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Clinical Pharmacology of Loop Diuretics

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Summary

The clinical pharmacology of torasemide, bumetanide, piretanide and furosemide (frusemide) is discussed. These drugs share a similar mechanism of action in inhibiting Na^+-K^+-$2Cl^-$ reabsorption at the thick ascending limb of the loop of Henle. They differ in their routes of metabolism, pharmacokinetics, and potency. Whether such differences are clinically important requires further study. Bumetanide and torasemide are metabolised by cytochrome P450 pathways, whereas furosemide is glucuronidated. These different routes of metabolism may have clinically important implications. Bumetanide, furosemide, and piretanide have similar pharmacokinetics, whereas the clearance of torasemide is less and the half-life concomitantly longer than the other 3 agents. Thus, torasemide has a longer duration of action. The rank order of potency is bumetanide > piretanide ≡ torasemide > furosemide, although efficacy appears the same. Despite much being known about these diuretics, many clinically important questions remain.

This review broadly discusses the clinical pharmacology of loop diuretics. Table I lists the following topics of importance: the pharmacology of these drugs, pharmacokinetics in normal subjects compared with patients with various disease states, pharmacodynamics in normal subjects, the inter-relationship between pharmacokinetics and pharmacodynamics to determine overall response, and the 'braking' phenomenon in which the response to these diuretics becomes diminished during therapy.

1. Pharmacology of Loop Diuretics

Figure 1 shows the chemical structures of 4 loop diuretics. There are obvious similarities between these drugs, yet their metabolism in the body is quite different. The main site of action of these diuretics is the thick ascending limb of the loop of Henle, where the sodium-potassium-2 chloride reabsorptive pump is inhibited (Burg 1976; Jacobson & Kokko 1976) [table II]. In addition, it appears that bumetanide and furosemide (frusemide) have an additional effect at the proximal tubule, particularly when administered intravenously (Burke et al. 1972; Kirkendall & Stein 1968; Puschett & Goldberg 1968; Stason et al. 1966). In contrast, Lupinacci and Puschett (1988) have shown that torasemide is devoid of a proximal tubular site of action. It is conceivable that this lack of a proximal effect accounts for the diminished kaliuresis reported to occur with torasemide (Herchuelz et al. 1988; Lesne 1988; Lupinacci & Puschett 1988). Torasemide, unlike other loop diuretics, is able to inhibit chloride conductance at the basolateral

Table I. Clinical pharmacology of loop diuretics

Pharmacology
Chemical structure
Site of action
Access to active site
Metabolism
Pharmacokinetics in normal subjects
Kinetic parameters
Duration of action
Pharmacodynamics
Dose-response relationships
Dose equivalency
Pharmacodynamic parameters
Determinants of overall response
Kinetic-dynamic
Braking

Table II. Renal tubular site of action of loop diuretics

Thick ascending limb of the loop of Henle: Na^+-K^+-2Cl pump
bumetanide
furosemide
piretanide
torasemide
Proximal tubule
bumetanide
furosemide
Thick ascending limb of the loop of Henle: chloride conductance (basolateral membrane)
torasemide – high dose (100 × that required for luminal effects)

membrane (Wittner et al. 1986). However, this effect occurs at very high concentrations (100 times greater than that required for the luminal effects), and so the clinical significance of this observation is questionable.

It appears that all of these diuretics must reach the tubular lumen to exert their effect of blocking the sodium-potassium-2 chloride pump (Brater et al. 1987; Odlind 1979; Odlind et al. 1983). These drugs are very tightly bound to serum proteins (> 95%; Brater 1987), and therefore, when the drug is delivered to the glomerulus of the kidney, it is not filtered. The protein bound drug traverses the glomerulus and is carried by the vasa recta to the organic acid transporting pumps of the proximal tubule. At this site, the diuretic is secreted into the tubular lumen, where it then flows to its site of action at the thick ascending limb of the loop of Henle. This mechanism of delivery into the lumen has been used to determine whether or not it is the amount of diuretic in the blood compared with that present in the urine which is important for determining response. By administering probenecid to a patient, this pump can be blocked, and the effects on the response to the diuretic can be assessed. Such a study results in a change in the relationship between serum and urinary diuretic concentrations, but response to amounts of diuretic in urine remains unchanged (Brater et al. 1987; Chennavasin et al. 1979; Lau et al. 1983; Odlind et al. 1983). This result clinically demonstrates that loop diuretics must reach the lumen to act effectively.

