald 1990; Wittner et al 1991; Swan & Brater 1993). In humans, furosemide is metabolised by a phase II metabolism into furosemide acyl glucuronide (1-*O*-glucuronide, Fgluc (Beerman et al 1975, 1977; Benet 1979; Benet et al 1983; Hammarlund et al 1984; Hammarlund-Udenaes & Benet 1989; Vree et al 1994).

Acyl glucuronides are unstable in alkaline media (pH >7·0), therefore, for analysis, urine (in-vivo) must be kept acidic at pH 5·0 in order to prevent hydrolysis and isomerization of acyl glucuronides (Faed 1984; Rachmel et al 1985; Vree et al 1992a, 1993a,b, 1994).

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Pharmacokinetic and pharmacodynamic studies have mostly reported the kinetic and dynamic behaviour of the parent drug or the sum of unconjugated and deconjugated furosemide (Brater 1978; Chennavasin et al 1980; Vree et al 1983a; Alván et al 1990). Furosemide and its rapidly formed acyl glucuronide are actively secreted by the kidney tubule, and it could be questioned whether furosemide or its acyl glucuronide is the active constituent (or indeed whether both are active). It is likely that the glucuronide group, attached to furosemide, does not harm the interaction with the receptor or the transport mechanism. Since the two compounds enter the body at almost the same time, they both may be pharmacodynamically active, or at least the individual effects may be inseparable (Vree et al 1995a,b, 1996).

The reported half-life of furosemide and its glucuronide is short (2 h) during the first 8 h after administration (Brater 1978; Hammarlund et al 1984; Vree et al 1983a, 1994), and thereafter a second, long half-life of 20 h for furosemide and its acyl glucuronide is observed (Vree et al 1995b).

The aim of this review is to discuss the disposition of furosemide and its acyl glucuronide, the possible dynamics of furosemide acyl glucuronide, and the clinical implications of these points.

Disposition of Furosemide and its Acyl Glucuronide

Analysis

The direct HPLC (high-performance liquid chromotography) analysis of furosemide with its (iso)-acyl glucuronide was reported by Vree et al (1994, 1995a,b) and Sekinawa et al (1995). The molecular structures of furosemide, its acyl glucuronide and hydrolysis products are shown in Figure 1. For a proper analysis of furosemide and its acyl glucuronide, samples must be protected from light (ring-opening in the molecule) and (in-vivo) urine samples must be kept slightly acidic (pH 5–6; isomerization of the glucuronide). All other reports concerning furosemide glucuronide are based on

