HAEMODYNAMIC EFFECTS OF INTRAVENOUS FRUSEMIDE IN PATIENTS WITH MYOCARDIAL INFARCTION AND LEFT VENTRICULAR FAILURE

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SUMMARY

1. Intravenous frusemide has been given to thirty-five patients with myocardial infarction and clinical signs of left ventricular failure. The haemodynamic changes following frusemide were then observed over the subsequent 6 h.

2. Frusemide produced a large diuresis, which was maximal during the first 2 h but fluid depletion was maintained at 24 h. The greatest diuresis occurred in patients with the highest stroke index.

3. All patients showed a fall in pulmonary artery pressure after frusemide. In patients with evidence of poor left ventricular function (low stroke index, high pulmonary artery pressure) this was associated with little change in stroke index. In patients with less severe impairment of left ventricular function there was an initial fall in stroke index at 1 and 2 h.

4. Six hours after frusemide there was a reduction in both pulmonary artery pressure and systemic arterial pressure; the latter correlated with the volume of the diuresis.

Key words: haemodynamic, frusemide, diuresis, myocardial infarction, left ventricular function.

In hospital practice left ventricular failure accounts for many of the deaths in acute myocardial infarction, particularly since coronary care units have improved the detection, treatment and prevention of arrhythmias. The majority of patients with myocardial infarction have some clinical or radiological evidence of left ventricular failure (McNicol, Kirby, Bhoola, Everest, Price & Freedman, 1965; Tattersfield, McNicol, Shawdon & Rolfe, 1969). It is generally accepted that severe heart failure should be treated energetically but it is not clear whether less severe cardiac failure should be treated or what the effects of treatment will be in these patients. In clinical practice the patients may receive either intravenous fluid or diuretic therapy, two apparently contradictory forms of treatment. Fluid infusion is often given as a...
vehicle for drugs such as lignocaine but may also be given in an attempt to ensure that ventricular filling pressures are adequate (Swan, Danzig, Sukumalchantra & Allen, 1969; Coltart & Hamer, 1971). Alternatively, diuretic therapy may be given routinely as treatment for heart failure. With more detailed knowledge of the consequences of both forms of treatment, therapy could be administered on a more rational basis. We have looked at the haemodynamic and respiratory changes which follow a potent intravenous diuretic, frusemide, in patients with myocardial infarction and left ventricular failure but without cardiogenic shock. In this paper we report the haemodynamic changes.

PATIENTS AND METHODS

The study was carried out on thirty-five male patients within 72 h of myocardial infarction. Full clinical and diagnostic details are given elsewhere (Tattersfield, McNicol & Sillett, 1972: patients 1–35). All the patients had acute myocardial infarction and persistent basal lung crepitations but did not have cardiogenic shock. They were not overtly anxious or agitated and did not have any disturbance of heart rhythm apart from occasional ventricular ectopic beats. The only exception was one patient with complete heart block, who was paced for 12 h before the study and maintained at 90 beats/min throughout the study. No patient was known to have heart or chest disease apart from ischaemic heart disease and none was receiving any therapy such as digitalis or adrenergic blocking agents which would alter haemodynamic responses. Six patients received a steady lignocaine infusion throughout the study. No patient was studied within 4 h of receiving atropine or a major analgesic.

The patients conforming to these criteria were given an explanation of the purpose of the study and the procedure involved. Only patients who accepted willingly were studied. Great care was taken to allay anxiety to make the patient as relaxed and basal as possible.

Protocol

A fine polyethylene catheter (PE60) was introduced into an antecubital vein and flow guided with continuous pressure recording into the pulmonary artery. A short cannula (Becton-Dickinson, Longdewel 18G) was inserted into the adjacent brachial artery. The patients then rested for at least 30 min. Fluid intake was measured but not restricted and patients were asked to pass urine whenever they wished and were also required to do so at 2 h intervals after frusemide. Measurements were not made for at least 10 min after passing urine and 30 min after meals. Patients were asked to have only light meals and did not receive oxygen.

Base-line measurements were made in duplicate over at least a 1–2 h period and frusemide was not given until stable values were obtained. The patient was then asked to pass urine and 80 mg of frusemide was given intravenously over 60 s. Haemodynamic measurements were then repeated 1, 2, 4 and 6 h after frusemide.