2. *Metabolism of Loop Diuretics*

Figure 2 shows the metabolic pathways for bumetanide (Halladay et al. 1975, 1978). About half the dose of bumetanide appears in the urine as un-

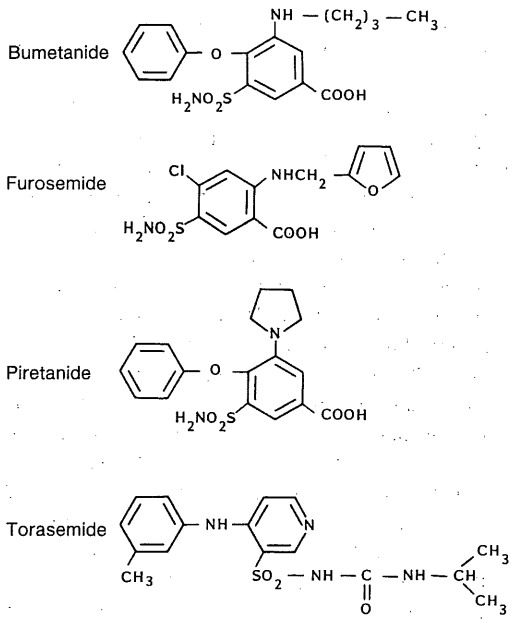

Fig. 1. Structures of loop diuretics.

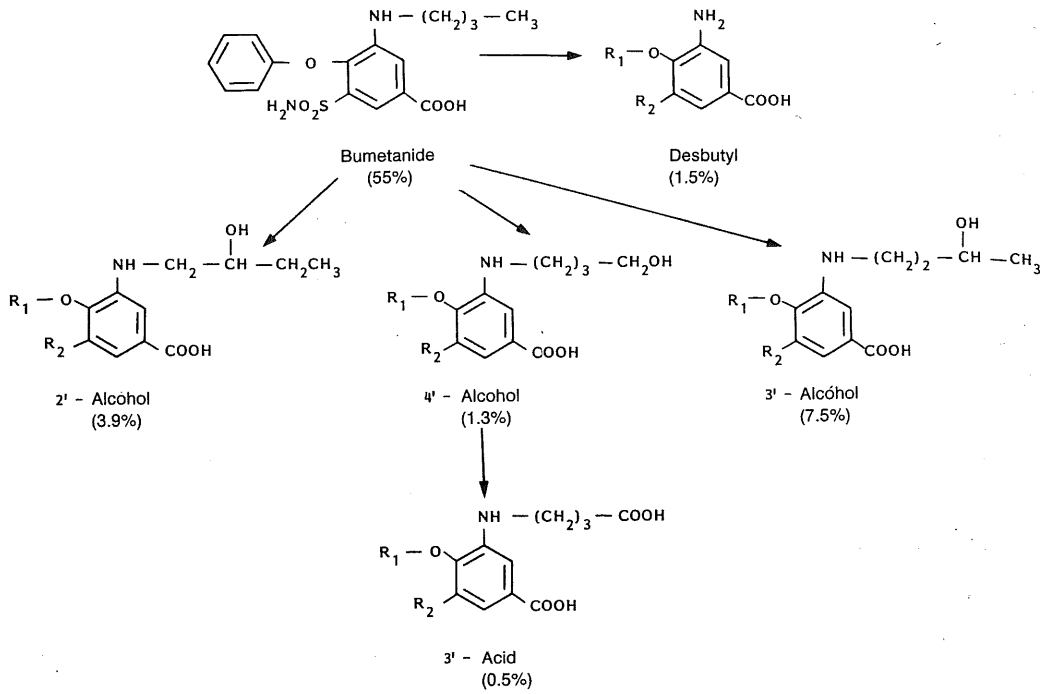

Fig. 2. Metabolic pathways for bumetanide. Values in parentheses indicate the percentage of an intravenous dose that appears in the urine in that form (after Halladay et al. 1975, 1978).

