The acute vascular effects of frusemide in heart failure

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Introduction

Diuretics effectively treat the sodium and water retention found in the syndrome of heart failure. When given intravenously, the loop diuretic frusemide brings about rapid symptomatic relief, an effect preceding the increase in urinary sodium and water output by up to 30 min.

In 1966, Weinstein & Solis-Gil [1] reported that the use of frusemide led to symptomatic improvement shortly after its administration. They proposed that a 'diuresis' was occurring through the skin, as their patients did not exhibit increased urine output before the improvement was noted, but instead seemed to sweat excessively. In 1967, Biagi & Bhapat [2] put forward the hypothesis of pulmonary venous dilatation as the mechanism of frusemide's action. In 1969, Bhatia *et al.* [3] studied this hypothesis by administering intravenous frusemide to patients with altitude induced pulmonary oedema. Yet it was not until the study by Dikshit *et al.* [4] in 1973 that this beneficial effect was shown to be due to the dilatation of peripheral capacitance vessels.

Since these early case reports and studies, the events preceding diuresis after frusemide administration have been widely studied. A venodilatory response has been reproduced with and without success. Any such effect is widely believed to occur due to the release of prostaglandins by the veins. The effect of frusemide on veins has been shown to be mostly an indirect one, but frusemide may also display direct venodilator properties.

Vasoactivity of frusemide

Venodilatation in response to frusemide

In 20 patients with acute heart failure secondary to myocardial infarction, Dikshit *et al.* [4] demonstrated that frusemide had a peripheral vascular effect clearly separate from the diuretic effect previously described. They showed that venous capacitance, as measured in the calf, increased and so, to a lesser extent, did peripheral blood flow. More importantly, however, they observed that both venous capacitance and blood flow in the calf had increased in just 5 min following the injection of frusemide. At this time, the mean urinary output was only 20 ml, and peak urine flow did not occur until 30 min after the patients had been given frusemide. At 5 min, the volume of urine produced was deemed insufficient to account for these haemodynamic responses. Also recorded by Dikshit and colleagues was a reduction in the right atrial pressure and the pulmonary capillary wedge pressure, presumably reflecting a systemic venodilator effect of frusemide. Thus, frusemide was shown to have reduced preload acutely, before diuresis had occurred and affected haemodynamics. This effect on the pulmonary capillary wedge pressure has also been reproduced by Franciosa *et al.* [5] in patients with acute left ventricular failure.

This early venodilatation in response to frusemide has also been seen in healthy volunteers, placed on a salt restricted diet [6–9] in an attempt to mimic the functional state of the kidney in chronic heart failure. The natiuretic effect of frusemide was dose dependent but its venodilatory effect did not seem to show the same dose–dependency [7]. A dose greater than 20 mg did not result in a further increase in venous capacitance.

Other loop diuretics have also been examined for the ability to produce acute venodilatation. Bumetanide does not appear to have the ability to increase venous capacitance [8]. In another study, 40 mg frusemide and 12 mg piretanide both produced venodilatation, although this study only used five healthy subjects and a slightly different technique to measure venodilatation [10]. We are unaware of any larger studies with piretanide, and its ability to induce venodilatation must be in doubt.

Direct and indirect venodilatation

In an attempt to clarify whether acute venodilatation is a direct or indirect effect, frusemide has been infused into the dorsal hand veins of healthy volunteers. It has been

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shown in one study to cause direct dilatation [8], and in another to have no effect [11]. The difference between these studies is most likely to be due to the use of a different preconstrictor and perhaps a different degree of preconstriction before the infusion of frusemide. It would seem that frusemide may have direct venodilator properties, but it is more likely that the acute venous effect of frusemide is predominantly indirect.

Acute arterial constriction in response to frusemide

Although frusemide seems to have an acute venodilator effect which may be beneficial to the failing heart its action on arteries may be detrimental. Studies examining patients with chronic heart failure have found that frusemide principally causes arterial vasoconstriction. These studies are often overlooked among the large number of studies which describe a mainly beneficial venodilatory action in patients with acute heart failure secondary to myocardial infarction or in salt depleted volunteers.