Methods

The methods used to measure and calculate cardiac output, intravascular pressures and packed cell volume have been described in detail elsewhere with the standard error of duplicate estimations (Tattersfield et al., 1972). Cardiac output was measured by the dye dilution technique, 5 mg of indocyanine green being injected into the pulmonary artery and blood sampled from the brachial artery. Intravascular pressures were measured with the patient...
at 45° from horizontal with reference zero as mid-thoracic point on a perpendicular line dropped from the anterior end of the third rib. If the patient's position had altered by less than 10–15°, zero was reset rather than disturb the patient, but if a larger change had occurred the patient was repositioned at 45° and 5 min was allowed to elapse before pressure was measured.

**Calculations**

Cardiac index (CI) was derived by dividing cardiac output (litres) by surface area (metres) and stroke index (SI) by dividing CI by heart rate (HR). Peripheral vascular resistance (PR) was obtained by dividing mean systemic arterial pressure (SAP) by cardiac output.

Standard statistical methods were used to calculate variance, and standard error of the mean, and the Spearman rank correlation coefficient to test correlation. To study the changes after frusemide, values have been compared to mean pretreatment values. For significance testing using the null hypothesis it has been assumed that the pretreatment values would have continued unchanged over the 6 h period in the absence of frusemide. This assumption is discussed below.

**RESULTS**

None of the thirty-five patients experienced side-effects at the time frusemide was given. In the following 12 h five patients had clinical complications. In three of these patients there was further chest pain at 2, 3 and 6 h after frusemide but in none was there any evidence of further infarction. One patient developed acute pulmonary oedema 2 h after frusemide and atrial tachycardia occurred in one patient at 10 h. Four patients died later during their stay in hospital, at 5, 6, 6 and 14 days after infarction.

**Urine output and fluid balance**

Frusemide produced a large diuresis, which ranged from 300 to 1900 ml during the first 2 h. The mean urine output for fifty patients with myocardial infarction who did not receive diuretics was 110 ml in 2 h. Table 1 shows the mean fluid balance studies for thirty-two patients, no account being taken of insensible water loss. Fluid depletion was maximum during the first 2 h but was maintained at both 6 and 24 h. All times refer to the time after the injection of frusemide. Individual fluid balance figures at 24 h ranged from 0 to −4300 ml.

**Haemodynamic measurements**

As it was not possible to perform all measurements on each patient the actual number carried out at each time is given in Table 2.

<table>
<thead>
<tr>
<th>Time after frusemide (h)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume (ml)</td>
<td>910</td>
<td>1240</td>
<td>1460</td>
<td>2380</td>
</tr>
<tr>
<td>Fluid intake (ml)</td>
<td>70</td>
<td>190</td>
<td>280</td>
<td>1110</td>
</tr>
<tr>
<td>Fluid balance (ml)</td>
<td>−840</td>
<td>−1050</td>
<td>−1180</td>
<td>−1270</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td></td>
<td></td>
<td>2 h</td>
</tr>
<tr>
<td>----------------</td>
<td>----------</td>
<td>--------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>No. of</td>
<td>P</td>
<td>Mean</td>
</tr>
<tr>
<td>PCV (%)</td>
<td>1.73</td>
<td>11</td>
<td>0.01</td>
<td>1.27</td>
</tr>
<tr>
<td>CI (l min⁻¹ m⁻²)</td>
<td>-0.15</td>
<td>17</td>
<td>0.05</td>
<td>-0.03</td>
</tr>
<tr>
<td>SI (ml beat⁻¹ m⁻²)</td>
<td>-4.4</td>
<td>17</td>
<td>0.0025</td>
<td>-4.9</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>5.0</td>
<td>20</td>
<td>0.0025</td>
<td>7.1</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>-2.8</td>
<td>22</td>
<td>0.0005</td>
<td>-3.1</td>
</tr>
<tr>
<td>Mean SAP (mmHg)</td>
<td>3.05</td>
<td>26</td>
<td>0.005</td>
<td>0</td>
</tr>
<tr>
<td>PR (units)</td>
<td>3.5</td>
<td>16</td>
<td>0.0025</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Frusemide in myocardial infarction

Packed cell volume (Fig. 1). Packed cell volume (PVC) was significantly raised at 1 and 2 h but not at 6 h.