changed drug, and it is this component which is responsible for its activity (Brater 1987). The other half undergoes several metabolic steps, with the metabolites present in small amounts in the urine. Presumably, the remaining metabolites are eliminated by conjugation or by excretion into the bile. The metabolism of bumetanide contrasts with that of furosemide, where only glucuronidation occurs (Hammarlund-Udenaes & Benet 1989; Smith et al. 1980). 50% of a dose of furosemide appears in the urine as unchanged drug, and another 20% of the dose appears in the urine as furosemide glucuronide. There is some indication that this glucuronidation may actually occur in the kidney as opposed to the liver (Smith et al. 1980). The disposition of the remaining 30% is unknown. Furosemide clearly follows a different type of metabolic or degradative route compared with bumetanide. Torasemide is similar to bumetanide in that it undergoes considerable metabolism (fig. 3) [Neugebauer et al. 1988]; about 25% of an intravenous dose appears in the urine as unchanged drug. There are 3 different metabolites, M1, M3 and M5, and they show some pharmacological activity. The M1 metabolite is about one-tenth as potent as torasemide. This is probably not enough to be clinically important, particularly since only 11% of a dose appears in the urine as M1. The M3 metabolite is as potent as torasemide, but again is probably not clinically important, because only 3% appears in the urine. The M5 metabolite is not active.

There may be some generalisations and predictions possible for metabolised drugs such as bumetanide and torasemide that would not apply to a drug such as furosemide (table III). Since bumetanide and torasemide are metabolised by cytochrome P450 pathways, their metabolism may be susceptible to induction and inhibition, but this

possibility may never have been assessed. In addition, these 2 drugs may be susceptible to phenotypic drug metabolism. Thus, there could be rapid and slow metabolisers of bumetanide and torasemide. Induction, inhibition or phenotypic metabolism could account for observed differences in response to these drugs. Another implication of the routes of metabolism of bumetanide and torasemide is that there may be less accumulation of the parent drug in uraemia, which would manifest as less or no prolongation of the half-life. This hypothesis has been tested with bumetanide in patients with severe renal insufficiency in whom the half-life is not prolonged, relative to patients with normal renal function (Voelker et al. 1987). It is explained by hepatic metabolism providing alternative routes for elimination of the drug in patients with renal disease. Furosemide, in contrast, has a considerably prolonged half-life in patients with renal insufficiency, since there are no alternative metabolic pathways (Voelker et al. 1987). A drug such as torasemide would be expected to be similar to bumetanide rather than furosemide. Indeed, Spahn et al. (1987) found that the half-life of torasemide was similar in healthy volunteers (5.1 ± 4.2 hours) and in patients with moderate to severe renal insufficiency (4.6 ± 2.2 hours). Lastly, for a drug such as furosemide, which is eliminated by conjugation with glucuronide, this metabolism is potentially susceptible to inhibition by probenecid. Indeed, it has been shown that probenecid inhibits glucuronidation of furosemide (Chennavasin et al. 1979). It is predicted that future drugs with metabolic routes similar to that of furosemide would also accumulate in uraemia and have glucuronidation affected by probenecid.

Table III. Potential implications of routes of metabolism

Bumetanide and torasemide via cytochrome P450 pathways:
1. Metabolism is potentially susceptible to induction and inhibition
2. Phenotypic drug metabolism
3. Less accumulation of parent drug in uraemia; less or no prolongation of half-life

Furosemide via glucuronide conjugation:
1. Metabolism potentially susceptible to inhibition by probenecid
2. Accumulation of parent drug in uraemia

