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Effects of the rate and composition of fluid replacement on the pharmacokinetics and pharmacodynamics of intravenous torasemide

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Abstract

The effects of differences in the rate and composition of intravenous fluid replacement for urine loss on the pharmacokinetics and pharmacodynamics of torasemide were evaluated in rabbits. Each rabbit received 2-h constant intravenous infusion of 1 mg kg^{-1} torasemide with 0% replacement (treatment 1, n = 6), 50% replacement (treatment 2, n = 9), 100% replacement with lactated Ringer's solution (treatment 3, n = 8), and 100% replacement with 5% dextrose in water (treatment 4, n = 6). Total body (4.53, 5.72, 10.0 and 4.45 mL min^{-1} kg^{-1} for treatments 1–4, respectively) and renal clearance (1.44, 1.87, 6.78 and 1.72 mL min^{-1} kg^{-1}) of torasemide, and total amount of unchanged torasemide excreted in 8-h urine ($A_{e\ 0-8\,h}$: 694, 780, 1310 and 1040 μg) in treatment 3 were considerably faster and greater compared with treatments 1, 2 and 4. Although the difference in $A_{e\ 0-8\,h}$ between treatments 1 and 3 was only 88.8%, the diuretic and/or natriuretic effects of torasemide were markedly different among the four treatments. For example, the mean 8-h urine output was 101, 185, 808 and 589 mL for treatments 1–4, respectively, and the corresponding values for sodium excretion were 10.1, 20.6, 89.2 and 29.9 mmol, and for chloride excretion were 14.5, 27.9, 94.0 and 37.2 mmol. Although full fluid replacement was used in both treatments 3 and 4, the 8-h diuretic, natriuretic and chloruretic effects in treatment 3 were significantly greater compared with treatment 4, indicating the importance of the composition of fluid replacement. Both treatments 1 and 4 received no sodium replacement, however, the 8-h diuretic, natriuretic and chloruretic effects were significantly greater in treatment 4 compared with treatment 1, indicating the importance of rate of fluid replacement for the diuretic effects. Therefore, the 8-h diuretic, natriuretic and chloruretic effects were significantly greater in treatment 3 compared with treatments 1, 2 and 4, indicating the importance of full fluid and electrolyte replacement. Some implications for the bioequivalence evaluation of dosage forms of torasemide are discussed.

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Introduction

Since the importance of fluid or electrolyte replacement for urine loss in the evaluation of diuretics was recognized (Earley & Martino 1970; Branch et al 1977; Homeida et al 1979; Kahn et al 1983; Wilcox et al 1983; Hammarlund et al 1985), quantitative aspects of the effects of the rate and composition of fluid replacement on the pharmacokinetics and pharmacodynamics of furosemide (Li et al 1986), bumetanide (Yoon et al 1995) and azosemide (Park et al 1997b) loop diuretics have been reported. The pharmacodynamics (urine output and urinary excretion of sodium) of furosemide (Li et al 1986), bumetanide (Yoon et al 1985) and azosemide (Park et al 1997b) were significantly different with different rates and compositions of fluid replacement in dogs (Li et al 1986) and rabbits (Yoon et al 1995; Park et al 1997b). A review of the literature on torasemide indicated considerable inconsistencies among various studies. For example, no replacement (no fluid replacement being mentioned in these articles) (Hermes & Heidenreich 1985; Uchida et al 1991; Gottlieb et al 1998), partial replacement (Dubourg et al 2000), full replacement (Ghys et al 1985a, b; Kramp et al 1985; Kim & Lee 2003), and fluids *ad libitum* (Ghys et al 1985a) have been used. Furthermore, the composition of fluid replacement also varied greatly; for example, intravenous infusion of 0.9% NaCl (Ghys et al 1985a, b; Kramp et al 1985) and lactated Ringer's solution (Dubourg et al 2000; Kim & Lee 2003), subcutaneous

injection of 0.9% NaCl (Ghys et al 1985a), and oral ingestion of tap water (Ghys et al 1985a) have been used. In addition, lactated Ringer's solution was continuously infused at a rate of 10 mL kg^{-1} h^{-1} (Dubourg et al 2000). It might be anticipated from studies of furosemide (Li et al 1986), bumetanide (Yoon et al 1995) and azosemide (Park et al 1997b) that if the rate and/or the composition of fluid replacement are critical, the inconsistencies mentioned above might have led to different interpretations or conclusions in the evaluation of the pharmacokinetics and/or pharmacodynamics of torasemide.