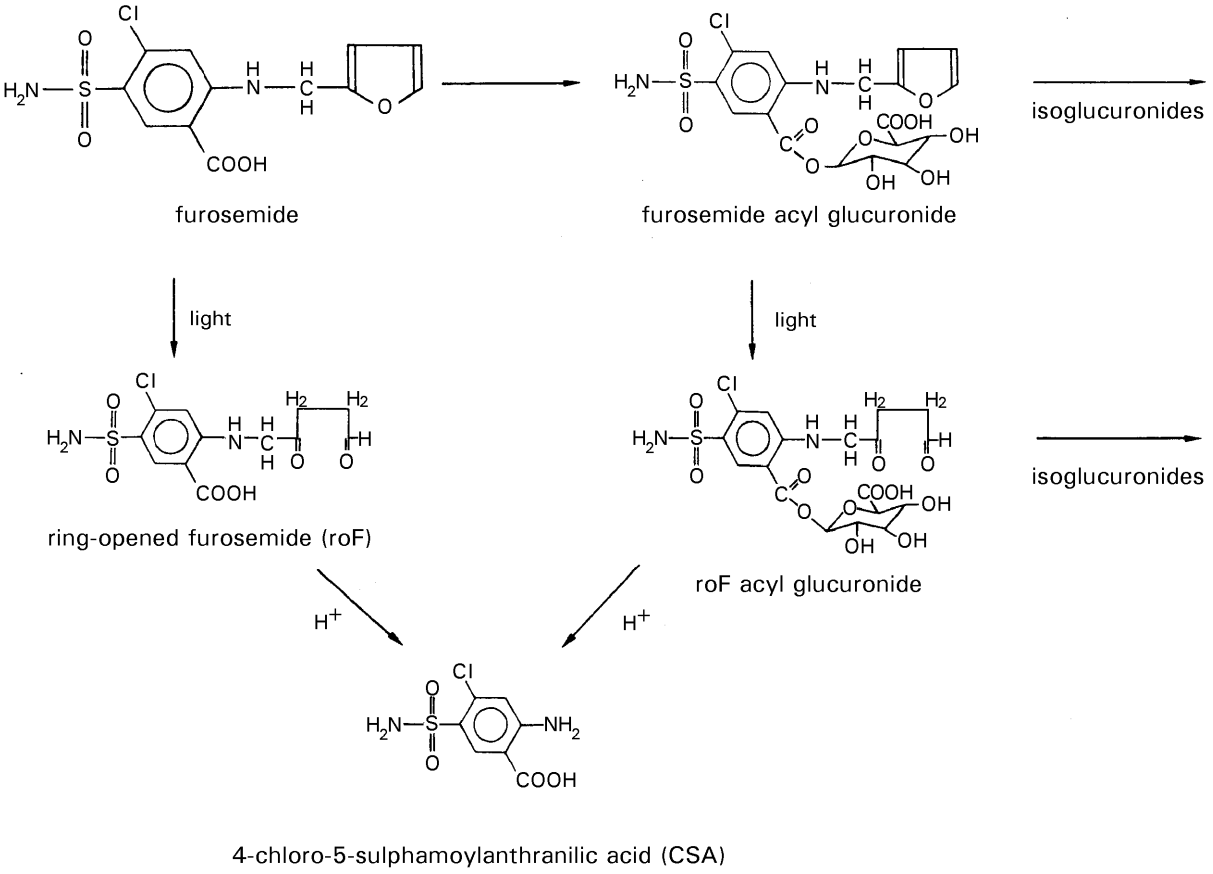

Figure 1. Structures of furosemide, its acyl glucuronide metabolite, the open-ring products and hydrolysis product chlorosulphamoylanthranilic acid (CSA). Plasma and urine samples must be protected from light in order to avoid opening of the furan ring; deproteinization of plasma samples must be carried out with acetonitrile in order to avoid hydrolysis by acidic pH; urine samples must be kept in-vivo at a pH between 5 and 6, in order to avoid isomerization of the acyl glucuronide group (Vree et al 1994).

hydrolysis of the compound by β-deglucuronidase treatment.

Pharmacokinetics

Furosemide and its acyl glucuronide exhibit two half-lives (Vree et al 1995b). The short half-life of approximately 2 h is well known and related to the pharmacodynamic effect of the stimulation of the overall urine production as a result of the increased excretion of Na^+ and Cl^- ions. The second half-life of approximately 20–30 h has been reported recently (Vree et al 1995b). During this slow elimination phase only $4{\cdot}6 \pm 1{\cdot}5\%$ of the administered dose is excreted, which is 14% of the amount excreted during the first 15 h. Examples of the pharmacokinetic behaviour of furosemide and its acyl glucuronide and the pharmacodynamic response (urine flow) are shown in Table 1 and Figures 2 and 3.

The short $t_{½\alpha}$ values of furosemide and its acyl glucuronide in plasma give rise to the assumption that both compounds are excreted by glomerular filtration plus active tubular secretion. Indeed, the apparent renal clearance of furosemide is $90\ mL\ min^{-1}$ during both the first and second phases of elimination (Cutler et al 1974; Vree et al 1995b). The apparent renal clearance value of the acyl glucuronide is extremely high during the first phase (0–6 h, $700\ mL\ min^{-1}$) and lower in the second phase ($100\ mL\ min^{-1}$). In the second phase, the renal clearance values of furosemide and its acyl glucuronide are similar. The extremely high renal clearance of the acyl glucuronide during the first phase may result from renal formation of the glucuronide (Smith et al 1980; Vree et al 1992a,b; Vergés et al 1995; Pichette & DuSouich 1996; Pichette et al 1996), a process which ceases in the second phase of the elimination.