In 1985, Francis *et al.* [12] gave intravenous frusemide to patients with chronic heart failure (who were receiving digoxin and diuretic therapy for their heart failure) and found no symptomatic improvement. Indeed potentially deleterious systemic effects were noted, i.e. an increase in heart rate, mean arterial pressure, right atrial and left ventricular filling pressure, and a decrease in stroke volume. All observations were before the onset of diuresis suggesting an acute response characterized by arterial constriction.

Kiely *et al.* [13] studied the response to frusemide of the pulmonary vascular system in healthy volunteers. Pulmonary and systemic vascular resistance (estimated by means of a technique using duplex ultrasound) rose in the subjects after receiving frusemide and increasing levels of hypoxia augmented this effect. This response could be detrimental in patients with chronic heart failure and even more so in those with acutely decompensated heart failure.

The acute arterial constrictor response to frusemide, as with the venodilatory response, is most probably due to an indirect effect. The only study, which to our knowledge has reported the effect of an intra-arterial infusion of frusemide, found that forearm blood flow remained unchanged [8]. However, as healthy, salt replete volunteers were examined, the possibility that frusemide may be directly active in arteries in patients with chronic heart failure (or acute heart failure secondary to myocardial infarction) cannot be excluded.

In summary, it would appear that in patients with acute heart failure secondary to myocardial infarction and in salt depleted volunteers, the beneficial venodilatory response to frusemide predominates over arterial constriction. However in those with chronic heart failure, a venous relaxant effect has not been demonstrated readily and a detrimental arterial vasoconstrictor effect seems to predominate, manifested as haemodynamic deterioration in these studies.

Mechanism of venous and arterial responses

Reports on the mechanism of any acute venodilatory effect brought about by intravenous frusemide are somewhat inconsistent. Again patients with chronic heart failure, acute heart failure secondary to myocardial infarction and sodium-depleted healthy volunteers have all been studied. Yet from these different groups, enough consistent observations have arisen to allow us to determine some of the events which follow the injection of frusemide.

Plasma renin activity has been consistently noted to rise in the minutes following the administration of frusemide [14], irrespective of whether venodilatation [4, 5, 15,] or arterial constriction [12] predominates. Prostaglandins are thought to be responsible for promoting the acute release of renin into the circulation [16]. Inhibition of prostaglandin synthesis by cyclooxygenase inhibition diminishes the level of plasma renin activity after frusemide [17, 18]. Plasma renin activity but not the venodilator effect increases with dose [7]. This seems to suggest, that the ability of frusemide to stimulate renin release is not instrumental in its venodilator action. However bumetanide, which does not appear to cause venodilatation, also does not cause an acute rise in plasma renin activity following intravenous administration [6]. Unfortunately no other studies have addressed the lack of association between renin release and venous relaxation, but it may simply be due to a finite degree of dilatation in the veins being achieved before the limit of renin release is reached.

Following the acute release of renin it has been assumed that angiotensin II is formed. Indeed pre–treatment of patients with an ACE inhibitor causes the venodilatation in response to frusemide in salt depleted subjects to diminish [19]. In patients with chronic heart failure, the arterial constricting effect is similarly reduced [20].

Angiotensin II is an arterial [21] and venous vasoconstrictor [21, 22] which induces contraction in internal mammary arteries greater than that in saphenous vein segments at the same concentration [23]. This effect is probably mediated through the AT1 receptor [24–26]. Activation of the AT2 receptor is thought to counter many of the effects of the AT1 receptor and therefore may cause dilatation in response to angiotensin II [27–29]. When the endothelium is removed from a vein segment, the constrictor response to angiotensin II is increased [21]. Human venous endothelial cells can produce prostaglandins, *in vitro*, in response to angiotensin II stimulation [30]. This implies that *in vivo*, the endothelial cell responds to the direct effect of angiotensin II, possibly via the AT2

receptor, by producing prostaglandins as a compensatory response to angiotensin II induced contraction mediated by the AT1 receptor. Prostaglandins, produced by the endothelium would be the obvious candidates through which frusemide induces venodilatation in capacitance vessels. This would also concur with the findings that pre–treatment with cyclooxygenase inhibitors diminishes the acute effects of frusemide [8, 15].

