Br. J. clin. Pharmac. (1986), **21**, 359–364

Comparison of the acute vascular effects of frusemide and bumetanide

G. D. JOHNSTON, D. P. NICHOLLS, G. B. KONDOWE & M. B. FINCH
Department of Therapeutics and Pharmacology, The Queen's University of Belfast, and Belfast City Hospital, Belfast, Northern Ireland

1 The acute peripheral vascular and diuretic effects of intravenous frusemide 10 mg and 20 mg were compared with those of bumetanide 250 μg and 500 μg in a group of 10 salt depleted volunteers.
2 Significant reductions in forearm blood flow (FBF) were observed after frusemide 10 mg (-0.77 ml 100 ml^{-1} min^{-1} $P < 0.05$) and 20 mg (-0.75 ml 100 ml^{-1} min^{-1} $P < 0.01$ at 15 min). No changes were observed after bumetanide. The reductions in blood flow produced by frusemide were significantly different from those of bumetanide ($P < 0.05$) at 15 min.
3 Increases in venous capacitance (VC) and mean arterial blood pressure (MAP) were observed after frusemide but these differences were not statistically different from placebo or bumetanide. No increases were seen after bumetanide.
4 Plasma aldosterone concentrations were unchanged after either drug but plasma renin activity (PRA) was increased after frusemide 10 mg ($4.42 \pm 1.01 \rightarrow 8.50 \pm 1.90$ ng A I ml^{-1} h^{-1} $P < 0.01$) and 20 mg ($4.01 \pm 0.72 \rightarrow 7.81 \pm 2.27$ ng A I ml^{-1} h^{-1} $P < 0.05$). No increases were observed after bumetanide and significant differences between bumetanide and frusemide were observed ($P < 0.01$).
5 This study demonstrates that the acute peripheral arterial effects of frusemide are not observed after comparable diuretic doses of bumetanide. The differences appear to be related to the ability of the drugs to stimulate acute renin release from the kidney.

Keywords frusemide bumetanide vascular effects diuretics

Introduction

It has been demonstrated that the acute non-diuretic vascular effects of bumetanide differ from those of frusemide and ethacrynic acid in patients with congestive heart failure (Ziacchi *et al.*, 1981). While bumetanide is known to produce increases in renal blood flow (Bollerup *et al.*, 1974), the acute effects on left ventricular filling pressure and venous capacitance are less well defined and unlike other diuretics (Lal *et al.*, 1969; Dikshit *et al.*, 1973; Ramirez & Abelmann, 1968) bumetanide is associated with a decrease in total peripheral systemic resistance (Ziacchi *et al.*, 1981).

We have previously shown that the acute peripheral vascular effects of frusemide on venous capacitance and forearm blood flow are related to renin release, prostaglandin formation and angiotensin II formation. In keeping with this hypothesis are the observations that indomethacin, salt overloading and propranolol prevent acute frusemide stimulated renin release and attenuate the peripheral vascular responses (Johnston *et al.*, 1983a, 1985). Reduction of angiotensin II formation with captopril also prevents the venodilator, arterial constrictor and pressor responses to intravenous frusemide

Correspondence: Dr G. D. Johnston, Department of Therapeutics and Pharmacology, The Queen's University of Belfast, The Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL

(Johnston *et al.*, 1983b). The following experiment was therefore undertaken to compare the peripheral venous and arterial effects of intravenous bumetanide and frusemide at comparable diuretic doses and to examine the relationship between these responses and the changes in plasma renin activity.