A similar mechanism plays a role in the glucuronidation of probenecid by the kidney (Vree et al 1992a; Pichette & DuSouich 1996; Pichette et al 1996); this process reaches a V_{max} value at a dose of 1000 mg probenecid (Vree et al 1992a).

Probenecid inhibits the renal clearance of both furosemide (Homeida et al 1977; Honari et al 1977; Chennavasin et al 1979; Smith et al 1980; Vree et al 1995a) and its acyl glucuronide (Vree et al 1995a) indicating active tubular secretion for both compounds. Probenecid does not inhibit the renal glucuronidation of furosemide (Vree et al 1992a, 1994, 1995a).

Renal excretion is the main route of elimination for furosemide (40%), with metabolic conjugation accounting for 12% (Vree et al 1995b). Thus 50% of the oral dose is unaccounted for by the investigated routes of elimination or not absorbed. When furosemide is glucuronidated in part by the liver and the acyl glucuronide is mainly excreted via the bile, then a second and slow phase in the plasma elimination can be observed due to enterohepatic cycling and hydrolysis of the acyl glucuronide by the gut bacterial flora. This phenomenon should explain the low plasma concentrations of furosemide acyl glucuronide. The relatively high urine concentrations and renal clearance of the acyl glucuronide must be due to renal glucuronidation. As a consequence the total body clearance of fur-

Table 1. Pharmacokinetic parameters of furosemide in plasma (Vree et al 1995b).

Parameter	Furosemide	Furosemide acyl glucuronide	*P*
F	0·53±0·07	0·15±0·04	0·0003
t_{lag} (h)	0·29±0·16	0·32±0·24	>0·8000
t_{max} (h)	1·98±0·98	1·50±0·74	0·5800
C_{max} ($\mu g\ mL^{-1}$)	2·20±0·84	0·11±0·07	0·0156
$t_{½abs}$ (h)	0·30±0·26	0·68±0·50	0·0340
$t_{½\alpha}$ (h)	1·25±0·75	1·31±0·60	0·4700
$t_{½\beta}$ (h)	33·2±28·0	30·4±11·5	1·0000
MRT (h)	10·2±11·6	14·8±15·9	0·8100
CL_o ($mL\ min^{-1}$)	131·0±26·5		0·0156
CL_r ($mL\ min^{-1}$)* (0–15 h)	90·2±16·9	702·0±221·0	
CL_r ($mL\ min^{-1}$)* (15–96 h)	91·5±29·3	109·0±51·0	
CL_{nr} ($mL\ min^{-1}$) (0–15 h)	41·0±16·5		
CL_{nr} ($mL\ min^{-1}$) (15–96 h)	32·1±19·6		
V_{ss} (L)	21·9±12·3	94·8±68·9	0·0013
excreted (% μmol dose) (0–15 h)	33·3±4·8	13·4±4·7	<0·0001
excreted (% μmol dose) (15–96 h)	4·6±1·5	1·9±1·1	<0·0001
protein binding (%)	98·0±2·0	96·1±2·0	0·02840

Data are presented as means±s.d.; n=7; furosemide dose=80 mg. *mg AUC^{-1}; *P*=difference between furosemide and its acyl glucuronide.