In view of the above, it is probable that frusemide causes prostaglandin mediated release of renin. It has been assumed that angiotensin II is formed as a result. Angiotensin II may cause contraction of the venous and arterial smooth muscle via the AT1 receptor. This effect would, seem to be outweighed in veins, but not arteries, through the relaxation of the smooth muscle in response to dilatory prostaglandins formed by the endothelium as a result of angiotensin II binding to the AT2 receptor. Therefore, in patients with acute heart failure secondary to myocardial infarction and salt depleted volunteers, venodilatation is primarily observed with arterial constriction being less evident. Hence, with venous dilatation rather arterial constriction being dominant, symptomatic relief occurs (before the onset of diuresis).

Yet in patients with chronic heart failure, the venous relaxant effect does not seem to take place, or at least seems to be outweighed by arterial constriction. There is no reason to suppose that this is due to any sort of tolerance. The additional angiotensin II produced by frusemide administration, and resultant arterial constriction, is compensated by venodilatation in patients with acute heart failure secondary to myocardial infarction. However, in patients with chronic heart failure veins may be already compensating for the higher levels of circulating angiotensin II [25]. Further angiotensin II may lead only to deleterious arterial constriction, unopposed by a venous response. Either the veins may be unable to effect any further dilatation, or, they are unable dilate enough to outweigh the effects of arterial vasoconstriction and produce a beneficial haemodynamic response.

The different outcome between salt deplete subjects and chronic heart failure patients is harder to explain. Possibly, chronically high angiotensin II concentrations could alter angiotensin II receptor density and the seemingly delicate balance between angiotensin II mediated contraction of arteries and compensatory dilatation in veins. Chronic structural changes may occur in the veins of patients with chronic heart failure and this could alter their responsiveness to frusemide.

Direct venodilatation

Most evidence would point to an indirect method of venodilatation for frusemide. Some investigators have found frusemide to be a direct *in vivo* dilator of veins [8], whilst others have not [11]. Pickkers *et al.* [8] found frusemide to have a direct dilatory effect on dorsal hand veins of normal volunteers and that this effect was independent of nitric oxide by inhibiting nitric oxide synthase with *N*-monomethyl-L-arginine (L-NMMA). The concentration of frusemide at the point in the vein where venodilatation was measured, was far less than the supra-therapeutic concentrations used by Ellory & Stewart [31] to inhibit the $Na^+/K^+/2$ CL-ion channels in human red blood cells. Thus Pickkers *et al.* [8] concluded that inhibition of these channels was not the mechanism by which frusemide was working. The direct effect of frusemide was inhibited by cyclooxygenase inhibition and was therefore deemed to be prostaglandin dependent. This finding concurs with that of investigators who advocate an indirect mechanism of action. Furthermore, in 1998, Stanke and colleagues [23] reported that frusemide in therapeutic concentrations can inhibit the response to angiotensin II of internal mammary artery and saphenous vein segments *in vitro*. Therefore, it can be speculated that frusemide might have very weak angiotensin receptor blocking properties.

The acute haemodynamic response to frusemide would seem to depend upon a balance between indirect and direct effects, with indirect mechanisms predominating. The balance between these mechanisms would appear to depend on the type of patient studied. The acute haemodynamic response in different patient groups would therefore appear to be dependent on how these mechanisms equilibrate.

Frusemide and drug therapy in heart failure

As the mechanism of action of frusemide involves the activation of the renin–angiotensin system and prostaglandin production it is possible that other drugs used in the treatment of heart failure may augment or attenuate any acute venodilatory effect produced by frusemide. The potential for pharmacological interaction is enormous.

Digitalis has been shown to be capable of inhibiting frusemide induced renin release [32]. Digoxin should therefore attenuate the acute rise in venous capacitance in the forearm capacitance vessels produced by frusemide. Yet in a study of salt depleted healthy volunteers, pretreatment with digoxin did not inhibit the increase in venous capacitance and vascular resistance after frusemide [9].

As with digoxin, propranolol has been shown to inhibit the acute renin release caused by frusemide [33]. Yet unlike digoxin, this does translate into an inhibition of the acute rise in venous capacitance and forearm vascular resistance brought about by frusemide [9]. This is obviously potentially important and needs confirmation.