Torasemide (1-isopropyl-3-(4-(*m*-toluidino-3-pyridyl)-sulfonyl)-urea; Torem) is a pyridine sulfonylurea loop diuretic closely resembling furosemide and bumetanide in its diuretic action (Knauf & Mutschler 1998). It inhibits, reversibly, the Na^+-K^+-$2Cl^-$ transport carrier system in the thick ascending limb of the loop of Henle (Wittner et al 1991). However, torasemide has a longer elimination half-life, more anti-aldosterone action and possibly fewer side-effects than furosemide (Dunn et al 1995).

This paper reports the results and implications of our study on the effects of the rate (no replacement or 50% and 100% replacement with lactated Ringer's solution) and the composition (100% replacement with lactated Ringer's solution as well as 5% dextrose in water) of fluid replacement on the pharmacokinetics and pharmacodynamics of intravenous torasemide in rabbits.

Materials and Methods

Chemicals

Torasemide and ketamine (100 mg mL^{-1}) were kindly supplied by Roche Pharmaceutical Company (Mannheim, Germany) and Yuhan Research Centre of the Yuhan Corporation (Kunpo, Korea), respectively. Tris buffer and polyethylene glycol 400 (PEG 400) were products from Sigma Chemical Company (St Louis, MO, USA) and Duksan Chemical Company (Seoul, Korea), respectively. Other chemicals were of reagent grade or HPLC grade and were used without further purification.

Pretreatment of rabbits

Male New Zealand white rabbits (1.7–2.2 kg) were purchased from Hanlim Laboratory of Animal Development (Hwasung, Korea) and randomly divided into four groups. All rabbits were provided with food (Sam Yang Company, Seoul, Korea) and water *ad libitum*, and were maintained in a light-controlled room (lights on 0700–1900 h) kept at a temperature of 22 ± 2 °C and humidity 55 ± 5% (Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University). Each rabbit was individually housed in a metabolic cage (Daejong Scientific Company, Seoul, Korea) under the supply of filtered pathogen-free air and water *ad libitum*. The protocol of the animal study was approved by the Animal Care and Use Committee of the College of Pharmacy, Seoul National University.

Rabbits were anaesthetized with 50–100 mg ketamine administered intravenously through the ear vein. The carotid artery and the jugular vein were catheterized with silastic tubing (Dow Corning, Midland, MI, USA) for blood collection and drug administration, respectively. Both cannulas were exteriorized to the dorsal side of the neck where each cannula terminated with a three-way stopcock (Connecta; Viggo AB, Helsingborg, Sweden). The exposed areas were closed using a surgical suture. A paediatric Foley catheter (16 Fr; Sewon Medical, Seoul, Korea) was introduced into the urinary bladder through the urethra for urine collection during the studies. Each rabbit was kept individually in a restraint cage for 4–5 h to recover from anaesthesia before the study began.

Intravenous infusion study

Torasemide stock solution (5 mg of torasemide powder was dissolved in 150 μL PEG 400 and 3.5 mL distilled water with a minimum amount of 10 M NaOH, and adjusted to a final pH of approx. 8 with Tris-HCl) was diluted with 0.9% NaCl injectable solution to make a final concentration of 1 mg mL^{-1}. The torasemide solution was infused over 2 h via the jugular vein with the assistance of an infusion pump (model 2400-006; Harvard Instruments, Southnatic, MA, USA). The total amount of torasemide infused over 2 h was 1 mg kg^{-1}. The loss of water and electrolytes in urine induced by torasemide was replaced by four different methods; 0% replacement (treatment 1, $n = 6$), 50% replacement with lactated Ringer's solution (treatment 2, $n = 9$), 100% replacement with lactated Ringer's solution (treatment 3, $n = 8$), and 100% replacement with 5% dextrose in water (treatment 4, $n = 6$). Each litre of lactated Ringer's solution contained approximately 130 mmol sodium, 4 mmol potassium, 6 mmol calcium, 109 mmol chloride and 28 mmol lactate.

Approximately 0.5-mL blood samples were collected at 0 (control), 15, 30, 45, 60, 90, 120 (end of infusion), 121, 125, 135, 150, 165, 180, 210, 240, 360 and 480 min after the start of intravenous infusion. Approximately 2 mL heparinized 0.9% NaCl injectable solution (20 units mL^{-1}) was used to flush the cannula after each blood sampling to prevent blood clotting. Blood samples were centrifuged immediately and two 0.1-mL plasma samples were stored in a freezer at −70 °C (Revco ULT 1490 DNS; Western Mednics, Asheville, NC, USA) until HPLC analysis of torasemide.

