Plasma and urinary kinetics of furosemide in newborn infants

Plasma and urinary furosemide kinetics were assayed by high-power liquid chromatography in six newborn infants receiving furosemide (1 mg/kg body weight IV) for the treatment of fluid overload. Mean ± SD for plasma half-life, apparent volume of distribution, and plasma clearance were, respectively, 9.5 ± 4.4 hours, 173 ± 28 ml/kg, and 15.3 ± 8.4 ml/hr/kg. There was close correspondence between plasma and urinary half-lives and between plasma clearance and renal clearance. In the first 24 hours, mean estimated urinary recovery of unchanged furosemide was 90% of the injected dose (range 61% to 106%). The results suggest that in the newborn infant furosemide is virtually all excreted unchanged in the urine and that the absence of significant nonrenal elimination, together with the immaturity of neonatal renal function, accounts for its prolonged half-life in newborn infants. (J PEDIATR 103:481, 1983)

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THE ELIMINATION OF FUROSEMIDE is remarkably slow in newborn infants and is associated with prolongation of its diuretic and saliuretic effects.[1,2] Plasma half-life of furosemide is between 33 and 100 minutes in normal adults,[3-6] compared with reported values between 4 and 44 hours in neonates.[7-9] In adults, plasma furosemide clearance is considerably influenced by renal function,[4] and neonatal values for plasma furosemide half-life are similar to those of adults with advanced renal failure.[10]

However, the relatively poor renal function of newborn infants[11] may not entirely explain the slowness with which they eliminate furosemide. In healthy adults, most of an intravenously administered dose of furosemide is excreted in the urine,[4-6,12] but in adults with severe renal failure, more than 90% of total plasma clearance is nonrenal (i.e., biliary and intestinal).[4,10] For newborn infants, in whom not only renal but also intestinal and hepatic function are immature, the relative importance of renal and nonrenal elimination is unknown.

We studied plasma and urinary kinetics in six neonates receiving furosemide intravenously for the treatment of fluid overload.

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PATIENTS

Six infants were enrolled in the study. Five were receiving furosemide for the first time, and the other had received none for 28 days (Table I). All were given furosemide because of fluid overload, of varying severity. Infants were not enrolled if thought likely to require a further dose within 24 hours. Four had clinical signs of patent ductus arteriosus, one had a ventricular septal defect, and one had peripheral and pulmonary edema without evidence of heart disease. Three infants (patients 1, 2, and 6) were receiving added oxygen (FIO_2 0.35, 0.43, and 0.75, respectively); of these, two were receiving intermittent positive pressure ventilation. These same three infants were also given ampicillin and gentamicin, but none received any other drugs. No infant was anemic, acidotic, or hypotensive, and none had clinical or biochemical evidence of renal disease. Only two infants (patients 2 and 6) were clinically jaundiced, with plasma bilirubin concentrations of 200 and 140 μmol/L (11.7 and 8.2

CSA	4-Chloro-5-sulfamoyl anthranilic acid
GFR	Glomerular filtration rate
PAH	Para-aminohippuric acid

Table I. Pharmacokinetic disposition of furosemide

Infant	Sex	Birth weight (kg)	Gestational age (wk)	Postnatal age (days)	$t_{½\alpha}$ (hr)	$t_{½\beta}$ (hr)	Urinary $t_{½}$ (hr)	Volume of dilution (ml/kg^{-1})	Plasma clearance ($ml/hr^{-1}/kg^{-1}$)	Renal clearance ($ml/hr^{-1}/kg^{-1}$)	Urinary excretion of unchanged furosemide† (% dose)
1	M	1.10	29	18	—	7.6	7.2	128.2	11.7	11.7	101
2	M	1.60	30	7	—	15.2	14.8	173.5	7.9	7.2	61
3	F	1.56	31	32	0.54	6.3	6.4	164.1	18.1	14.0	81
4	M	2.08	35	21	0.42	4.0	4.3	181.1	31.1	29.5	99
5	M	2.78	39	6	—	14.2	14.9	215.1	10.5	11.9	90
6	M	3.18	40	3	0.66	9.8	9.8	178.7	12.6	15.1	106
Mean		2.05	34	14.5	0.54	9.5	9.6	173.5	15.3	14.9	90
SD		—	—	—	0.12	4.4	4.5	28.1	8.4	7.7	17

*Calculated from approximately 4 until approximately 24 hours after injection.
†Over approximately 24 hours after injection.

mg/dl), respectively. All had normal plasma albumin, electrolyte, and glucose concentrations.