Methods

Ten healthy volunteers, six females and four males aged 19–34 years, were studied after full clinical examination and having given informed consent. The subjects had normal renal function as assessed by serum creatinine (92.8 ± 2.4; range 84–109 μmol 100 ml^{-1}). The protocol of the study had been approved by the Ethics Committee of The Queen's University of Belfast. The study was carried out at the same time of day on five separate occasions with a period of at least 1 week between studies. For the 3 days before each study day subjects were asked to restrict the sodium content of their diet to 50 mmol 24 h^{-1} by avoiding added salt and restricting sodium rich foods. In addition the volunteers received 80 mg of oral frusemide for 3 days. On the day of each experiment, urine was collected over a 4 h period before the study to estimate urinary sodium excretion. A 19 gauge butterfly needle was then inserted into an antecubital vein of the left arm for blood sampling and drug administration. Blood pressure was measured using a Hawksley random zero sphygmomanometer (Wright & Dore, 1970) and heart rate from a direct writing electrocardiograph as the mean of ten consecutive R-R intervals. Mean blood pressure was calculated as the diastolic blood pressure + ⅓ (systolic – diastolic pressure). Forearm blood flow and venous capacitance were measured in the right arm by venous occlusion plethysmography (Whitney, 1953). Venous capacitance was determined by the equilibration technique at a venous occlusion pressure of 30 mm Hg (4kPa) and forearm blood flow determined from the initial rate of change in forearm circumference at an occlusion pressure of 60 mm Hg (8 kPa). Changes in forearm circumference were measured with a mercury-in-silastic strain gauge. Room temperature throughout was maintained at 24 ± 0.5°C.

After a 1 h period of rest in the supine position, three baseline measurements of venous capacitance, forearm blood flow, blood pressure and heart rate were made at 5 min intervals and a blood sample taken for the measurement of plasma renin activity and plasma aldosterone concentrations. Subjects then received 10, 20 mg of frusemide, 250, 500 μg of bumetanide or placebo according to a double-blind, randomised cross-over design. On each occasion, the drug (or placebo) was administered as a 2 ml intravenous bolus given over a 10 s period. The injection had been prepared beforehand by an independent observer to maintain blindness. Venous capacitance, forearm blood flow, blood pressure and heart rate were again measured at 5 min intervals over the next 15 min. Plasma renin activity and plasma aldosterone concentrations were measured before and ten minutes after the diuretic or placebo. Urine samples were obtained at 20 min after drug administration for estimation of urinary sodium output.

For estimation of plasma renin activity 10 ml of blood was immediately placed in glass tubes at 0°C containing 0.3 ml of 10% sodium ethylenediamine tetra-acetate (EDTA), centrifuged at 4°C and plasma stored at −40°C. Plasma renin activity was expressed as ng of angiotensin I (A I) generated h^{-1} ml^{-1} of plasma at pH 7 and at 37°C. A I was measured by radioimmunoassay with a Gamma Coat Kit, Clinical Assays Travenol Laboratories Inc. (Haber *et al.*, 1969). Plasma aldosterone concentrations were measured with a radioimmunoassay kit supplied by C.I.S. (UK) Ltd, North Finchley, London, and urinary sodium concentrations by flame photometry. Comparisons of absolute data at each time point were made using Friedman's two-way analysis of variance for non-parametric measurements. If significant differences between treatments were detected then a Wilcoxon's matched pairs signed rank test for paired data was used to identify differences between individual drugs. The level of significance was chosen as $P < 0.05$ for the analysis of variance and $P \leq 0.025$ for the Wilcoxon's test to reduce the frequency of random positive results. Values $P < 0.25 > 0.01$ are expressed as $P < 0.05$.

Results

Frusemide 10 mg and 20 mg caused significant reductions in forearm blood flow (FBF) at 15 min when compared with placebo (−0.77 ml 100 ml^{-1} min^{-1} $P < 0.05$ and −0.75 ml 100 ml^{-1} min^{-1} $P < 0.01$ respectively, Figure 1). No reductions in FBF were observed after the two doses of bumetanide. The differences between frusemide 10 mg and bumetanide 250 μg and between frusemide 20 mg and bumetanide 500 μg were significant ($P < 0.05$). A significant difference ($P < 0.05$) was observed in venous