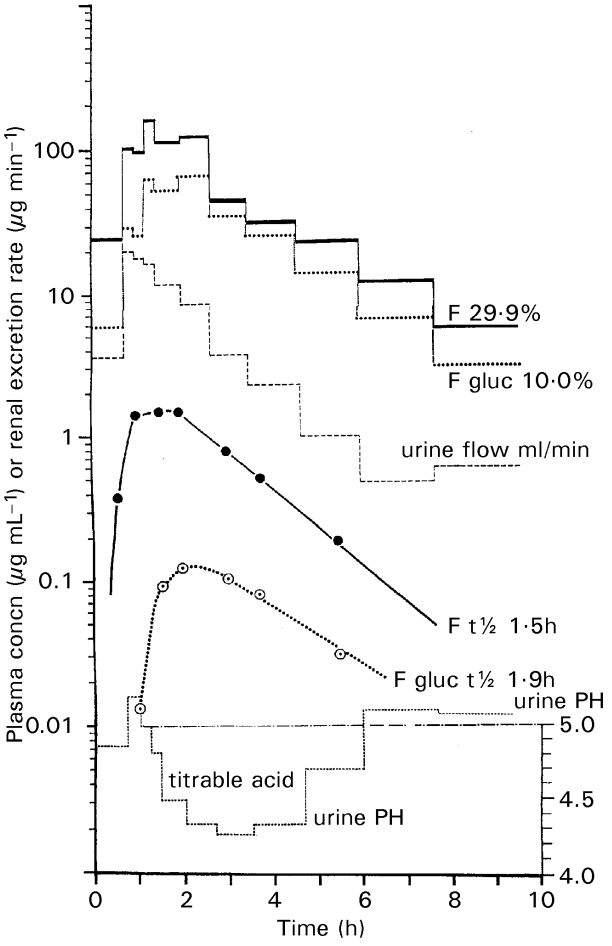

Figure 2. Plasma concentration-time curve and renal excretion rate–time profiles of furosemide (F, solid line) and furosemide acyl glucuronide (Fgluc, dotted line), in a representative human volunteer after an oral dose of 80 mg furosemide. Also the urine flow ($mL\,min^{-1}$) and urine pH vs time profiles are given. This decrease in urine pH was dose dependent and was only present in this particular subject who possibly had a weak buffer capacity of the kidney (Vree & Van Kerrebroeck 1994; Vree et al 1994, 1996). Threshold values for diuresis ($>1\,mL\,min^{-1}$) occur at a renal excretion rate of $20\,\mu g\,min^{-1}$ for furosemide and at $15\,\mu g\,min^{-1}$ for furosemide acyl glucuronide. The half-life value of the diuresis is 1 h.

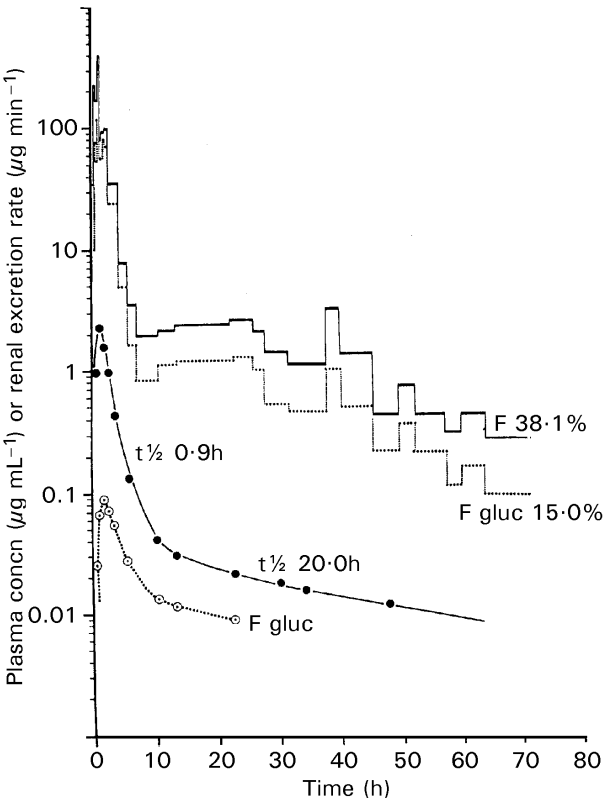

Figure 3. Plasma concentration–time curve and renal excretion rate–time profiles of furosemide (F, solid line) and furosemide acyl glucuronide (Fgluc, dotted line), in a representative volunteer after an oral dose of 80 mg of furosemide. The long $t_{1/2\beta}$ is visible in both the plasma and the urine curve (Vree et al 1995b).

osemide occurs by hepatic and renal glucuronidation (50%) and by renal excretion (50%) (Sekinawa et al 1995; Vergés et al 1995; Vree et al 1995b; Pichette & DuSouich 1996; Pichette et al 1996).

Pharmacodynamics of Furosemide Acyl Glucuronide

The relationship between stimulation of diuresis and the tubular presence of furosemide has been demonstrated. The relationship between stimulation of diuresis and the renal formation of the furosemide acyl glucuronide may be coincidental, or it may indicate that the pharmacodynamic effect is the result of the action of the renal acyl glucuronide.

