

LETTER TO THE EDITOR

**DIURETIC ACTIVITY OF 3-N-BUTYLAMINO-4-PHOENOXY-5-SULPHAMYL
BENZOIC ACID (BUMETANIDE) IN HAMSTER**

Sir,

Bumetanide is a 3-aminobenzoic acid derivative. Of the several analogues having various substituents which are about equally active in test animals (3), Ostergaard *et al.* (5) selected 3-n-butylamino-4-phenoxy-5-sulphamyl benzoic acid (bumetanide) and studied its pharmacological properties, including its diuretic action in rats and dogs. Besides the diuretic effect, bumetanide displayed hardly any significant pharmacological activity. It is almost inactive in rat, except at extremely high doses. In the dog, it is about 100 times more active when given orally. In the present study, its diuretic activity in hamster is described. It is a potent diuretic after oral administration in hamster. Its type of action is comparable with furosemide but it is nearly 40 to 80 times more active than furosemide in relation to excretion of water and sodium respectively.

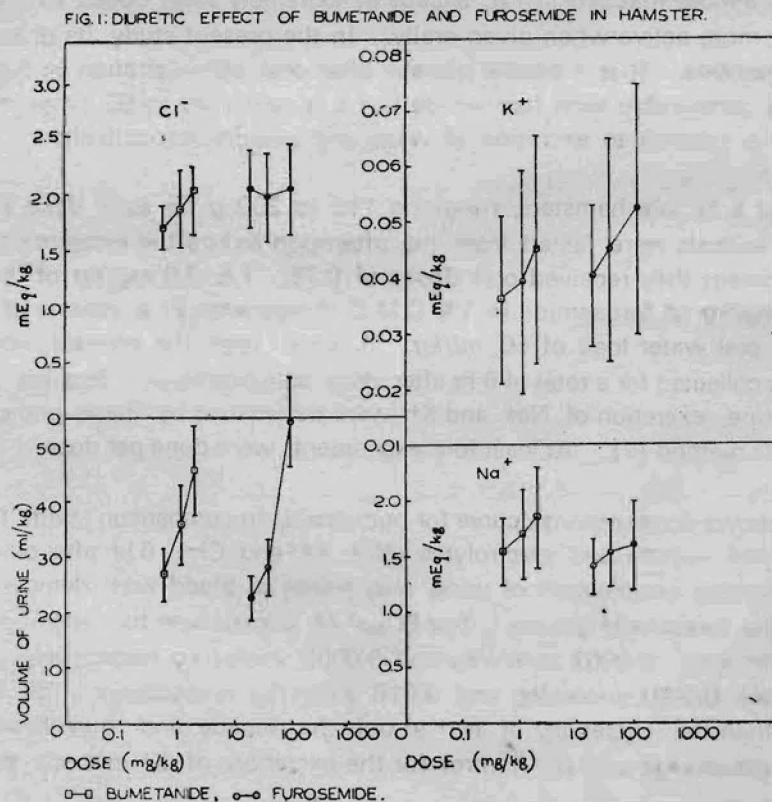
Groups of 6 female hamsters, weighing 150 to 200 g for each dose of the drug were used. The animals were fasted from the afternoon before the experimental day. On the day of experiment they received oral doses of 0.75, 1.5, 3.0 mg/kg of bumetanide and 30, 60, 120 mg/kg of furosemide in 1% C.M.C suspension in a volume of 10 ml/kg, together with an oral water load of 50 ml/kg. A week later, the animals were crossed over. Urine was collected for a total of 6 hr after drug administration. Besides measuring the volume of urine, excretion of Na⁺ and K⁺ were determined by flame photometry and Cl⁻ by Whitehorn's method (7). At least four experiments were done per dose.

Figure 1 shows dose response curve for bumetanide in comparison with furosemide for excretion of urine volume and electrolytes (Na⁺, K⁺ and Cl⁻) 6 hr after oral administration. On qualitative examination of urine, only traces of blood was detected in both the bumetanide and furosemide groups. The EC_{50s} of bumetanide for excretion of urine volume and of Na⁺ were 0.0002 moles/kg and 0.0002 moles/kg respectively and those of furosemide were 0.0091 moles/kg and 0.018 moles/kg respectively. The excretion of Cl⁻ was more than the excretion of Na⁺ in both furosemide and bumetanide group. There was not much change over the control for the excretion of K⁺ in both the groups.

Although a sulphonamide compound the structure of bumetanide differs from the benzothiadiazines and related diuretics such as furosemide in possessing a phenoxy (C_6H_5O) group rather than a chloro or trifluoromethyl (CF_3) substituent ortho to the sulfamyl group (4).

Ostergaard *et al.* (5) reported that the diuretic activity of bumetanide was 40 to 60 times greater than that of furosemide in unanaesthetised dog, using graded iv doses. Bumetanide is ineffective in the rat where it is extensively metabolised (1,5). Bumetanide given intravenously produced no greater response than oral administration indicating that no advantage can be obtained from parenteral administration (6).

Bumetanide produced a rapid, intense and shortlasting diuretic response with a pattern of salt and water excretion resembling that of furosemide in hamster. The maximum amount of water, Na^+ and Cl^- that can be excreted by this group is considerably higher than with thiazide diuretics, and excretion of K^+ remains low. Another characteristic



which bumetanide shares with furosemide is that the excretion of chloride was always more than that of sodium.

In our study, bumetanide is nearly 40 and 80 times more active than furosemide in relation to the excretion of water and Na^+ respectively. This is explained by the tissue distribution of the two agents. Comparative tissue distribution indicates a 3-fold greater uptake of bumetanide by kidney giving a partial explanation, since a greater proportion of the dose reaches the target organ (2). In conclusion as in dog, bumetanide also displays higher diuretic activity than furosemide in hamsters on oral administration.

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REFERENCES

1. Asbury, M.J., P.B.B. Gatanby, S. Osullivan and E. Bourke. Bumetanide, potent new loop diuretic. *Br. Med. J.*, **1** : 211-213, 1972.
2. Cohen, Michael, R. Elaine Hinsch, Ronald Vergona, John Ryan, Stanley, J. Kolis and Morton A. Schwartz. A comparative diuretic and tissue distribution study of bumetanide and furosemide in the dog. *J. Pharmacol. Exp. Ther.*, **197** : 697-702, 1976.
3. Feit, P.W. Aminobenzoic acid diuretics, 2,4-substituted-3-amino-5-sulfamylbenzoic acid derivatives. *J. Med. Chem.*, **14** : 432-439, 1971.
4. Feit, P.W., O.B.T. Nilsen and H. Bruun. Structure activity studies on sulfamyl diuretics. *J. Med. Chem.*, **15** : 437-440, 1972.
5. Ostergaard, E.H., M.P. Magnussen, C.K. Nielsen, E. Eilertsen and H.H. Frey. Pharmacological properties of 3-n-butylamino-4-phenoxy-5-sulfamylbenzoic acid (bumetanide), a new potent diuretic. *Arzneim Forsch. (Drug Res.)*, **22** : 66-72, 1972.
6. Olesen, K.H., B. Sigurd, E. Steiness and A. Leth. Bumetanide, a new potent diuretic. *Acta Med. Scand.*, **193**: 119-131, 1973.
7. Whitehorn, J.C. *J. Biol. Chem.*, **45** : 449, 1921. Estimation of chloride in urine as described in "Practical Biochemistry for Medical Students" By P.G. Tikekar, 5th edition, Bharat Book Corporation, Bombay, page 142.