Urine samples were collected at the following intervals: 0–1, 1–2, 2–3, 3–4, 4–6, 6–8 and 8–24 h. Approximately 30 mL air was used at the end of each urine collection period to flush the bladder and thereby ensure complete urine collection. Fluid (treatments 2–4) was replaced via the jugular vein for up to 8 h as soon as the urine was voided (spontaneously, especially during the strong diuresis period) or collected. After measuring the exact volume of each urine collection, two 0.1-mL samples were stored at −70 °C until HPLC analysis of torasemide and for the measurement of sodium, potassium and chloride.

Analysis of torasemide, sodium, potassium and chloride

Concentrations of torasemide in plasma and urine were analysed by the HPLC method reported by Besenfelder (1987) with a slight modification. Acetonitrile (125 μL) for plasma samples, or methanol (150 μL) for urine samples, was added to 50-μL plasma or urine samples. After vortex-mixing and centrifugation at 9000 *g* for 10 min, a 50-μL sample of the supernatant was injected directly onto the HPLC column. The separation was achieved using a reversed-phase (C_{18}) column (Nucleosil 100-5; 25 cm in length, 4.6 mm i.d.; particle size 5 μm; Macherey-Nagel, MN, USA). The HPLC system consisted of a variable wavelength UV detector (UV/vis 151; Gilson, Middleton, WI, USA), HPLC pump (model 305/306; Gilson), sampling injector (model 231 XL; Gilson), syringe pump (model 402; Gilson), dynamic mixer (model 811D, Gilson), column heating control system (CH-500; Eppendorf, Westbury, NY, USA) and operation software (UniPoint 3.0 for Windows; Gilson). The mobile phases, 0.01 M $Na_2H_2PO_4$ (pH 3)/acetonitrile (50:50, v/v) for plasma sample and 0.01 M $Na_2H_2PO_4$ (pH 3)/acetonitrile (70:30, v/v) for urine sample, were run at a flow rate of 1 mL min^{-1} and the column effluent was monitored by UV detection at 290 nm. The retention times for torasemide were approximately 4.5 and 11 min for plasma and urine, respectively. Concentrations of sodium, potassium and chloride in urine were determined using the Hitachi 747 automatic analyser (Tokyo, Japan).

Pharmacokinetic analysis

The total area under the plasma concentration–time curve from time zero to infinity (AUC) was calculated by the trapezoidal rule extrapolation method. This method used the logarithmic trapezoidal rule (Chiou 1978) for the calculation of the area during the declining plasma level phase and the linear trapezoidal rule for the rising plasma level phase. The area from the last data point to infinity was estimated by dividing the last measured concentration by the terminal rate constant.

Standard methods (Gibaldi & Perrier 1982) were used to calculate the following pharmacokinetic parameters: the time-averaged total body clearance (Cl), area under the first moment of the plasma concentration–time curve (AUMC), mean residence time (MRT), apparent volume of distribution at steady-state (Vd_{ss}), and time-averaged renal (Cl_R) and non-renal (Cl_{NR}) clearance (Kim et al 1993).

$$Cl = dose/AUC \quad (1)$$

$$AUMC = \int_0^\infty t \times C_p dt \quad (2)$$

$$MRT = (AUMC/AUC) - (T/2) \quad (3)$$

$$Vd_{ss} = Cl \times MRT \quad (4)$$

$$Cl_R = A_e/AUC \quad (5)$$

$$Cl_{NR} = Cl - Cl_R \quad (6)$$

where C_p is the plasma concentration of torasemide at time t, T is the infusion time, and A_e is the total amount of unchanged torasemide excreted into the urine up to time infinity (this was assumed to be equal to the total amount of torasemide excreted in 24-h urine, since no detectable torasemide could be detected in the urine collected after 24 h).

The mean values of each Cl (Chiou 1980a), Vd_{ss} (Chiou 1979), and terminal half-life (Eatman et al 1977) were calculated by the harmonic mean method.

Pharmacodynamic analysis

The diuretic, natriuretic, kaluretic and chloruretic efficiencies were calculated by dividing the total urine output (mL) and total amount (mmol) of sodium, potassium and chloride excreted in the 8-h urine by the total amount (mg) of torasemide excreted in the 8-h urine, respectively.