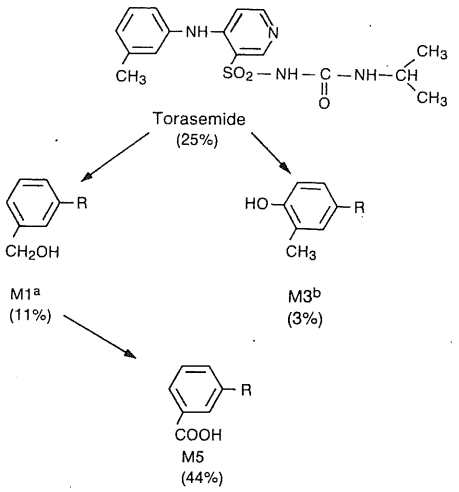

Fig. 3. Metabolic pathways for torasemide. Values in parentheses indicate the percentage of an intravenous dose that appears in the urine in that form (after Neugebauer et al. 1988).
a M1 is 1/10 as potent as torasemide.
b M3 is as potent as torasemide.

3. *Pharmacokinetics*

Table IV presents a compilation from published studies of the kinetic parameters of the loop diuretics (Brater 1987; Hammarlund-Udenaes & Benet 1989). The bioavailability of bumetanide is reported to range from 59 to 89% with a median value of about 80%. For furosemide, the range, 11 to 90%, is very wide, with a median value of about 50%. For piretanide and torasemide, bioavailability is estimated at about 80%. Thus, in terms of bioavailability, furosemide differs from the other drugs. In addition, there may be considerably more variability in the extent of absorption of furosemide, although this question has not been directly addressed.

The time of peak plasma concentration occurs quickly and is about the same for all of the loop

Table IV. Comparative pharmacokinetics of loop diuretics in normal subjects (Brater 1987). Values are presented as ranges with medians in parentheses

	Bumetanide (n = 95)	Furosemide (n = 337)	Piretanide (n = 50)	Torasemide (n = 54)
Bioavailability (%)	59-89 (80)	11-90 (53)	80[a]	79-91 (80)
Time of peak plasma concentration (h)	0.5-2 (1.3)	1-5 (1.6)	0.5-1 (1.2)	1
Volume of distribution (L/kg)	0.14-0.28 (0.17)	0.07-0.35 (0.16)	0.24-0.27 (0.27)	0.09-0.31 (0.16)
Clearance (ml/min/kg)	1.8-3.8 (2.6)	1.5-4.4 (2.2)	2.8-3.8 (3.6)	0.33-1.1 (0.6)
Fraction of dose excreted in urine unchanged (%)	36-69 (65)	49-94 (60)	51[a]	22-34 (27)
Half-life (h)	0.3-1.5 (1.2)	0.3-3.4 (1.0)	0.6-1.5 (0.8)	0.8-6.0 (3.3)

a Estimated.

diuretics (Brater 1987). When administered orally, the peak occurs within 0.5 to 2 hours. The volumes of distribution of these drugs seem to be similar, as might be expected because of their similar chemical characteristics and degrees of protein binding. Clearance is similar for bumetanide, furosemide and piretanide, but seems to be considerably lower with torasemide. This difference is reflected in the fact that there is less unchanged torasemide in the urine and that it has a longer half-life. With bumetanide, furosemide and piretanide, about half of the dose enters the urine unchanged after intravenous administration, in contrast with torasemide, where about one-quarter of the dose reaches the urine. The elimination half-life, of about 1 hour, is also similar in these 3 drugs, but with torasemide it is up to 4 hours. It is predicted that torasemide has a longer duration of action.

Table V. Duration of action of loop diuretics in normal subjects (Brater et al. 1983a,b, 1987)

Bumetanide	2h
Furosemide	2-2.5h
Piretanide	2-2.5h
Torasemide	6h

Table V presents the duration of effect of loop diuretics after intravenous administration in patients with normal renal function (Brater et al. 1983a,b, 1987). For bumetanide, furosemide and piretanide it is about 2 to 2.5 hours, whereas for torasemide the duration is about 6 hours. This difference is consistent with the lower clearance of torasemide and its longer half-life.

