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Original Article

Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study

I. R. Shilliday[1], K. J. Quinn[2] and M. E. M. Allison[1,3]

[1]The Renal Unit, Glasgow Royal Infirmary, [2]Boehringer Mannheim (UK) Pharmaceuticals and [3]The Department of Medicine, The University of Glasgow, Scotland, UK

Abstract

Background. Studies on the role of loop diuretics in patients with acute renal failure (ARF) are largely retrospective, anecdotal, and poorly controlled. We report the results of a prospective, randomized, placebo-controlled, double-blind study examining the effect of loop diuretics on renal recovery, dialysis, and death in patients with ARF.

Methods. Ninety-two patients with ARF were enrolled into the study. All received intravenous dopamine, 2 μg/kg body weight/min throughout, 20% mannitol, 100 ml every 6 h for the first 3 days, and, in a double-blind manner, either torasemide, frusemide, or placebo, 3 mg/kg body weight i.v. every 6 h for 21 days or until renal recovery or death.

Results. Renal recovery, the need for dialysis, and death were no different in the three groups. Patients given a loop diuretic had a significant rise in urine flow rate in the first 24 h compared to placebo ($P=0.02$). Based on the urine flow rate during the first post-medication day patients were divided into two groups—oliguric (<50 ml/h) and non-oliguric ($\geqslant 50$ ml/h). Non-oliguric patients had a significantly lower mortality than oliguric patients (43% *vs* 69%, $P=0.01$). However, they were less ill (APACHE II score 17.2 *vs* 20.6, $P=0.008$) and had less severe renal failure at entry (creatinine clearance 14 ml/min *vs* 4 ml/min, $P<0.0001$).

Conclusion. The use of loop diuretics in oliguric patients with ARF can result in a diuresis. There is no evidence that these drugs can alter outcome.

Key words: acute renal failure; dopamine; loop diuretics; mannitol; oliguria; placebo-controlled trial; randomized

Introduction

In clinical practice the temptation to use high doses of loop diuretics to increase urine flow rate and thereby perhaps ameliorate the progress of ARF in patients with acute oliguria is strong. The evidence for this practice is poor. Most reported studies have been largely anecdotal, retrospective, non randomized or uncontrolled [1–9].

Theoretically, administration of loop diuretics should reduce the energy requirements of the cells of the thick limb of the loop of Henle [10]. These drugs act by inhibiting the $Na^+/2Cl^-/K^+$ pump in the luminal cell membrane resulting in a fall in transcellular sodium transport. Basal Na/K ATPase activity becomes unnecessary and the requirement of the cell for oxygen falls. Brezis *et al.* [11] have shown that reducing active transport with frusemide significantly reduces the damage to the thick ascending limb of Henle's loop in the isolated perfused kidney. It is therefore possible that loop diuretics might 'protect' the cells of the thick ascending limb during the hypoxia which accompanies hypotension and sepsis, frequent predisposing factors in ARF, by reducing the need for energy consumption

In 1983 a new loop diuretic, torasemide (*Boehringer Mannheim)* became available for clinical trials. We set up a prospective, double-blind, randomized, placebo-controlled study in 1990 to compare the effect of frusemide, torasemide, and placebo on the outcome of patients with ARF in Glasgow Royal Infirmary. Our aim was to answer the following questions:

Can loop diuretics convert oliguric ARF to non-oliguric ARF and is this associated with an improvement in outcome?

Can loop diuretics shorten the period of renal failure and reduce the need for dialysis?

Can loop diuretics decrease mortality in ARF?

Subjects and methods

Patient selection

Patients aged 18 years and over referred to the Renal Unit of Glasgow Royal Infirmary with potential ARF were seen by one of us (IS) over a 3-year period. All had potentially

Correspondence and offprint requests to: Dr I.R. Shilliday, Renal Unit, Stobhill Hospital, Balornock Road, Glasgow G21 3UW, UK.

reversible acute intrinsic renal failure as defined by a rise in serum creatinine to over 180 μmol/l (2.03 mg/dl).

When first assessed each patient had bladder catheter drainage established and attempts were made to correct all reversible prerenal factors. A central venous catheter or pulmonary artery catheter was inserted, arterial blood gases were measured and pulse oximetry established. Obstructive uropathy was excluded by ultrasonography.

Those patients whose ARF did not respond to correction of prerenal factors and who were not obstructed were then considered for enrolment into the study. Exclusion criteria are listed in Table 1. Written consent for the study was obtained either from the patient or, if unconscious, from the next of kin, after explaining the various options and risks. The protocol was approved the Ethics committee of Glasgow Royal Infirmary.