Indomethacin has been shown to diminish the

venodilatory effects of frusemide [8, 15] but not the arterial vasoconstriction [15]. Most patients with chronic heart failure take aspirin as an anti–platelet agent. Aspirin being a cyclooxygenase inhibitor like indomethacin, could possess the ability to inhibit the acute venodilatation produced by frusemide. Wilson *et al*. [14] studied the effect of low dose aspirin (0.5 mg kg^{-1} day^{-1} and 1.5 mg kg^{-1} day^{-1}) on frusemide induced renin release. At this dose acute renin release was not inhibited but platelet cyclooxygenase function was. Therefore it may be possible to preserve the cardioprotective effects of aspirin yet not interfere with the acute venodilatation produced by frusemide.

The greatest potential for interaction with frusemide is with those drugs which modify the renin–angiotensin system or the response to angiotensin II. ACE inhibitors limit the acute venodilatation [19] and arterial constriction [20] produced by frusemide. More recently the advent of AT1 selective antagonists has provided an alternative method of inhibiting the actions of angiotensin II. Losartan can inhibit the arterial constriction produced by angiotensin II in the human forearm [24, 25]. It is possible that frusemide induced venodilatation could be similarly augmented by AT1 selective receptor antagonists, should angiotensin II mediate prostaglandin synthesis via the AT2 receptor.

Conclusions

A number of factors have been shown to determine the precise response to an intravenous bolus of frusemide in acute heart failure. A patient's sodium status and degree of renin-angiotensin system activation primarily determine the acute haemodynamic response witnessed. It would also appear that the length of time for which such activation has been present also alters the response to frusemide. Finally concomitant medication taken by the patient will also have a bearing on the haemodynamic response in a patient in the minutes following frusemide administration. All of these variables change the delicate balance of basal vascular tone and hence the level of arterial or venous tone from which frusemide may effect a response, irrespective by which mechanism it may ultimately prove to operate.

References

1 Weinstein FR, Solis-Gil V. The treatment of acute pulmonary edema with frusemide. *Curr Ther Res* 1966; **8**: 435–440.

2 Biagi RW, Bapat BN. Frusemide in acute pulmonary oedema. *Lancet* 1967; **i**: 849.

3 Bhatia ML, Singh I, Manchanda SC, Khanna PK, Roy SB. Effect of frusemide on pulmonary blood Volume. *Br Med J* 1969; **2**: 551–552.

4 Dikshit K, Vyden JK, Forrester JS, Chaterjee K, Prakash P, Swan HJC. Renal and extrarenal haemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N Engl J Med* 1973; **288**: 1087–1090.

5 Franciosa JA, Silverstein SR. Haemodynamic effects of nitroprusside and furosemide in left ventricular failure. *Clin Pharmacol Ther* 1982; **32**: 62–69.

6 Johnston GD, Nicholls DP, Kondowe GB, Finch MB. Comparison of the acute vascular effects of frusemide and bumetanide. *Br J Clin Pharmacol* 1986; **21**: 359–364.

7 Johnston GD, Nicholls DP, Leahey WJ. The dose–response characteristics of the acute non-diuretic peripheral vascular effects of frusemide in normal subjects. *Br J Clin Pharmacol* 1984; **18**: 75–81.

8 Pickkers P, Dormans TPJ, Russel FGM, *et al*. Direct vascular effects of furosemide in humans. *Circulation* 1997; **96**: 1847–1852.

9 Johnston GD, O'Conner PC, Nicholls DP, Leahey WJ, Finch MB. The effects of propranolol and digoxin on the acute vascular responses to frusemide in normal man. *Br J Clin Pharmacol* 1985; **19**: 417–421.

10 Valette H, Duhaze P, Apoil E. Plethysmographic studies with frusemide and piretanide in healthy volunteers. *Br J Clin Pharmacol* 1979; **7**: 219.

11 Harada K, Ohmori M, Fujimura A, Ohashi K. No evidence of a direct venodilatory effect of furosemide in healthy human subjects. *J Clin Pharmacol* 1996; **36**: 271–273.

12 Francis GS, Siegal RM, Goldsmith SR, Olivari MT, Levine B, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. *Ann Int Med* 1985; **103**: 1–6.

13 Kiely DG, Cargill RI, Lipworth BJ. Effects of frusemide and hypoxia on the pulmonary vascular bed in man. *Br J Clin Pharmacol* 1997; **43**: 309–313.