4. Pharmacodynamics

If the dose needed to cause the same amount of sodium excretion in the urine is determined, 1mg of bumetanide ≈ 40mg of furosemide ≈ 12mg of piretanide ≈ 10 to 20mg of torasemide (Brater et al. 1983a,b, 1987). This dose potency is very similar to that observed in studies of isolated perfused nephrons *in vitro* (Wittner et al. 1987). The relative potency of loop diuretics in man can also be determined *in vivo* by relating the excretion rate of the diuretic in the urine (and thereby the amount at the active site) to the response quantified as sodium excretion. This has been performed in healthy

volunteers administered conventional doses of the 4 diuretics (fig. 4; Brater et al. 1983a,b, 1987). By this method, the rank order of potency is fundamentally the same as with the previous analysis. One can computer-fit the curves depicted in figure 4 and derive parameters for maximal response, the slope of the curve, the amount causing half-maximal response and the lower asymptote (table VI). By doing so, efficacy (the upper asymptote) appears to be the same for all loop diuretics, as is the slope factor. The amount of urinary diuretic which causes half-maximal response gives the same rank order of potency as other types of studies. Thus, there is considerable consistency in these kinds of data.

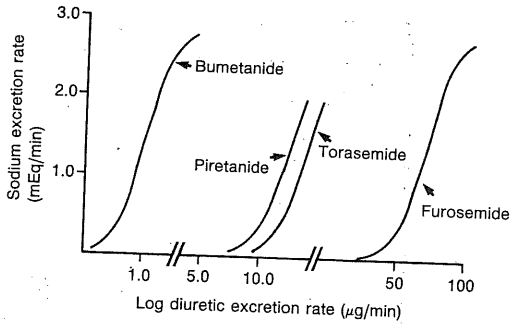

Fig. 4. Pharmacodynamics of loop diuretics depicted as the relationship between urinary excretion rate of diuretic and response quantified as sodium excretion rate (Brater et al. 1983a,b 1987).

5. Determinants of Overall Response

The determinants of overall response link pharmacokinetics with pharmacodynamics. It should be apparent that one of the determinants is the shape of the urine concentration-response curve; the other determinant is the time course of entry of the drug into the urine, relative to the shape of the concentration-response curve (Kaojarern et al. 1982). This results in a 3- rather than a 2-dimensional depiction of the relationship, as shown in figure 5. The total amount of sodium excretion caused by a loop diuretic is the area under the 2-dimensional projection of sodium excretion versus time (the YZ axis shown in fig. 5). This type of depiction can be used to assess the influence of disease states and of drug interactions on diuretic response. Fundamentally, in assessing the determinants of response to a loop diuretic, one must think in 3-dimensional as opposed to 2-dimensional terms.

Finally, the diminished response to loop diuretics that occurs over time should be considered (table VII). This may be divisible into 2 different phenomena. Firstly, one occurs during the acute response and has been called 'braking'. The mechanism of 'braking' is unknown and is the focal point of a number of studies (Christensen et al. 1986; Hammarlund et al. 1985; Kelly et al. 1983; Wilcox et al. 1983, 1987). It could be accounted for by increased proximal tubular reabsorption of sodium,

Table VI. Comparative pharmacodynamics of loop diuretics in man (Brater et al. 1983a,b, 1987)

	Bumetanide	Furosemide	Piretanide	Torasemide
Maximal response [fractional excretion of sodium (%)]	17	16	11	16
Sodium excretion rate (mEq/min)	2.8	2.7	1.9[a]	2.7
Slope factor (mEq/μg)	1.8	1.2	2.1	2.0
Diuretic excretion rate at half maximal response (μg/min)	1.0	69.8	12.1	13.7

[a] Parameter estimated, not defined.