In the literature, activity–concentration relationships have been constructed for furosemide alone, following the a-priori assumption that the acyl glucuronide is not active. Theoretically, however, the acyl glucuronide has pharmacodynamic activity.

Comparing the molecular structures of the loop diuretics furosemide, bumetanide, pirimetamide and indapamide, the moiety in common is the 5-sulphamoyl-4-substituted benzoic acid structure. Compared with sulphonamides, which decreases urine flow, and probenecid (a 4-sulphamoyl substituted benzoic acid) which increases urine flow, the 5-sulphamoyl group and a substituent with a negative inductive effect at the 4-position of benzoic acid, appear essential for the inhibition of the reabsorption of chloride ions. In indapamide, the carboxyl group is heavily substituted. Thus substitution of the carboxyl group by a glucuronyl group must not alter the diuretic effect (Vree et al 1995b).

By inhibiting the tubular reabsorption of Cl^- and Na^+ ions, furosemide increases the net urine flow or urine production rate per minute (Branch et al 1977; Duchin et al 1977; Hammarlund et al 1984). This effect can be related to the plasma concentration–time curve, or to the renal excretion rate (Hammarlund-Udenaes & Benet 1989; Sjöström et al 1989; Alván et al 1992; Paintaud et al 1995; Yagi et al 1996; Murray et al 1997). The constructed concentration-effect (urine flow, sodium excretion rate) curves of furosemide for the descending part of the elimination curves of the plasma concentrations and renal excretion rates run nearly parallel. When it is possible to measure the concentration of furosemide acyl glucuronide, similar dose–response curves could be constructed (Vree et al 1995b) as shown in Figure 4.

The following hypothesis can be made: when the parent drug is extremely rapidly converted to a metabolite, and both compounds appear with a similar lag time in plasma and in the urine, then one or both compounds might be pharmacodynamically active. The pharmacodynamic effect of furosemide (+ acyl glucuronide) becomes manifest when the compound (or compounds) pass(es) the kidney, reach(es) a furosemide lumen threshold concentration or excretion rate of $21\ \mu g\ min^{-1}$ (Kaojarern et al 1982; Vree et al 1995a,b) and inhibit(s) the reabsorption of Cl^- ions, resulting in a decrease in water reabsorption and increase in overall urine flow. As soon as furosemide reaches its threshold excretion-rate value ($21\ \mu g\ mL^{-1}$) for diuresis its glucuronide shows a threshold value of $15\ \mu g\ min^{-1}$ (Vree et al 1995a,b).

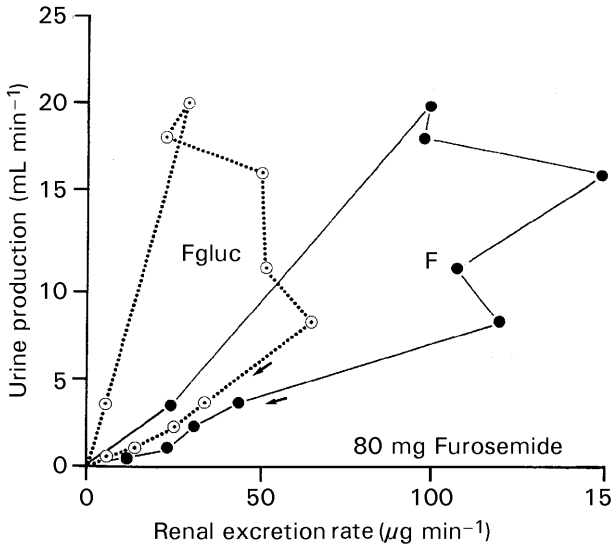

Figure 4. The intrinsic urine flow (observed value minus base-line value of $1\ mL\ min^{-1}$) plotted as effect parameter vs the renal excretion rates of furosemide (F, solid line) and furosemide acyl glucuronide (Fgluc, dotted line) resulting in a clockwise hysteresis loop indicated by the arrows (Vree et al 1996). The hysteresis loop is called acute tolerance by Hammarlund (Hammarlund et al 1984; Hammarlund-Udenaes & Benet 1989). This figure gives the impression that the conjugate Fgluc is more active than furosemide itself, if both compounds are administered separatedly.