METHODS

Furosemide (1 mg/kg body weight over one minute) was given intravenously as soon as possible (within four minutes in all but one case) after a spontaneous micturition. Urine was collected in an adhesive bag, which was emptied immediately after each micturition, using a syringe and fine catheter. The time of each micturition was noted to the nearest minute, and the volume of urine passed was measured using an appropriate measuring cylinder. Complete urine collections, without apparent fecal contamination, were obtained over approximately 24 hours after furosemide administration, the exact duration depending on the timing of micturition. An aliquot of urine from each micturition was stored within five minutes, in darkness, at −20° C, for later estimation of furosemide concentration. Blood samples (0.4 ml from heel prick or venipuncture) were collected in lithium heparin tubes at 0.5, 1, 2, 4, 6, 12, 18, and 24 hours, centrifuged immediately, and the plasma stored in darkness at −20° C.

Informed parental consent was obtained for the collection of blood and urine samples.

Furosemide assay. Furosemide concentrations in plasma and urine were measured by high-power liquid chromatography using the method of Broquaire and Mitchard,[13] with minor modifications, as described elsewhere.[9] The method has been shown to detect concentrations of 0.1 μg/ml, with standard errors of 6.5% at 2 μg/ml and 2.7% at 7.5 μg/ml. It is specific for furosemide, giving excellent separation from the acid metabolite, CSA.

To look for furosemide glucuronide, furosemide concentrations were measured in paired urine samples from each infant, preincubated for 12 hours with and without β-glucuronidase type 1 (Sigma Chemical Co., St. Louis).

Pharmacokinetic analysis. Pharmacokinetic analysis was done by computer (Tektronic 4051) using the IGPHARM program.[14] Plasma data for three infants (patients 3, 4, and 6) were analyzed using a two-compartment model; for the other three, a one-compartment model was applied to the last 4 or 5 points of the graph of furosemide concentration against time. Urinary data were analyzed using the excretion rate method.[14] Plasma clearance was estimated by the formula $Cl = Dose/AuC_{\infty}$, where AuC_{∞} represents the area under the plasma concentration time curve, extrapolated to infinity. Renal clearance was estimated by dividing urinary recovery by the area under the plasma concentration time curve during the corresponding time.

RESULTS

Examples of the graphs of plasma furosemide concentration and of urinary furosemide excretion rate against time are shown in the Figure.

Plasma half-life, apparent volume of dilution, and clearance all showed considerable variation between individuals, but plasma and urinary half-lives corresponded very closely for each infant (regression equation $y = 0.9995x + 0.038$; $r = 0.97$; $P < 0.005$; Table I). There was also a good correlation between plasma clearance and renal clearance ($r = 0.96$; $P < 0.005$). Between four and 24 hours after furosemide injection, renal clearance was estimated to account for a mean of 99% of total plasma clearance (range 74% to 120%). After 24 hours, mean urinary recovery of unchanged drug was 90% of the injected dose (range 61% to 106%). Furosemide glucuronide was not detected in the urine of any infant. The acid metabolite, CSA, was only found in traces (not quantifiable) in the urine of patient 2.

Neither the proportion of injected furosemide recovered in the urine nor any of the other listed pharmacokinetic