14 Wilson TW, McCauley FA, Wells HD. Effects of low-dose aspirin on responses to furosemide. *J Clin Pharmacol* 1986; **26**: 100–105.

15 Johnston GD, Hiatt WR, Nies AS, Payne A, Murphy RC, Gerber JG. Factors modifying the early nondiuretic vascular effects of furosemide in man. *Circ Res* 1983; **53**: 630–635.

16 Goldiner WH, Valente WA, Hamilton BP, Mersey JH. The effect of prostaglandin inhibition on renin release. *J Lab Clin Med* 1981; **98**: 929–937.

17 MacKay IG, Muir AL, Watson ML. Contribution of prostaglandins to the systemic and renal vascular response to frusemide in normal man. *Br J Clin Pharmacol* 1984; **17**: 513–519.

18 Tan SY, Mulrow PJ. Inhibition of the renin-aldosterone response to furosemide by indomethacin. *J Clin Endocrinol Metab* 1977; **45**: 174–176.

19 Johnston GD, Nicholls DP, Leahey WJ, Finch MB. The effects of captopril on the acute vascular responses to frusemide in man. *Clin Sci* 1983; **65**: 359–363.

20 Goldsmith SR, Francis G, Cohn JN. Attenuation of the pressor response to intravenous frusemide by angiotensin converting enzyme inhibition in congestive heart failure. *Am J Cardiol* 1989; **64**: 1382–1385.

21 Barker JE, Anderson J, Treasure T, Piper PJ. Influence of endothelium and surgical preparation on responses of human saphenous vein and internal thoracic artery to angiotensin II. *Br J Clin Pharmacol* 1994; **38**: 57–62.

22 De Pasquale NP, Burch GE. Effect of angiotensin II on the intact forearm veins of man. *Circ Res* 1963; **13**: 239–245.

23 Stanke F, Devillier P, Breant D, *et al*. Frusemide inhibits angiotensin II-induced contraction on human vascular smooth muscle. *Br J Clin Pharmacol* 1998; **46**: 571–575.
24 Baan J, Chang PC, Vermeij P, Pfaffendorf M, van Zweiten PA. Venoconstriction by angiotensin II in the human forearm is inhibited by losartan but not by nicardipine. *J Cardiovasc Pharmacol* 1998; **31**: 50–55.
25 Newby DE, Masamouri S, Johnston NR, Boon NA, Webb DJ. Endogenous angiotensin II contributes to basal peripheral vascular tone in sodium deplete but not sodium replete man. *Cardoivasc Res* 1997; **36**: 268–275.
26 Newby DE, Goodfield NER, Flapan AD, Boon NA, Fox KAA, Webb DJ. Regulation of peripheral vascular tone in patients with heart failure: contribution of angiotensin II. *Heart* 1998; **80**: 134–141.
27 Scheuer DA, Perrone MH. Angiotensin type 2 receptors mediate depressor phase of biphasic pressure response to angiotensin. *Am J Physiol* 1993; **33**: R917–R923.
28 Hein L, Barsh GS, Pratt RE, DzauVJ, Kobilka BK. Behavioural and cardiovascular effects of disrupting the angiotensin type-2 receptor gene in mice. *Nature* 1995; **377**: 744–747.
29 Ichiki T, Labosky PA, Shiota C, *et al*. Effects on blood pressure and exploratory behaviour of mice lacking angiotensin type-2 receptor. *Nature* 1995; **377**: 748–750.
30 Gimbrone MA, Alexander RW. Angiotensin II stimulation of prostaglandin production in cultured human vascular endothelium. *Science* 1975; **189**: 219–220.
31 Ellory JC, Stewart CW. The human erythrocyte Cl-dependent Na-K cotransport system as a possible model for studying the action of loop diuretics. *Br J Pharmacol* 1982; **75**: 183–188.
32 Ferrari M. Effects of digoxin and digoxin plus furosemide on the plasma renin activity of hypertensive patients. *Circ Res* 1979; **44**: 295.
33 Bravo EL, Tarazi RC, Dustan H. On the mechanism of suppressed plasma-renin activity during β-adrenergic blockade with propanolol. *J Lab Clin Med* 1974; **83**: 119–128.