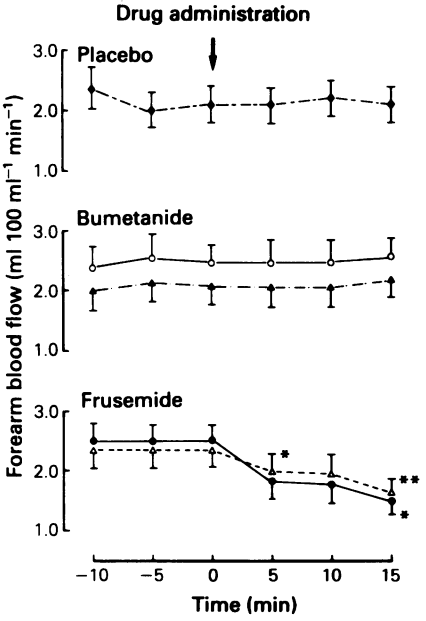

Figure 1 Changes in forearm blood flow (ml 100 ml^{-1} min) 15 min before and after the administration of placebo (◆—·—◆), bumetanide 250 μg (○—○), bumetanide 500 μg, (▲—·—▲), frusemide 10 mg (●—●) and frusemide 20 mg (△-----△). Changes are compared with the corresponding placebo values. * $P < 0.05$, ** $P < 0.01$.

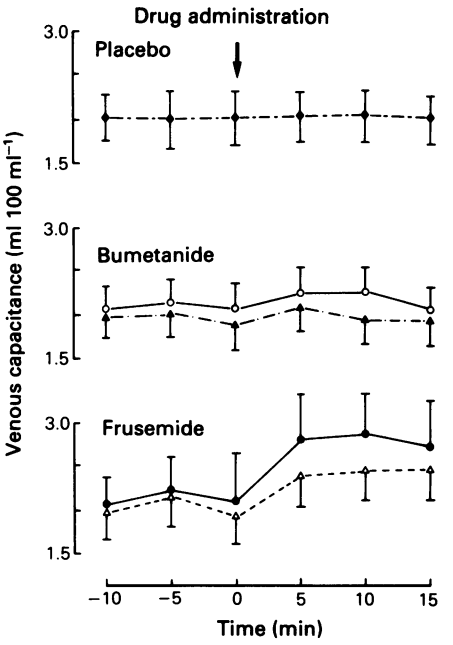

Figure 2 Changes in venous capacitance (ml 100 ml^{-1} at 30 mm Hg) 15 min before and after the administration of placebo (◆—·—◆), bumetanide 250 μg (○—○), bumetanide 500 μg (▲—·—▲), frusemide 10 mg (●—●) and frusemide 20 mg (△----△). Changes are compared with the corresponding placebo values.

capacitance (VC) between treatments 5 min after drug administration but it was not possible to identify any individual differences which were significant. No overall differences were seen at 10 or 15 min after drug administration. The increase in VC observed after frusemide (Figure 2) was not statistically different from placebo or bumetanide. A small increase in mean arterial blood pressure (MAP) was seen after frusemide (Figure 3) but this also did not achieve statistical significance when compared to placebo or bumetanide.

The pre-treatment urinary sodium excretions were all less than 2.5 mmol h^{-1} indicating that subjects had adhered to the protocol and that a measure of sodium depletion had been achieved. After drug administration a significant increase in sodium and water excretion was observed after each active drug ($P < 0.01$) as compared to placebo. No differences were seen between the natriuretic effects of any of the active drugs although the larger doses did appear to have greater natriuretic activity (Figure 4). The changes in plasma aldosterone concentrations were not significantly different from placebo after diuretic administration (Figure 4). By contrast when compared to placebo significant increases in PRA were observed after frusemide 10 mg (4.42 ± 1.01 → 8.50 ± 1.90 ng A I ml^{-1} h^{-1}, $P < 0.01$) and 20 mg (4.01 ± 0.72 → 7.81 ± 2.27 ng A I ml^{-1} h^{-1}, $P < 0.05$, Figure 4). No changes in PRA were observed after bumetanide. The effects of 10 mg frusemide and 250 μg of bumetanide on PRA were significantly different ($P < 0.01$). The coefficients of variation based on values in 50 salt depleted subjects were 52% for PRA and 43% for plasma aldosterone.