Cardiac index, stroke index and heart rate (Fig. 1). There was a small but significant fall in cardiac index at 1 h but it then gradually rose to slightly above pretreatment values at 6 h, though this was not statistically significant. Stroke index showed a large initial fall of 16% but this also returned gradually to pretreatment values. Heart rate increased and remained above the control level throughout the period of observation.

Pulmonary artery pressure (Fig. 2). There was a small but consistent fall in pulmonary artery pressure (PAP) at 1 h and this was maintained at 6 h. Continuous pressure measurements during the first hour in four patients showed that the fall occurred gradually during this time. In five patients simultaneous measurements of right atrial pressure and PAP were made from

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Fig. 1. Mean change in packed cell volume (eleven patients), heart rate (twenty patients), cardiac and stroke index (seventeen patients) after frusemide. O, Values significantly different ($P<0.05$) from pretreatment values.
a second flow-guided catheter and both measurements showed a similar, parallel fall in pressure after frusemide.

*Systemic artery pressure and peripheral resistance* (Fig. 2). There was an initial rise in SAP and PR but then both showed a gradual fall so that at 6 h SAP was 6 mmHg lower than the pretreatment values.

*Interrelation between fluid balance and haemodynamic changes after frusemide*

It can be seen from Figs. 1 and 2 that the initial findings 1 and 2 h after frusemide often differ from the later findings at 4 and 6 h and these have therefore been considered separately as the initial and late changes.

*Initial changes (1 and 2 h).* The correlation between the initial changes after frusemide and the pretreatment measurements are shown in a correlation matrix (Table 3). Patients with a low pretreatment PAP and high SI had the greatest diuresis and the rise in PCV correlated closely with the urine output. They also showed the largest fall in SI at 1 h (Fig. 3). The three patients with the lowest pretreatment SI showed no fall in SI after frusemide.

*Later changes.* At 6 h the fall in SAP correlated with the extent of fluid depletion (negative fluid balance) \( r = 0.72, P < 0.01 \).
Frusemide in myocardial infarction

Fig. 3. Initial fall in stroke index in seventeen patients after frusemide, related to the pretreatment measurement.

Table 3. Correlation between pretreatment measurements and initial changes after frusemide. Values shown are the Spearman Rank correlation coefficient $r_s$. NS, not significant; * $P<0.05$; ** $P<0.01$. Significance testing has been tested against the null hypothesis, which assumes that the expected correlation is zero.

<table>
<thead>
<tr>
<th>Pretreatment measurements</th>
<th>Diuresis (2 h)</th>
<th>$\Delta$ PCV</th>
<th>$\Delta$ CI</th>
<th>$\Delta$ SI</th>
<th>$\Delta$ PAP</th>
<th>$\Delta$ SAP</th>
<th>$\Delta$ PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV (%)</td>
<td>-</td>
<td>-0.37 NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CI (l min$^{-1}$ m$^{-2}$)</td>
<td>0.47*</td>
<td>-</td>
<td>0.61**</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SI (ml beat$^{-1}$ m$^{-2}$)</td>
<td>0.70**</td>
<td>-</td>
<td>-</td>
<td>0.84**</td>
<td>0.03 NS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>-0.41*</td>
<td>-</td>
<td>-</td>
<td>-0.42*</td>
<td>0.27 NS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean SAP (mmHg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.59**</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diuresis (2 h) (ml)</td>
<td>-</td>
<td>0.8**</td>
<td>0.72**</td>
<td>0.66**</td>
<td>0.15 NS</td>
<td>-0.01**</td>
<td>0.76**</td>
</tr>
</tbody>
</table>
DISCUSSION

The study was designed to observe the changes after intravenous frusemide over a 6 h period. The significance of the results has been assessed by comparison with stable pretreatment values, assuming that these were an accurate representation of the observation period and that they would not have altered significantly during the 6 h of the study. The low standard error of duplicate estimations during the pretreatment period (Tattersfield et al., 1972) suggests that both random errors in measurement and biological fluctuations were small and there seems little doubt that the initial changes in the first 2 h must result from frusemide. The assumption is less certain at 4 and 6 h. However, analysis of the few reports of sequential changes after acute myocardial infarction (Murphy, Glick, Schreiner & Yu, 1963; Malmcrona & Varnauskas, 1964; Fluck, Valentine, Treister, Higgs, Reid, Steiner & Mounsey, 1967) permits calculation of the expected changes over this 6 h period and these calculations would lead us to expect no change or a small fall in SI and PAP (<1 ml beat\(^{-1}\) m\(^{-2}\) and <1 mmHg respectively). In the present study SI at 6 h did not differ significantly from the predicted changes or from pretreatment values but the fall in PAP was greater than predicted and greater than the fall observed in patients we have studied not receiving frusemide, so we believe this change is significant and due to frusemide. There are varying reports of the changes in SAP after myocardial infarction (Malmcrona & Varnauskas, 1964; Nager, Thomas & Shillingford, 1967) but the fall of 6 mmHg in 6 h is much greater than any reports in untreated patients and as it correlated with the diuresis it can also be reasonably attributed to frusemide.