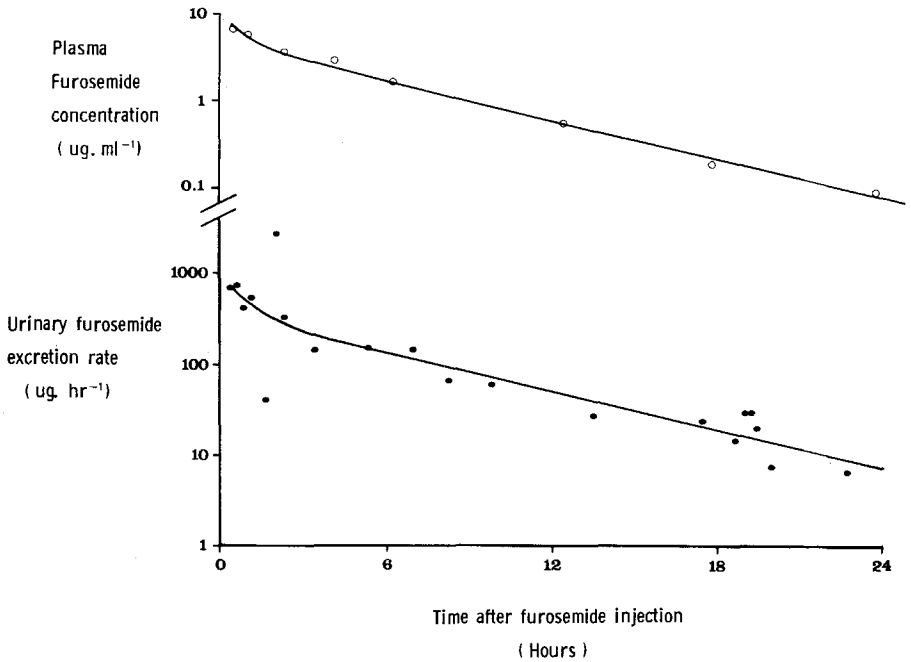

Figure. Plasma furosemide concentration and urinary furosemide excretion rate over 24 hours (patient 4).

values was significantly correlated with gestational, postnatal, or post-conceptional age or with birth weight or weight at the time of the study. However, the ratio of renal clearance to plasma clearance (C_r/C_p) did appear to decrease with increasing postnatal age ($r = -0.81$; $P < 0.05$). Plasma bilirubin concentration was measured only in the two infants with clinical jaundice. They had plasma bilirubin concentrations of 200 and 140 μmol/L, and showed the lowest (61%) and highest (106%) urinary furosemide recovery, respectively.

DISCUSSION

In healthy adults, just over half of total plasma clearance of furosemide is accounted for by renal clearance.[4-6, 12] Furosemide is thought to enter the urine partly by glomerular filtration, but mainly via an active tubular transport mechanism, similar to that for para-aminohippuric acid.[15] Adult values for renal clearance of furosemide are directly correlated with the glomerular filtration rate (as reflected by endogenous creatinine clearance), and the relative contribution of renal clearance to total plasma furosemide clearance falls when the GFR is low.[4, 10]

During the first month of life, mean GFR (corrected for body surface area) is approximately one fourth that in normal adults, and tubular secretion of PAH is also reduced.[11] Nevertheless, our results suggest that in newborn infants, renal clearance of furosemide accounts for virtually all of total plasma clearance. Even allowing for the inaccuracies inherent in our method for calculating renal furosemide clearance, the contrast with data from adults is striking (Table II).

In adults, unchanged furosemide is the major urinary product in the first four hours, after which metabolites such as furosemide glucuronide and the free amine derivative CSA have been recovered.[3, 12] Aranda et al.[16] have recently reported substantial urinary excretion of both glucuronide and CSA in newborn infants. In their study, the mean fraction of furosemide excreted in the urine as CSA (21.2% over six hours) was markedly higher than that which they had previously found in adults with pulmonary edema (0.1% to 3.9%), and the corresponding mean fraction excreted as glucuronide (23.3%) was similar to that in adults.[12, 17] The high proportion of glucuronide is surprising, as newborn infants tend to exhibit reduced glucuronidation, not only of bilirubin but also of a number of drugs.[18, 19] Substantial early glucuronidation of drugs such as phenytoin has followed prolonged prenatal exposure.[20, 21] In our infants, furosemide was virtually all excreted in the urine unchanged. Expressed as a proportion of the injected dose, total urinary furosemide recovery was very similar in our and Aranda's studies (mean ± SE 89.7 ± 15.2% and 84.4 ± 14.9%, respectively), but we found no glucuronide and no CSA except for traces in one infant. This discrepancy is difficult to explain on methodological grounds, because we used the same technique to detect glucuronide and a specific furosemide assay that gives good separation from CSA. It may perhaps be significant that the majority of Aranda's patients had

Table II. Renal clearance of intravenously administered furosemide in newborn infants and in adults*

	Plasma clearance ($ml/kg^{-1}/hr^{-1}$)	*Renal clearance* ($ml/kg^{-1}/hr^{-1}$)	*Cr/Cp* (%)
Newborn infants	15.3 ± 8.4	14.9 ± 7.7	99.0 ± 15.0
Healthy adults	171.0 ± 23.0	85.0 ± 21.0	51.0 ± 15.0
Adults with severe renal failure	87.0 ± 51.0	4.8 ± 4.7	4.2 ± 2.6

Values are mean ± SD.
*Adult data derived from Beermann et al.[4]

previously received furosemide. Unfortunately, results for individuals were not reported, so the relevance of this and other potentially important factors (such as concomitant drug treatment and prior exposure to inducing agents) remains unknown.