Discussion

This study demonstrates that comparable diuretic doses of frusemide and bumetanide have different acute effects on the peripheral vasculature and the renin-angiotensin system. We have previously demonstrated that the acute peripheral vascular effects of intravenous frusemide on venous capacitance, peripheral blood flow and blood pressure only occur when the kidney is in a salt retaining state and when frusemide gives rise to acute renin release (Johnston *et al.*, 1983a, b, 1985). We postulated that the peripheral arterial

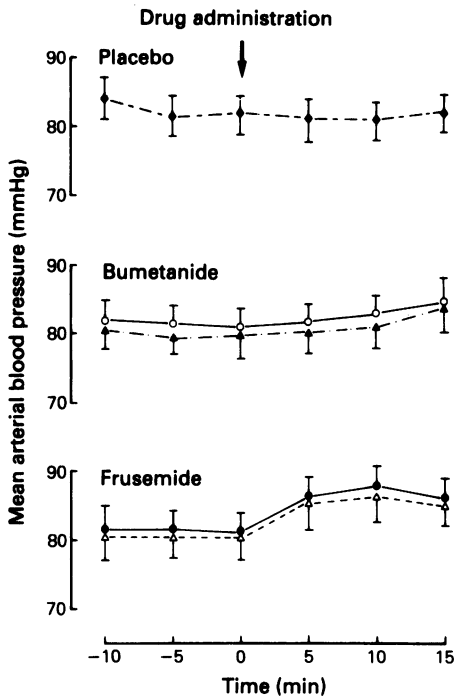

Figure 3 Changes in mean arterial blood pressure (mm Hg) 15 min before and after the administration of placebo (◆—·—◆), bumetanide 250 μg (○—○), bumetanide 500 μg (▲—·—▲), frusemide 10 mg (●—●) and frusemide 20 mg (△----△). Changes are compared with the corresponding placebo values.

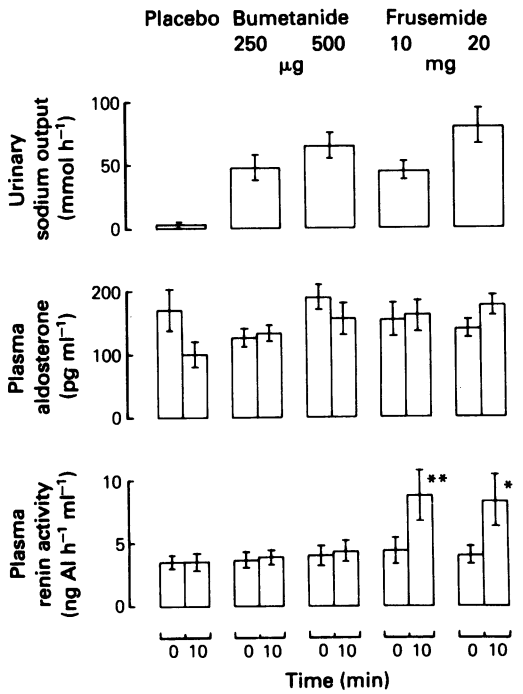

Figure 4 Plasma aldosterone (pg ml^{-1}) and plasma renin activity (ng A I h^{-1} ml^{-1}) before and 10 min after the administration of placebo, bumetanide (250, 500 μg) and frusemide (10 mg, 20 mg). Urinary sodium output (mmol h^{-1}) following these drugs is also illustrated. Changes are compared with the corresponding placebo. * $P < 0.05$, ** $P < 0.01$