Statistical analysis

A value of $P < 0.05$ was considered to be statistically significant using Duncan's multiple range test of SPSS posteriori analysis of variance program among three means for the unpaired data. All results are expressed as mean ± s.d.

Results

Pharmacokinetics of torasemide

The plasma concentrations of torasemide rose rapidly during infusion in all four treatments and reached an apparent steady state from 45 min of infusion in treatments 1–3 (Figure 1). This was consistent with the prediction based on the plasma area method of Chiou (1980b), since the 0–45-min plasma area could account for greater than 95% of the AUC after an intravenous bolus administration of 1 mg kg^{-1} torasemide to seven rabbits (unpublished data). This could be at least partly owing to the high degree of plasma protein binding (99%) at torasemide concentrations ranging from 0.1 to 100 μg mL^{-1} in humans (Neugebauer et al 1988) and 94.1% at a torasemide concentration of 10 μg mL^{-1} in rats (Kim & Lee 2003), and relatively small value of the initial volume of distribution (0.2 L kg^{-1}) (Knauf & Mutschler 1998) of torasemide in rabbits and Vd_{ss} of 0.148–0.225 L kg^{-1} (Table 1). Post-infusion plasma levels of torasemide decayed rapidly (Figure 1) with mean terminal half-lives of 21.6, 27.2, 15.8 and 52.0 min for treatments 1–4, respectively; the value in treatment 4 was significantly longer compared with treatments 1–3 (Table 1). The plasma concentrations of torasemide for each rabbit during steady state (between 45 min and 2 h) were fairly constant for treatments 1–3 (mean 1.36, 1.13 and 0.782 μg mL^{-1}, respectively; Figure 1). The plasma concentrations of torasemide in treatment 4 kept increasing during infusion and did not

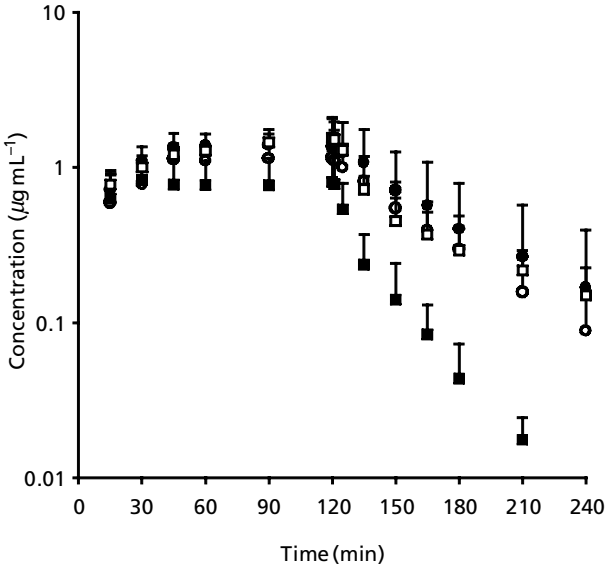

Figure 1 Mean arterial plasma concentration–time profiles of torasemide in treatments 1 (●; n = 6), 2 (○; n = 9), 3 (■, n = 8) and 4 (□, n = 6). Vertical bars represent s.d.

reach an apparent steady state for up to 2 h after infusion (Figure 1); the reasons for this are not known.

The plasma concentrations of torasemide were the lowest in treatment 3 (Figure 1) and this resulted in a significantly smaller AUC compared with treatments 1 (119% increase), 2 (74.3% increase) and 4 (123% increase) (Table 1). This could be owing to the significantly faster Cl of torasemide in treatment 3 compared with treatments 1 (54.7% decrease), 2 (42.8% decrease) and 4 (55.5% decrease) (Table 1). The faster Cl in treatment 3 was owing to significantly faster Cl_R, since Cl_{NR} was not significantly different among the four treatments (Table 1). The Cl_R in treatment 3 was significantly faster compared with treatments 1 (78.8% decrease), 2 (72.4% decrease) and 4 (74.6% decrease) (Table 1). The faster Cl_R in treatment 3 could be mainly owing to the significantly greater total amount of unchanged torasemide excreted in 8-h urine ($A_{e\ 0-8\,h}$) and significantly smaller AUC; the $A_{e\ 0-8\,h}$ in treatment 3 was significantly greater compared with treatments 1 (47.0% decrease), 2 (40.5% decrease) and 4 (20.6% decrease) (Table 1). The MRT in treatment 3 was significantly shorter compared with treatments 1 (167% increase), 2 (150% increase) and 4 (208% increase) (Table 1).