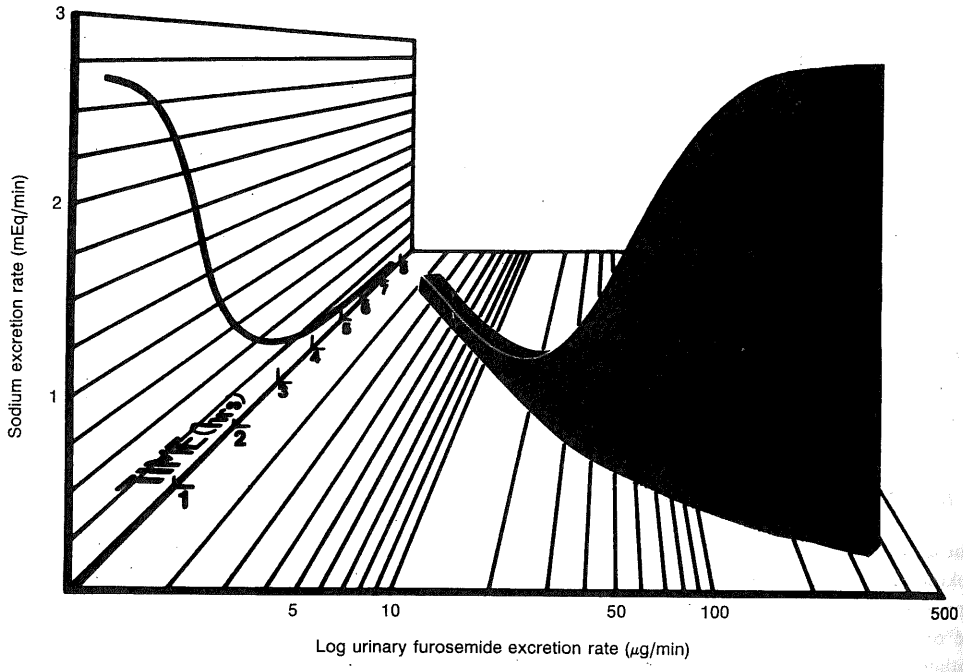

Fig. 5. Three dimensional figure of the determinants of response to loop diuretics showing the relationships between amounts of diuretic in the urine, the time course of delivery of diuretic into urine and sodium excretion.

increased distal tubular reabsorption of sodium or changed responsiveness of the loop of Henle itself, as might result from down regulation of receptors, etc. It appears that the renin-angiotensin system does not play a role (Kelly et al. 1983; Wilcox et al. 1987). Similarly, studies have addressed the potential role of the α-adrenergic nervous system and have found negative results (Kelly et al. 1983). This remains an area for further study.

There is another type of 'braking' that may occur chronically and which is perhaps related to hypertrophy of distal tubular epithelia. Studies in animals, which may be extrapolated to man, show that persistently increased distal delivery of sodium, such as occurs with long term administration of diuretics, actually causes hypertrophy of distal tubular epithelium that can be quantified histologically (Ellison et al. 1989; Kaissling & Stanton 1988; Stanton & Kaissling 1988). In addition, it is important to note that these nephrons are not only hypertrophied in terms of size, but also in terms of function (Ellison et al. 1989; Stanton & Kaissling 1988). Thus, the ability to reabsorb sodium increases at least 3-fold concomitant with the hypertrophy. If this phenomenon occurs in patients who are treated long term with diuretics, much of the sodium that is rejected from the thick ascend-

Table VII. Diminished response to loop diuretics over time

Acute ('braking')
Increased proximal tubular reabsorption of sodium?
Increased distal tubular reabsorption of sodium?
Change responsiveness of loop of Henle
'receptors'?
changed haemodynamics – segmental or global?
renin-angiotensin?
renal nerves?
circulating catecholamines?
Chronic
Hypertrophy of distal tubular epithelium

ing limb of the loop of Henle under the influence of a loop diuretic could be absorbed by these hypertrophied and hyperfunctioning distal nephrons. In this instance, if a thiazide diuretic is added that blocks distal reabsorption, then a natriuresis, which would appear to be synergistic or supra-additive, would be expected to occur. This type of synergism has been demonstrated repeatedly, particularly in patients with congestive heart failure when combinations of diuretics have been used (Epstein et al. 1977; Olesen & Sigurd 1971; Ram & Reichgott 1977; Sigurd et al 1975; Wollam et al. 1982). Thus, there is reasonable evidence that hypertrophy of distal tubular epithelia may account for the braking that occurs with long term use of loop diuretics.

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