constrictor effects occurred secondary to angiotensin II formation while the venous effects were due to the release of vasodilatory substances—prostaglandins, kinins, etc. from the vessel wall in response to angiotensin II. These effects, combined with acute pressor responses are observed at low dose (5 mg intravenously) and there appears to be no relationship with the degree of diuresis (Johnston *et al.*, 1984). Ziacchi *et al.* (1981) demonstrated that bumetanide, a diuretic with similar properties to frusemide, did not produce an increase in peripheral resistance in patients with congestive heart failure. If our original theory was correct then bumetanide would not produce acute renin release under these circumstances. However, bumetanide has been reported to cause a marked increase in plasma renin activity in laboratory animals (Imbs *et al.*, 1977; Olsen & Ahnfelt-Ronne, 1976) and man (Pedrinelli *et al.*, 1980; Pierucci *et al.*, 1980) probably secondary to increases in renal plasma flow (Sigurd *et al.*, 1975) and decreases in extracellular volume. At first glance the effects of bumetanide on renin release described in this study appear to be at variance with most of the published literature on the subject but the dose of bumetanide and the timing of the renin sample must be taken into consideration when making comparisons. Loop diuretics, unlike other diuretics, have a biphasic effect on renin release: an acute response which is due to a direct effect of the drug on the macula densa, accompanied by an increase in renal blood flow and a late response which occurs secondary to salt and water retention (Imbs *et al.*, 1977). In this experiment we examined only the acute effects on renin release, i.e. changes occurring within 10 min of drug administration since this is the time scale of the acute peripheral vascular responses. In two studies which reported an increase in man following bumetanide, the plasma renin activity was not measured before 30 min (Pierucci *et al.*, 1980; Velasquez *et al.*, 1978) and therefore no evidence of an acute increase in renin release was described. There appears to be no evidence that bumetanide, at these doses, causes acute renin release in man.

The acute vascular effects of frusemide seem to be unrelated to diuresis (Johnston *et al.*, 1984) and it may be that at higher doses bumetanide could give rise to acute renin release and acute peripheral vascular effects. Animal studies have demonstrated that the acute increases in renal blood flow and renin release seen with frusemide occur at normal diuretic doses while with bumetanide these effects are only seen at the highest or even supramaximal diuretic doses (Friedman & Roch-Ramel, 1977; Duchin & Hutcheon, 1978). One might speculate that if we had used higher doses of bumetanide plasma renin activity would have increased acutely and the peripheral vascular effects would have been observed. On a weight for weight basis, bumetanide is clearly a more potent diuretic. These differences are in part related to lipid solubility and to the concentrations achieved within the renal tubule (Schlossman, 1974). Loop diuretics produce their effects on sodium and chloride transport on the thick ascending loop of Henle from within the renal tubule and the diuretic effects can be related to this concentration. The ability of these drugs to stimulate renin release acutely seems to depend on their concentrations at the macula densa (Freeman *et al.*, 1974) which is not necessarily related to the concentration in the ascending limb of the loop of Henle. The diuretic activity and the ability of loop diuretics to produce acute increases in plasma renin activity are probably not related.

Whatever the reasons for the differences between the two drugs, bumetanide at lower therapeutic doses, unlike frusemide, is not associated with acute increases in forearm vascular resistance and probably total peripheral resistance. These differences could be related to their effects on acute renin release and subsequent angiotensin II formation. The implications of these findings in patients with congestive heart failure treated with loop diuretics has yet to be assessed.

We would like to thank Leo Laboratories Ltd for their financial assistance.

References

Bollerup, A. C., Hesse, B. & Sigurd, B. (1974). Changes of glomerular filtration rate and renal plasma flow following intravenous bumetanide in organic heart disease. *Acta Pharmac. Tox.*, **34**, 305–311.

Dikshit, K., Vyden, J. K., Forrester, J. S., Chatterjee, K., Prakash, R. & Swan, H. J. C. (1973). Renal and extra renal haemodynamic effects of frusemide in congestive heart frailure after acute myocardial infarction. *New Engl. J. Med.*, **288**, 1087–1090.

Duchin, K. L. & Hutcheon, D. E. (1978). Distribution of intra cortical renal blood flow induced by bumetanide in the dog. *J. Pharmac. exp. Ther.*, **204**, 135–140.

Freeman, R. H., Davis, J. O., Gotshall, R. W., Johnston, J. A. & Spielman, W. S. (1974). The signal perceived by the macula densa during changes in renin release. *Circ. Res.*, **35**, 307–315.

Friedman, P. A. & Roch-Ramel, F. (1977). Haemodynamic and natriuretic effects of bumetanide and furosemide in the cat. *J. Pharmac. exp. Ther.*, **203**, 82–91.

Haber, E., Koerner, T., Page, L. B., Kliman, B. & Purnode, A. (1969). Application of a radioimmunoassay for angiotensin to the physiologic measurements of plasma renin activity in normal human subjects. *J. clin. Endocrinol. Metab.*, **29**, 1349–1355.