The Vd_{ss} was not significantly different among the four different treatments (Table 1); this was similar to our earlier observations that the Vd_{ss} was not significantly different by prolonging the intravenous infusion time from 1 min to 2 h for the delivery of the same total dose of torasemide in rabbits (unpublished data); in that study, lactated Ringer's solution was immediately replaced volume for volume with intravenous infusion for the urine loss. However, infusion-time-dependent Vd_{ss} has been reported for furosemide in dogs (Lee et al 1986; Li et al 1986) and for bumetanide (Ryoo et al 1993; Yoon et al 1995) and azosemide in rabbits (Park et al 1997a, b).

Pharmacodynamics of torasemide

In treatment 3, the 8-h urine output and 8-h urinary excretion of sodium, potassium and chloride were significantly greater compared with treatments 1, 2 and 4 (Table 1). In treatment 3, the diuretic efficiency was significantly higher compared with treatments 1 and 2 and natriuretic and chloruretic efficiencies were significantly higher compared with treatments 1, 2 and 4; kaluretic efficiencies were not significantly different among the four treatments (Table 1). The mean hourly urine output and urinary excretion of torasemide, sodium, potassium and chloride for up to 3 h are shown in Figure 2. In treatments 1–3, the greater urinary excretion rate of torasemide resulted in greater urine output and urinary excretion rate of sodium and chloride (Figure 2).

The negative fluid balance (Figure 3A) was obtained from treatments 1 (–102 mL) and 2 (–87.1 mL), and negative sodium (Figure 3B) and chloride (Figure 3C) balances from treatments 1 (–10.1 and –17.4 mmol for sodium and chloride, respectively), 2 (–8.98 and –19.3 mmol for sodium and chloride, respectively) and 4 (–31.2 and –35.6 mmol for sodium and chloride, respectively). However, neutral fluid balance was obtained from treatments 3 and 4 (Figure 2A) and positive sodium and chloride balance from treatment 3 (+20.4 and +10.0 mmol for sodium and chloride, respectively) (Figure 2B and C).

Discussion

Greater than 95% of torasemide excreted over 24-h urine collection was excreted during the first 8 h of urine collection in all rabbits studied, and the loss of water in urine induced by torasemide was replaced only for up to 8 h in treatments 2–4. Therefore, the following discussion on the pharmacodynamics of torasemide will be confined to this period of time (i.e. 8 h). In treatment 3, 8-h urine output was significantly larger compared with treatments 1, 2 and 4 (Table 1). Some factors are proposed to explain this phenomena. The increased free fraction of torasemide in plasma and increased glomerular filtration rate (GFR) in treatment 3 could have been a factor. However, this was ruled out because although the GFR was not measured in the present study, it has been reported that torasemide does not alter GFR in dogs (Ghys et al 1985b) and newborn rabbits (Dubourg et al 2000). It has been reported that the extent of plasma protein binding of torasemide in human plasma was 99% at torasemide concentrations ranging from 0.1 to 100 $\mu g\,mL^{-1}$ (Neugebauer et al 1988), and in rat and dog plasma was 99.5% at torasemide concentrations ranging from 25 to 50 $\mu g\,mL^{-1}$ and 98.4% at torasemide concentrations ranging from 5 to 20 $\mu g\,mL^{-1}$, respectively, using an ultrafiltration method (Ghys et al 1985a). When considering the Cl_R of torasemide in Table 1 and greater plasma protein binding of

Table 1 Mean ± s.d. pharmacokinetic and pharmacodynamic parameters of torasemide following 2-h infusion of the drug at a dose of 1 mg kg^{-1} in rabbits.