Rebound effects

In healthy volunteers the pharmacodynamic effect–time curve shows a biphasic character. First, there is binding to one of the Cl^- binding sites of the $Na^+/2Cl^-/K^+$ co-transport system of the thick ascending part of the loop of Henle, resulting in an increase in urine production (greater than $1\ mL\ min^{-1}$)(Greger & Schlatter 1983; Wittner et al 1991; Swan 1994). A rebound phase follows in which the urine production is less than the base-line value of $1\ mL\ min^{-1}$.

During the diuresis, 2260 ± 755 mL was excreted above the base line value of $1\ mL\ min^{-1}$ for the unmedicated and well-hydrated subjects (Paintaud et al 1995; Vree et al 1995b; Dormans et al 1996). Despite the fact that the subjects maintained their normal drinking and eating patterns, during and after this excess urine excretion period, it took three days for the body to regain this amount of fluid. The average urine production over those three days was 990 ± 294 mL less than what would have been excreted with the base-line value of $1\ mL\ min^{-1}$ (Vree et al 1995b) (n=7, 80 mg furosemide).

The base-line urine production of $1\ mL\ min^{-1}$ (=1440 mL per 24 h) was taken as a conservative estimate; the subjects showed values of $1–2\ mL\ min^{-1}$ in other long-lasting pharmacokinetic experiments with naproxen (Vree et al 1993a,b) and sulphamethoxazole (Vree et al 1995c). The recovery time was found to be 65 h, and the total time of diuresis plus recovery time was 6 h + 65 h=71 h (3 days). The reported 24-h recovery period that had been reported by Reyes (Reyes 1991; Reyes & Leary 1993) was based on a collection period of 24 h.

During the recovery period, furosemide and its acyl glucuronide were slowly eliminated from the body with a long half-life of 20–30 h. This recovery period has been termed ''rebound effect'' by Reyes (Reyes 1991; Reyes & Leary 1993) and Russo et al (1992). This recovery or rebound period coincides with the long phase $t_{½\beta}$ of 20–30 h for both furosemide and its acyl glucuronide.

The rebound effect may be the result of a biphasic effect of furosemide or its acyl glucuronide (or both) or may be triggered by the rapid and intense renal excretory action that loop diuretics exert within the first few hours after dosing (Knauf et al 1991; Reyes & Leary 1993). These functional

changes which tend to conserve water, sodium and electrolytes, include activations of the sympathetic and renin-angiotensin-aldosterone systems, a decrease in atrial natriuretic factor and local renal processes (Heidland & Henneman 1969; Sjöström et al 1988; Reyes & Leary 1993; Ritz et al 1994; Wakelkamp et al 1996).

The term acute tolerance was mentioned by Hammerlund et al (Hammarlund et al 1984; Sjöström et al 1988) and refers to the difference in diuresis between the onset of inhibition of the $Na^+/2Cl^-/K^+$ co-transport system with furosemide during the pharmacokinetic absorption phase and the elimination phase (clockwise hysteresis as shown in Figure 4). This tolerance may be the acute response of the body to maintain the homoeostasis. Figure 4 also shows the clockwise hysteresis for the metabolite furosemide acyl glucuronide.

Peculiar side effect

In one study, one subject showed a time-dependent increase in urine acidity, the lowest pH reached being 4·2, the pH of the pre-urine sample (Vree & Van Kerrebroek 1994) (Figure 2). Thereafter, the pH returned to base-line values. Apparently the buffer capacity of the kidney in this subject was less than that in the other subjects. This effect appeared in a series of pilot experiments in a dose-dependent manner (furosemide dose 20–100 mg). This increase in titratable acid has been previously reported by Puschett & Goldberg (1968).

Clinical Implications

Pharmacodynamics

The pharmacodynamic effect of the increased diuresis arising from inhibition of the active reabsorption of chloride ions in the ascending limb of the loop of Henle, lasts for 4 h, the maximum effect occurring between 0·5 and 1 h after oral administration of furosemide. Most if not all of the pharmacodynamic and pharmacokinetic measurements reported in the literature have their end-point at 6–8 h after administration.