Imbs, J. L., Schmidt, M., Velly, J. & Schwartz, J. (1977). Comparison of the effect of two groups of diuretics on renin secretion in the anaesthetised dog. *Clin. Sci. mol. Med.*, **52**, 171–182.

Johnston, G. D., Hiatt, W. R., Nies, A. S., Payne, N. A., Murphy, R. C. & Gerber, J. G. (1983a). Factors modifying the early non-diuretic vascular effects of furosemide in man: the possible role of renal prostaglandins. *Circ. Res.*, **53**, 620–635.

Johnston, G. D., Nicholls, D. P. & Leahey, W. J. (1984). The dose response characteristics of the acute non diuretic peripheral vascular effects of frusemide in normal subjects. *Br. J. clin. Pharmac.*, **18**, 75–81.

Johnston, G. D., Nicholls, D. P., Leahey, W. J. & Finch, M. B. (1983b). The effects of captopril on the acute vascular responses of frusemide in man. *Clin. Sci.*, **65**, 359–363.

Johnston, G. D., O'Connor, P. C., Nicholls, D. P., Leahey, W. J. & Finch, M. B. (1985). The effects of propranolol and digoxin on the acute vascular responses to frusemide in normal man. *Br. J. clin. Pharmac.*, **19**, 417–421.

Lal, S., Murtagh, J. G., Pollock, A. M., Fletcher, E. & Binnion, P. F. (1969). Acute haemodynamic effects of frusemide in patients with normal and raised left atrial pressure. *Br. Heart J.*, **31**, 711–717.

Olsen, U. B. & Ahnfelt-Ronne, I. (1976). Bumetanide induced increase of renal blood flow in conscious dogs and its relation to local hormones (PGE, kallikrein and renin). *Acta Pharmac. Tox.*, **38**, 219–228.

Ostergaard, E. H., Magnussen, M. P., Nielson, E., Eilertsen, E. & Frey, H. H. (1972). Pharmacological properties of 3n butylamino-4 phenoxy-5-sulfamylbenzoic acid (bumetanide), a new potent diuretic. *Arzneimittel-Forsch.*, **22**, 66–72.

Pedrinelli, R., Magagua, A., Arzilli, F., Sassano, P. & Salvetti, A. (1980). Influence of indomethacin on the natriuretic and renin stimulating effect of

bumetanide in essential hypertension. *Clin. Pharmac. Ther.*, **6**, 722–731.

Pierucci, A., Simonetti, B. M., Stirati, G. & Cinotti, G. A. (1980). Effects of bumetanide upon PRA and urinary kallikrein excretion in normal subjects before and after indomethacin treatment. *Minerva Nefrologia*, **27**, 421–424.

Ramirez, A. & Abelmann, W. H. (1968). Hemodynamic effects of diuresis by ethacrynic acid. *Arch. int. Med.*, **121**, 320–325.

Schlossmann, K. (1974). Pharmakokinetik der Diuretika. In *Diuretika*, eds. Hostmann, P. & Schlossmann, K., pp. 28–43. Stuttgart: Georg Thieme Verlag.

Sigurd, B., Bollerup, A. C., Hesse, B. & Valentin, N. (1975). Investigations with intravenous bumetanide. *Postgrad. med. J.*, **51** (Suppl. 6), 27–34.

Velasques, M. T., Wan, S. H. & Maronde, R. F. (1978). Bumetanide-induced rise in plasma renin activity. *Clin. Pharmac. Ther.*, **24**, 186–191.

Whitney, R. J. (1953). The measurement of volume changes in human limbs. *J. Physiol.* (Lond.), **121**, 1–27.

Wright, B. M. & Dore, C. F. (1970). A random zero sphygmomanometer. *Lancet*, **i**, 337–338.

Ziacchi, V., Rossi, A. & Lomanto, B. (1981). Haemodynamic modifications induced by intravenous bumetanide in congestive heart failure. *J. ital. Cardiol.*, **11**, 104–109.

(Received 17 June 1985, accepted 13 November 1985)