Parameter	Treatment 1 (0% replacement, n = 6)	Treatment 2 (50% replacement with lactated Ringer's solution, n = 9)	Treatment 3 (100% replacement with lactated Ringer's solution, n = 8)	Treatment 4 (100% replacement with 5% dextrose in water, n = 6)
Bodyweight (kg)	1.71 ± 0.128	1.98 ± 0.424	1.94 ± 0.194	1.91 ± 0.124
Terminal half-life (min)[a]	21.6 ± 17.4	27.2 ± 9.80	15.8 ± 10.2	52.0 ± 16.1
AUC (μg min mL^{-1})[b]	221 ± 77.7	176 ± 47.6	101 ± 38.5	225 ± 61.9
MRT (min)[b]	45.4 ± 25.9	42.5 ± 14.4	17.0 ± 7.75	52.4 ± 17.3
Cl (mL min^{-1} kg^{-1})[b]	4.53 ± 1.61	5.72 ± 1.53	10.0 ± 4.65	4.45 ± 1.07
Cl_R (mL min^{-1} kg^{-1})[b]	1.44 ± 1.82	1.87 ± 1.16	6.78 ± 4.77	1.72 ± 1.36
Cl_{NR} (mL min^{-1} kg^{-1})	2.33 ± 1.26	3.44 ± 1.39	2.71 ± 3.27	2.21 ± 0.620
Vd_{ss} (mL kg^{-1})	175 ± 65.9	225 ± 88.0	148 ± 132	224 ± 65.4
$A_{e\ 0-8\,h}$ (μg)[b]	694 ± 246	780 ± 305	1310 ± 185	1040 ± 139
$A_{e\ 0-8\,h}$ (% of dose)[b]	40.6 ± 14.5	39.2 ± 13.1	68.0 ± 11.9	54.9 ± 8.50
8-h Urine output (mL)[c]	101 ± 37.1	185 ± 69.6	808 ± 255	589 ± 159
8-h Urinary excretion of sodium (mmol)[d]	10.1 ± 3.55	20.6 ± 8.08	89.2 ± 20.3	29.9 ± 5.08
8-h Urinary excretion of potassium (mmol)[b]	4.30 ± 3.12	4.31 ± 1.85	7.23 ± 2.20	4.28 ± 0.941
8-h Urinary excretion of chloride (mmol)[e]	14.5 ± 5.18	27.9 ± 9.54	94.0 ± 16.9	37.2 ± 2.70
8-h Diuretic efficiency (mL mg^{-1})[f]	153 ± 56.5	251 ± 79.9	638 ± 239	607 ± 202
8-h Natriuretic efficiency (mmol mg^{-1})[d]	15.5 ± 6.01	28.2 ± 10.4	72.4 ± 18.7	30.2 ± 7.28
8-h Kaluretic efficiency (mmol mg^{-1})	4.89 ± 2.10	6.08 ± 2.93	5.71 ± 1.84	3.90 ± 0.681
8-h Chloruretic efficiency (mmol mg^{-1})[d]	22.4 ± 8.81	38.5 ± 13.3	76.4 ± 16.9	35.5 ± 5.96

[a]Treatment 4 was significantly different ($P < 0.05$) compared with treatments 1, 2 and 3 (treatments 1, 2 and 3 were not significantly different). [b]Treatment 3 was significantly different ($P < 0.05$) compared with treatments 1, 2 and 4 (treatments 1, 2 and 4 were not significantly different). [c]Treatments were significantly different ($P < 0.05$) except for treatments 1 and 2, which were not significantly different). [d]Treatment 3 was significantly different ($P < 0.05$) compared with treatments 1, 2 and 4, and treatment 1 was significantly different ($P < 0.05$) compared with treatment 4. (treatments 1 and 2 were not significantly different). [e]Treatment 3 was significantly different ($P < 0.05$) compared with treatments 1, 2 and 4, and treatment 1 was significantly different ($P < 0.05$) compared with treatments 2 and 4 (treatments 2 and 4 were not significantly different). [f]Treatments 1 and 2 were significantly different ($P < 0.05$) compared with treatments 3 and 4 (treatments 3 and 4 were not significantly different, and treatments 1 and 2 were also not significantly different).

torasemide, the Cl_R of torasemide based on free (unbound in plasma proteins) fraction was considerably greater than the reported GFR in rabbits (3.12 mL min^{-1}kg^{-1}; Davies & Morris 1993). This indicated that torasemide is mostly excreted in rabbit urine by tubular secretion and the contribution of torasemide by glomerular filtration to its diuretic effect could be minimal. Therefore, plasma protein binding and GFR could contribute little to the urine output induced by torasemide in rabbits. Similar results have also been reported with furosemide (Ponto & Schoenwal 1990a, b), bumetanide (Odlind et al 1983) and azosemide (Brater et al 1979; Kuzuya 1983). The significantly larger urine output in treatment 3 could be owing to significantly greater $A_{e\ 0-8\,h}$ and the significantly higher diuretic efficiency in treatment 3 (Table 1).