The largest diuresis occurred in the patients with the highest CI, in keeping with previous observations of an association between cardiac output and renal blood flow in patients with myocardial infarction (Hutton, Pack, Lindsay & Lawrie, 1970). The diuresis, though maximal in the first 2 h, continued through the 6 h period and fluid depletion was maintained at 24 h. The positive correlation between the volume of the diuresis and rise in packed cell volume suggests that a reduction in plasma volume occurred initially, as recorded in previous studies with frusemide (Wolfer, Schneider, Gattenlohner & Gunther, 1964; Finnerty, Davidov & Kakavitos, 1968), but the subsequent fall in haematocrit at 4 and 6 h despite continuing fluid depletion suggests some re-expansion of plasma volume. This has been observed in oedematous patients receiving long-term frusemide (Jewkes, Burki & Guz, 1970).

Initial changes

The main initial haemodynamic findings after frusemide were a fall in both PAP and SI. This is consistent with most previous acute studies following potent diuretics despite differences in the dose and diuretic used, in patient selection and in the cause and severity of heart failure (Nash, Fitz, Wilson, Kirkendall & Kioschos, 1966; Samet & Bernstein, 1968; Lal, Murtagh, Pollock, Fletcher & Binnion, 1969; Bhatia, Singh, Manchanda, Khanna & Roy, 1969; Scheinman, Brown & Rapaport, 1971; Sjogren, 1970; Dikshit, Vyden, Forrester, Chatterjee, Prakash & Swan, 1973). Some of the apparent differences in the results of previous studies can be explained by the different time-intervals at which measurements were made. There is general agreement that a potent diuretic such as frusemide or ethacrynic acid will cause a fall in PAP and SI initially in the majority of patients with heart failure. Other studies have shown an associated fall in right atrial pressure, as in the present study (Bhatia et al., 1969; Coltart & Hamer, 1971; Dikshit et al., 1973) and in left atrial pressure (Lal et al., 1969; Dikshit et al., 1973).
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It has generally been assumed that the haemodynamic changes after diuretics are due to the resulting fluid depletion causing a fall in venous pressure and thus a fall in stroke volume, and this sequence of events could explain our results (Tattersfield & McNicol, 1970). However, Dikshit et al. (1973) have looked in detail at the early changes after frusemide, and have shown an increase in venous capacitance in calf veins and a fall in left ventricular filling pressure before any appreciable diuresis had occurred. If the changes in calf veins are representative of changes in the venous system as a whole then the haemodynamic consequences of diuretics are probably secondary to both fluid depletion and increased venous capacitance.

![Graph showing initial fall in stroke index after frusemide, related to the initial fall in mean pulmonary artery pressure, in seventeen patients.](image)

**Fig. 4.** Initial fall in stroke index after frusemide, related to the initial fall in mean pulmonary artery pressure, in seventeen patients. ●, Pretreatment value; →, after frusemide.