It would appear from our data that the reason for the prolonged half-life of furosemide in newborn infants is that slow renal excretion, related to immature renal function, is compounded by the absence of any significant nonrenal elimination, at least after a first dose. The capacity for nonrenal elimination of furosemide must be presumed to develop at some time between birth and adulthood, and our results suggest that the ratio of renal clearance to plasma clearance may fall with increasing postnatal age. The negative correlation between this ratio and postnatal age just reached statistical significance ($r = -0.81$; $P < 0.05$), but numbers were too small and estimates of renal clearance insufficiently precise for any firm conclusions to be drawn about the development of nonrenal furosemide clearance during the neonatal period.

The major dependence of newborn infants on renal excretion for the elimination of furosemide would explain the almost perfect match we found between plasma and urinary half-lives, and also the tendency, observed by previous authors, for furosemide half-life to decrease with increasing post-conceptional age.[9] Both GFR and PAH secretion increase with advancing gestational and postnatal age, and Peterson et al.[8] have published evidence suggesting that plasma furosemide clearance follows a similar maturational pattern to that for PAH elimination. We are not aware of any published studies of furosemide kinetics in newborn infants with renal failure, but our results would suggest that furosemide should be used with caution in these circumstances, to avoid the risk of drug accumulation and hence of potential ototoxicity.[22]

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REFERENCES

1. Ross BS, Pollak A, Oh W: The pharmacologic effects of furosemide therapy on the low-birth-weight infant. J PEDIATR **92**:149, 1978.
2. Woo W-CR, Dupont C, Collinge J, Aranda JV: Effects of furosemide in the newborn. Clin Pharmacol Ther **23**:266, 1978.
3. Rupp W: Pharmacokinetics and pharmacodynamics of lasix. Scot Med J **19**:5, 1974.
4. Beermann B, Dalen E, Lindström B: Elimination of furosemide in healthy subjects and in those with renal failure. Clin Pharmacol Ther **22**:70, 1977.
5. Rane V, Villeneuve JP, Stone WJ, Neis AS, Wilkinson GR, Branch RA: Plasma binding and disposition of furosemide in the nephrotic syndrome and in uremia. Clin Pharmacol Ther **24**:199, 1978.
6. Chennavasin P, Seiwell R, Brater DC, Liang WMM: Pharmacodynamic analysis of the furosemide-probenecid interaction in man. Kidney Int **16**:187, 1979.
7. Aranda JV, Perez J, Sitas DS, Collinge J, Portuguez-Malavasi A, Duffy B, Dupont C: Pharmacokinetic disposition and protein binding of furosemide in newborn infants. J PEDIATR **93**:507, 1978.
8. Peterson RG, Simmons MA, Rumack BH, Levine RL, Brooks JG: Pharmacology of furosemide in the premature newborn infant. J PEDIATR **97**:139, 1980.
9. Vert P, Broquaire M, Legagneu M, Morselli PL: Pharmacokinetics of furosemide in neonates. Eur J Clin Pharmacol **22**:39, 1982.
10. Huang CM, Atdinson AJ, Levin M, Levin NW, Quintanilla A: Pharmacokinetics of furosemide in advanced renal failure. Clin Pharmacol Ther **16**:659, 1974.
11. Houston IB, Oetliker O: The growth and development of the kidneys. *In* Davis JA, Dobbing J, editors: Scientific foundations of paediatrics, ed 2. London, 1981, Heinemann, pp 486-496.
12. Beermann B, Dalen E, Lindström B, Rosen A: On the fate of furosemide in man. Eur J Pharmacol **9**:57, 1975.
13. Broquaire M, Mitchard M: Détermination quantitative rapide du furosemide dans le plasma, le sang, our l'urine par chromatographie liquide à haute performance. Feuill Biol **1**:1, 1979.
14. Gomeni C, Gomeni R: IGPHARM: Interactive graphic package for pharmacokinetic analysis. Comp Biomed Res **11**:354, 1978.
15. Bowman RH: Renal secretion of ^{35}S furosemide and its depression by albumin binding. Am J Physiol **229**:93, 1975.
16. Aranda JV, Lambert C, Perez J, Turmen T, Sitar DS: Metabolism and renal elimination of furosemide in the newborn infant. J PEDIATR **101**:777, 1982.
17. Perez J, Sitar DS, Ogilvie RI: Biotransformation of furosemide in patients with acute pulmonary edema. Drug Metab Dispos **7**:383, 1979.