Repetitive dosing

Each furosemide administration results in a stimulation of diuresis and increase in natriuresis, which lasts 4 h, while in healthy volunteers this period is followed by a 3-day recovery period. In clinical practice, furosemide is administered repetitively to shift the pathological homoeostasis (water, sodium balance; oedematous state associated with congestive heart failure) of the body in cardiac failure or decompensatio cordis. Repetitive intravenous administration of furosemide results in a gradual decrease in urine and sodium output (Kaissling et al 1985; Gerlag & VanMeyel 1988; Brater 1991; Lahav et al 1992; VanOlden et al 1992, 1995). The diuretic as well as the post-diuretic effect (rebound effect) add to the overall effect of dehydration upon repetitive dosing (Copeland et al 1983; VanMeyel et al 1994; Kang et al 1995). Physiological counteraction occurs by an increase in plasma active renin concentration and a decrease in atrial natriuretic peptide concentration and by development of a negative sodium balance (Wakelkamp et al 1996). When patients grow resistant to conventional doses of furosemide up to 500 mg, continuous infusion may be the alternative to achieve a controllable diuresis (Gray et al 1978; Lawson et al 1978).

Infusions

Repetitive dosing can be replaced by infusions or slow-release equimolar dosing, resulting in a prolonged presence/disposition of furosemide and its acyl glucuronide in the body and the kidney.

A slow but continuous delivery of furosemide at the site of the proximal tubule results in slightly increased cumulative excretion of urine and sodium (VanMeyel et al 1992). Increase of daily urinary volume and sodium excretion were higher after infusion than after bolus injection after equal dosages in patients with severe heart failure (Krasma et al 1986; Lee et al 1986; Magovern & Magovern 1990; Rudy et al 1991; Lahav et al 1992; VanMeyel et al 1994; Dormans et al 1996). With infusion the effect is maintained during the infusion period, while after an intravenous bolus injection it wears off parallel with the elimination half-life.

Impaired kidney function

In healthy volunteers a 100-mg oral dose of furosemide results in a maximum urine production of $30\,mL\,min^{-1}$ and an overall loss of 3 L of water during 4 h. This effect occurs with a normal number of kidney tubules. In impaired kidney function there is a loss of active tubules and possible accumulation of endogenous organic acids. In impaired kidney function the half-life of furosemide increases 2·5 fold from 30 min to 80 min (Cutler et al 1974) and the contribution of the non-renal clearance to the overall total body clearance is increased. In these patients the dose–response curve is therefore shifted to the right and downward

(Allison & Kennedy 1971; Brater et al 1980, 1986; Kindler 1993; Dormans et al 1996). There is a relationship between the percentage loss of active tubules and the percentual increase in the dose of furosemide needed to maintain a diuretic effect on the body: diuresis = dose × number of nephrons ≈ tubular concn × creatinine clearance. Alternatively in impaired kidney, this active tubular secretion of furosemide (and its acyl glucuronide) is competitively blocked by endogenous organic acids which accumulate in chronic renal insufficiency (Voelker et al 1987) and impair the diuretic secretion. To circumvent this inhibitory effect, larger doses of furosemide are routinely administered to increase the serum concentration, thereby providing sufficient delivery ($>20\,\mu g\,min^{-1}$) of furosemide in the renal tubule and urine (Burg et al 1973). Thereby a continuous infusion is more efficacious than a bolus dose (Rudy et al 1991).

No data concering furosemide acyl glucuronide in impaired kidney function are available. These high dosages do increase the residual diuresis in the short term. During long-term treatment this effect wears off (Gerlag & VanMeyel 1988; Brater 1991; VanOlden et al 1992, 1995). Furosemide has significant renal and extrarenal haemodynamic effects in congestive heart failure (Dikshit et al 1973; Brater et al 1980). There is a rise in venous capacitance and a fall in vascular resistance, which reduce preload. Also renal plasma flow is increased within 15 min (Dikshit et al 1973; Risler et al 1991; Taylor 1993).