The acute time-dependent tolerance of furosemide (Li et al 1986), bumetanide (Yoon et al 1995) and azosemide (Park et al 1997b) was owing to incomplete replacement of fluid. This was also shown with torasemide. The development of acute time-dependent tolerance in diuresis, natriuresis and chloruresis was most pronounced in treatment 1, which had no replacement for fluid or electrolyte loss. The mean magnitude of diuresis (Figure 2A), natriuresis (Figure 2C) and chloruresis (Figure 2E) at 0–1 h was only 26.9, 28.6 and 37.2% of those in treatment 3, respectively, and the corresponding values at 1–2 h and 2–3 h were 5.44, 5.24 and 7.18%, and 3.46, 3.85 and 6.21%.

The following conclusions can be made from the present study. First, although full fluid (referring to water) replacement was used in both treatments 3 and 4, the 8-h diuretic (1.37 times), natriuretic (2.98 times), and chloruretic (2.53 times) effects in treatment 3 were significantly greater compared with treatment 4, even after considering the fact that the $A_{e\ 0-8\,h}$ of torasemide decreased by only

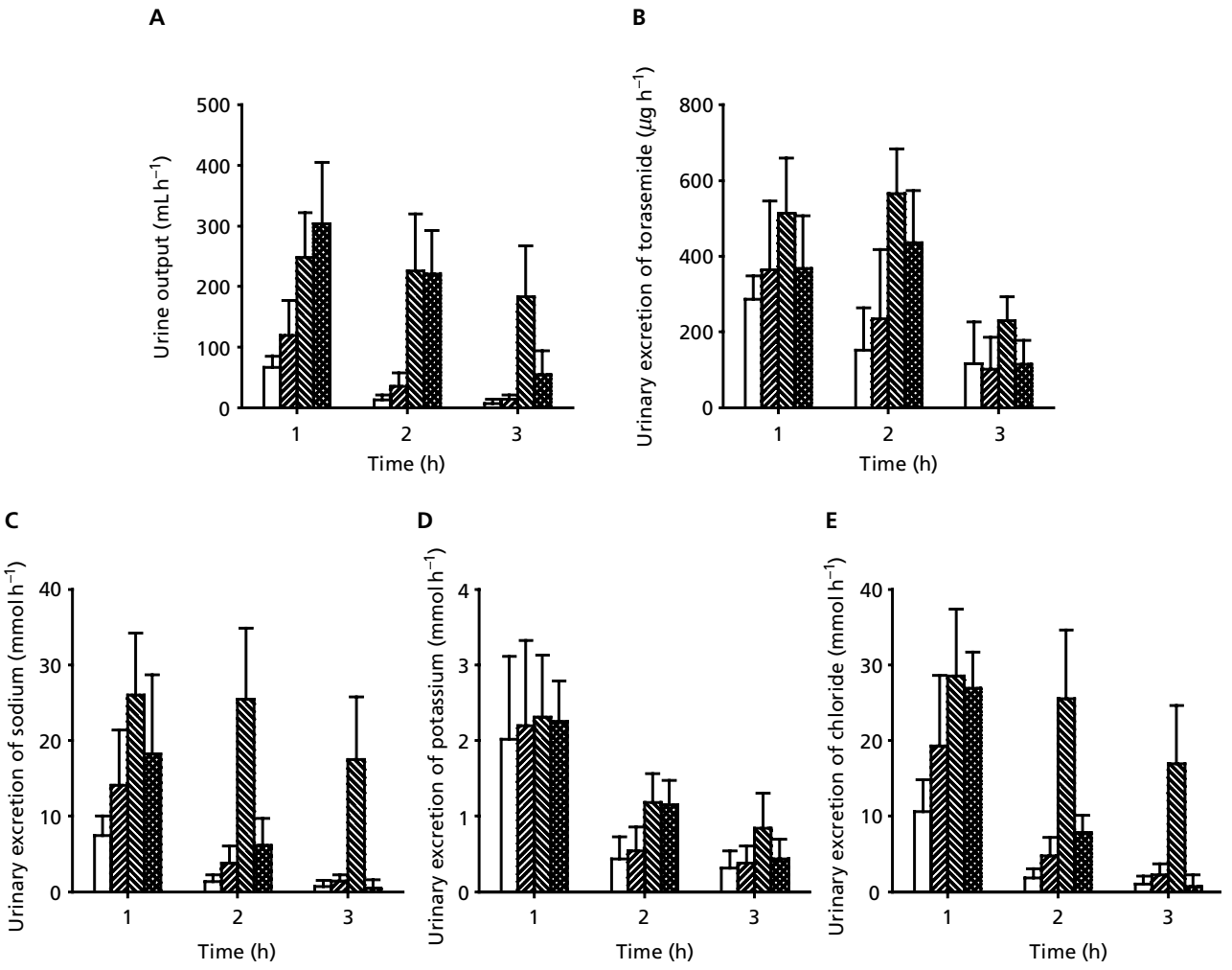

Figure 2 Mean hourly urine output (A) and urinary excretion of torasemide (B), sodium (C), potassium (D) and chloride (E) as a function of time in treatments 1 (□), 2 (▨), 3 (▩) and 4 (■). Vertical bars represent s.d.