18. Dutton GJ: Developmental aspects of drug conjugation, with special reference to glucuronidation. Ann Rev Pharmacol Toxicol **18**:17, 1978.
19. Di Toro R, Lupi L, Ansanelli V: Glucuronidation of the liver in premature babies. Nature **219**:265, 1968.
20. Reynolds JW, Mirkin BL: Urinary corticosteroid and diphenylhydantoin metabolite patterns in neonates exposed to anticonvulsant drugs in utero. Clin Pharmacol Ther **14**:891, 1973.
21. Rane A: Urinary excretion of diphenylhydantoin metabolites in newborn infants. J PEDIATR **85**:543, 1974.
22. Wigand ME, Heidland A: Ototoxicity side-effects of high doses of furosemide in patients with uremia. Postgrad Med J **47**:54, 1971.

Clinical and laboratory observations

Management of chloramphenicol intoxication in infancy by charcoal hemoperfusion

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CHLORAMPHENICOL has again become a widely used antimicrobial agent in the initial therapy of infants with suspected meningitis.[1] Elevated blood concentrations of the drug can lead to the so-called gray baby syndrome.[2] Treatment of this potentially lethal complication is often unsuccessful.[2-7] We report our experience with an infant who developed the gray baby syndrome and who was treated with both exchange transfusions and charcoal hemoperfusion. Charcoal hemoperfusion proved to be far superior in lowering the toxic blood chloramphenicol concentrations, although it did not prevent death.

CASE REPORT

This 7-week-old, 5 kg infant boy was admitted to the University of Miami/Jackson Memorial Medical Center with the presumptive diagnosis of meningitis. One day prior to admission, he was noted to be febrile and irritable, and vomited twice. On admission, he appeared irritable and well hydrated; body temperature was 38.6° C, and systolic blood pressure 90 mm Hg. Except for a small left parietal cephalohematoma, the rest of the examination was unremarkable. Spinal fluid, urine, and blood cultures were all sterile. The patient was initially given antibiotics: ampicillin 400 mg/kg/day in four divided doses and chloramphenicol (through an arithmetic error) 75 mg/kg/dose four times daily, instead of the intended dose of 75 mg/kg/day.

The patient became afebrile during the first 24 hours, and the vital signs remained stable. By the third hospital day, after having received nine doses of the antibiotics, the infant suddenly became lethargic, tachypneic, hypotonic, ashen-gray, and unresponsive to stimuli. Systolic blood pressure was 40 mm Hg, and pulse was 150/minute and faint; peripheral circulation appeared decreased (mottling). The infant sustained cardiopulmonary arrest, and was successfully resuscitated after endotracheal intubation, assisted ventilation, and the administration of sodium bicarbonate plus several vasoactive medications. The serum chloramphenicol concentration was 136 μg/ml.

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Shortly thereafter, two consecutive single-volume exchange transfusions were undertaken. Serum chloramphenicol values after having completed each transfusion were 127 and 115 μg/ml, respectively (Figure).

The patient's clinical status remained unchanged. Supportive measures (assisted ventilation, administration of fluids and vasoactive drugs) were continued for the ensuing four hours. Because of persistent hemodynamic and cardiopulmonary compromise, hemodialysis and hemoperfusion were instituted, and successful removal of chloramphenicol was achieved (Figure). After four hours, the serum chloramphenicol concentration was 29 μg/ml, at which point the procedures were discontinued. Five hours later, the patient developed irreversible cardiac standstill.

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