In patients with impaired kidney function or those undergoing CAPD, the half-life of furosemide was increased from 66 ± 13 min to 195 ± 98 min, measured over a period of 8 h (Riva et al 1982; Martin et al 1995), while the total body clearance was reduced from $138 \pm 27\,mL\,min^{-1}$ to the residual $62 \pm 20\,mL\,min^{-1}$ due to non-renal clearance. In CAPD patients the peritoneal clearance was only 1% of the dose, while 0·3% of the dose was excreted unchanged in 200 mL urine in 24 h (Riva et al 1982; Martin et al 1995).

Impaired kidney glucuronidation?

Does the loss of kidney tubules result in a decrease of acyl glucuronide in the urine? Up to now the effect of furosemide has been attributed to furosemide alone. If the effect of furosemide diminishes in impaired kidney function, it might be that the glucuronidating capacity is reduced, that there is less acyl glucuronide in the kidney tubule and that this governs the stimulation of the diuresis. In volunteers with a normal kidney function, these processes are too fast to discriminate between the effect of furosemide and its metabolite (Vree et al 1996). If only furosemide is active, then the glucuronidation of furosemide is seriously impaired in end-stage renal failure. The plasma concentration-time curves of furosemide acyl glucuronide have not yet been measured in patients with impaired renal function or end-stage renal failure. The kinetic behaviour of furosemide and its acyl glucuronide must therefore be (re)investigated in these patients.

Dosage adjustment in impaired kidney function

Dose reduction. Kidney impairment results in a prolonged elimination half-life for those compounds for which elimination depends mainly on renal excretion. For instance, the half-lives of sulphamethizole or aminoglycosides in a CAPD patient is 70 h, as compared with 2 h in a patient with normal kidney function. Dosage adjustment is then achieved either by reducing the dose or by increasing the dosage interval (Vree et al 1983b). The kidney is the organ of elimination and not the effector organ.

Dose increment. With furosemide impaired kidney function leads to an increase in the half-life of the first (or rapid) elimination phase from 2 to 9 h (but not higher) (Vree et al 1983b; Taylor 1993; Martin et al 1995). This observation explains the following:

The renal elimination of furosemide accounts for 50% (Table 1) of oral as well as intravenous administration (Vree et al 1995a; Dormans et al 1996). This means that there must be 50% extrarenal elimination (= hepatic + renal glucuronidation). The hepatically formed furosemide glucuronide is predominantly excreted into the intestinal tract, giving rise to hydrolysis, reabsorption and the slow phase with a long elimination half-life of 20 h. Therefore in patients with impaired kidney function or end-stage renal failure, the slow elimination half-life must be prolonged from 20 to 70 h, because the renal excretion elimination is diminished and endless hepatic cycling results.

To maintain a required level of diuresis, dosage adjustment now implies that the dose of furosemide must be increased from 80 mg to much higher doses (250–2000 mg) (Allison & Kennedy 1971; Gerlag & VanMeyel 1988). With diuretic drugs the effector organ is the kidney. The upper limit of the dose is determined by the side effect of ototoxicity. This effect is seen with overzealous diuretic use in patients who have diminished renal function or are also receiving other potentially ototoxic agents (i.e. aminoglycoside antibiotics) (Ritz et al 1994).

The clinical impact of the accumulation of furosemide and its acyl glucuronide in patients with end-stage renal failure has to be determined.

Conclusion

With correctly collected and processed plasma and urine samples from volunteers and patients treated with furosemide it is possible to measure the kinetic curves of both furosemide as well as its acyl glucuronide. It is possible that the acyl glucuronide is formed in part by the kidney tubules and that the compound is pharmacologically active by inhibiting the $Na^+/2Cl^-/K^+$ co-transport system, although this mechanism of action has been solely attributed to furosemide to date. When furosemide is administered, furosemide and its acyl glucuronide are always present in the proximal tubule and each of them may be responsible for diuresis. After each dosage of furosemide, there is first a short stimulation of urine flow (4 h), which is followed by a 3-day recovery period of the body.

Impaired kidney function may result in impaired glucuronidation and diuresis. Accumulation of furosemide and its acyl glucuronide in patients with end-stage renal failure might be a real clinical problem to be recognized. It is advisable to include the pharmacokinetics and pharmacodynamics of the metabolite furosemide acyl glucuronide in efficacy analyses of furosemide.

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