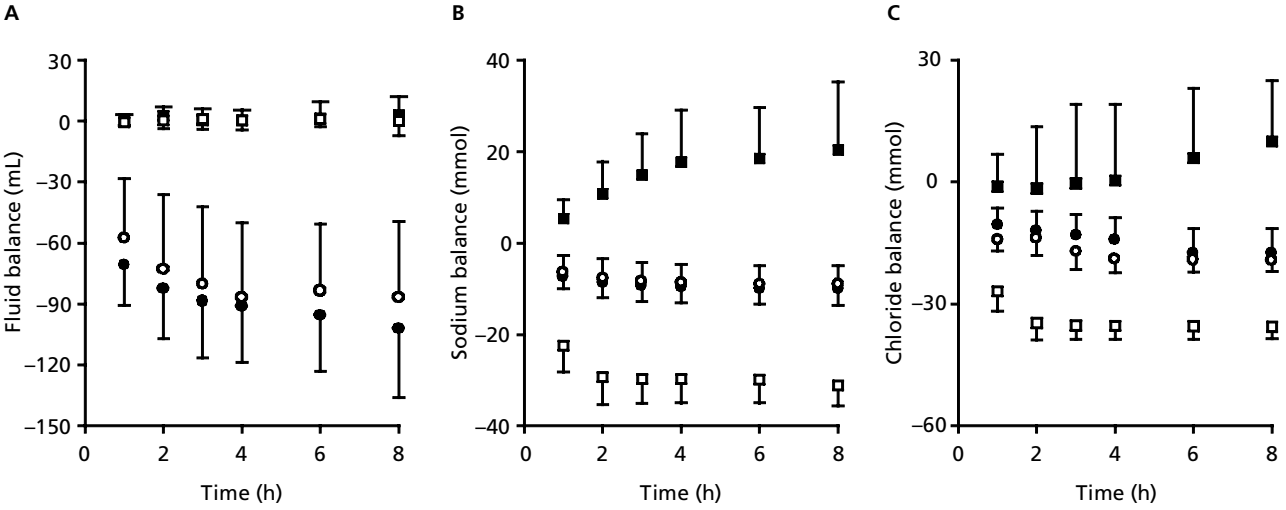

Figure 3 Time course of the fluid (A), sodium (B) and chloride (C) balance in treatments 1 (●), 2 (○), 3 (■) and 4 (□). Vertical bars represent s.d.

20.6% in treatment 4 (Table 1). This clearly illustrates the importance of the composition of the fluid used for replacement. Similar results have been reported with furosemide (Li et al 1986), bumetanide (Yoon et al 1995) and azosemide (Park et al 1997b). Second, both treatments 1 and 4 received no sodium replacement and there was no significant difference in the $A_{e\ 0-8\,h}$ of torasemide (Table 1). However, the 8-h diuretic (5.83 times), natriuretic (2.96 times) and chloruretic (2.57 times) effects were significantly greater in treatment 4 compared with treatment 1 (Table 1). This indicates that water replacement (the rate of fluid replacement from zero to 100%) per se may have significant effects on diuresis, natriuresis and chloruresis, even though sodium intake is zero or perhaps minimal. Different results have been reported with furosemide (Li et al 1986), bumetanide (Yoon et al 1995) and azosemide (Park et al 1997b). If the present study in rabbits can be directly extrapolated to patients receiving zero-order input of torasemide, then more negative sodium and chloride balance can both be achieved as long as the patients receive the same amount of water that is lost from the body. The above results clearly indicate that the rate, extent and composition of intravenous fluid replacement can significantly influence the time-dependent relationship between kinetics and dynamics of torasemide in rabbits.

One obvious implication of the present study might be in the area of bioequivalence evaluation. It is possible that the same dosage form of torasemide may yield markedly different diuretic and/or natriuretic profiles in the same subject, depending solely on the rate, extent and composition of the replacement fluid.

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