The data provided by the present study have been used to analyse left ventricular function. In a recent study in patients with myocardial infarction, mean PAP was closer to left ventricular end-diastolic pressure than pulmonary artery diastolic pressure (Rahimtoola, Loeb, Ehsani, Sinno, Chuquimia, Lal, Rosen & Gunnar, 1972). We used mean PAP because we have found it to be a more reproducible measurement when using fine flow-guided catheters. Any change in left ventricular filling pressure will be reflected in a change in mean PAP provided that there is little change in flow, pulmonary vascular resistance or pulmonary venous distensibility. We have therefore looked at the change in SI and mean PAP after frusemide to provide an approximate assessment of left ventricular function (Fig. 4). The results show great variation in the extent to which ventricular function is impaired. Patients on the left-hand side of Fig. 4 with a low PAP and relatively high SI have fairly good function and these patients
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show a large fall in SI with a moderate fall in filling pressure. Patients on the right have a high PAP and low SI, indicating poor ventricular function and they showed little or no change in SI for a similar fall in filling pressure. These findings are similar to other recent studies in patients with myocardial infarction when filling pressure has been altered by fluid infusion or by volume depletion from phlebotomy or diuretics (Russell, Rackley, Pombo Ramos, Hunt, Potanin & Dodge, 1970; Coltart & Hamer, 1971; Broder & Cohn, 1972). In the study by Russell et al. (1970) stroke index increased after fluid infusion only when the left ventricular filling pressure was less than 20 mmHg.

In the experimental situation, increases of filling pressure cause an increase in SI initially, but thereafter further increases produce no change and finally a stage is reached when a further increase in filling pressure causes a fall in SI (Braunwald, 1965). This latter situation, the ‘descending limb’, is inherently unstable and once SI starts to fall the filling pressure will rise rapidly. This sequence clinically would end in acute left ventricular failure. This appeared to be the course of events in the patient who developed acute pulmonary oedema who was one of the two patients with the most depressed ventricular function. The changes are described in more detail elsewhere but during the acute episode there was a rapid rise in mean PAP from 38 to 53 mmHg (Tattersfield, McNicol & Sillett, 1973).

Later changes

The later changes were a fall in SAP, PR and PAP. In hypertensive patients frusemide causes a fall in SAP in the short term and this appears to be due to a reduction in extracellular fluid volume (Davidov, Kakaviatos & Finnerty, 1967; Finnerty et al., 1968; Davidov, Gavrilovitch, Mroczek & Finnerty, 1969). In our patients the close correlation between the volume of the diuresis and the fall in SAP suggests that a similar mechanism may be responsible. The reduction in SAP may cause a reduction in cardiac work, but more direct measurements would be needed to confirm this (Hamer, 1968; Pool & Braunwald, 1968).

Conclusions and clinical implications

Frusemide was not associated with any obvious adverse side-effects and there were few complications in the subsequent 12 h period. In one patient chest pain did occur when cardiac output was maximally reduced and it is possible that the two were causally related. The only serious complication encountered was acute pulmonary oedema in a patient with very poor ventricular function and we do not believe that this can be attributed to frusemide (Tattersfield, McNicol & Sillett, 1973).

It is known that PAP is highest in patients with more extensive pulmonary oedema and these patients have a high mortality (Fluck et al., 1967; Sjogren, 1970; Tattersfield et al., 1972). Frusemide consistently caused a reduction in PAP, which should be beneficial in two ways. It represents a reduction in pulmonary capillary hydrostatic pressure, which will reduce the rate of oedema formation in the lung. Secondly, the ventricle will function at a lower filling pressure, moving away from the ‘descending limb’ and reducing the risk of developing acute left ventricular failure. In the patients most at risk this will be accompanied by little change in SI. The later finding of a reduction in both SAP and PAP was associated with no untoward clinical effect and this may represent a reduction in cardiac work, which would be beneficial. Our results suggest that diuretic therapy as used in this study should be advantageous to patients with more severe heart failure. In patients with relatively good ventricular function the fall in
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PAP is of less value as these patients have less heart failure and a better prognosis and the larger fall in SI is undesirable. There would not seem to be any real indication for a potent intravenous diuretic in these patients. However, in clinical practice the degree of heart failure is usually assessed on clinical and radiological findings which can be difficult to assess, and our findings suggest that if doubt does exist intravenous frusemide should be safe. It would be expected that infusion of fluid to patients with myocardial infarction would cause changes opposite to those produced by diuretics and the studies of fluid infusion by Russell et al. (1970) and Coltart & Hamer (1971) would lend support to this suggestion. Thus all patients would show an increase in filling pressure after the infusion, but only the patients with less-severe heart failure would show an increase in stroke volume and cardiac output. It is arguable whether a higher cardiac output would confer any advantage in the fitter patients with relatively good ventricular function, particularly since it can only be achieved at the expense of increased filling pressures and increased pressure in the pulmonary circulation. This seems to be unnecessary in the good-risk group of patients and could be dangerous in the absence of accurate indices of left ventricular function.

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REFERENCES