Methods

Patients were enrolled into the study at time (t) = 0, after a run-in period of a minimum of 2 h. During this time two consecutive baseline hourly urine collections were made and a blood sample taken. Urine flow rate (ml/h), creatinine clearance (ml/min), and fractional excretion of sodium were calculated. In addition, the serum concentrations of sodium, potassium, calcium, C reactive protein (CRP) and γ glutamyl transferase (γGT) were measured. An APACHE II score was calculated for each patient during the run-in period [12].

Serum biochemistry was repeated at t = 24 h and thereafter on a daily basis at 0800 hours until day 21 or, if sooner, death. In addition, serum osmolality was measured for the first 3 days while mannitol was being used. This value was compared with that obtained by calculating the serum osmolality using the formula:

$(1.86 \times \text{serum sodium}) + \text{urea} + \text{glucose in} + 9$ [13].

Urine was collected every 6 h for the first 48 h and thereafter every 24 h. Hourly urine flow rates were calculated. Creatinine clearance and fractional excretion of sodium were calculated as before.

Treatment

All patients were given dopamine (continuous infusion of 2 μg/kg estimated body weight/min) and mannitol (infusion of 100 ml of a 20% solution for 1 h every 6 h for a maximum of 3 days), and were randomized to receive either frusemide, torasemide, or placebo as an intravenous infusion over 1 h every 6 h for up to 21 days. A previous study suggested that in chronic renal failure, when given intravenously, torasemide is equipotent to frusemide [14]. This study has made the assumption that this holds for ARF. The study drug was given in a double-blind fashion, initially in a dose of 3 mg/kg estimated body weight per dose. If the serum creatinine fell thereafter the dose of study drug was decreased from 3 mg/kg to 2 mg/kg, to 1 mg/kg, and finally stopped as renal function recovered. Both the study drug and dopamine were continued if the patient became dialysis dependent or failed to recover renal function, for a maximum of 21 days, or until death within 21 days. Although the study ended at day 21 the survivors have continued on long-term follow up.

Mannitol was discontinued before day 3 if the patient remained severely oliguric or anuric or became hyperosmolar (measured osmolality–calculated osmolality > 17).

Table 1. Exclusion criteria

Patients with either pre- or post-renal failure.
Patients given a loop or osmotic diuretic within the preceding 12 h.
Patients given frusemide > 100 mg (or equivalent loop diuretic) in the preceding 48 h.
Administration of any investigational substance within 30 days preceding the first dose of the study drug.
Women using inadequate contraception.
Women who were pregnant or lactating.

Statistical analysis

A sample size of 90 was determined to be sufficient to detect a clinically significant difference in outcome between the three groups. The absolute values of the primary variables (recovery, death, or dialysis) were compared using chi-squared analysis. Other variables were analysed by means of analysis of variance (ANOVA).

Results

A total of 278 oliguric patients were assessed for entry into the study, 25% of whom recovered with adequate rehydration. A further 40% were excluded as they did not fit the entry criteria or refused consent. The remaining patients ($n = 96$) were enrolled into the study. Of these, four patients are excluded from the statistical analysis; two died in the run-in phase before the study drug was given, and a further two patients were inappropriately enrolled as they had been in another study within the preceding 30 days. Ninety-two patients are therefore available for analysis on an intention to treat basis. The sample size for each group is as follows: torasemide $n = 30$, frusemide $n = 32$, and placebo $n = 30$.

Table 2 shows demographic and clinical features. Patients in each of the groups were well matched for age, sex, severity of illness, and degree of renal impairment. The causes of acute renal failure were similar in all three groups and have been amalgamated. In 48% ARF occurred in association with overwhelming infection. In 15% ARF was preceded by surgery for an abdominal aortic aneurysm. The remainder were due to a number of causes including rhabdomyolysis, hae-

Table 2. Demographic and clinical features

	Torasemide	Frusemide	Placebo	*P*
Age (years)	58.7 ± 13.8	59.2 ± 16.5	58.3 ± 14.1	0.97
Sex (%)				
Male	53	50	63	
Female	47	50	37	0.55
Apache II score (pre-study)	19.6 ± 4.5	19.1 ± 7.2	18.4 ± 5.8	0.77
Creatinine clearance (ml/min)	10 ± 11	8 ± 9	7 ± 8	0.45
Hourly urine volume (ml/h)	24 ± 18	32 ± 4.5	20 ± 16	0.32

molytic–uraemic syndrome, acute liver failure, and drug toxicity.

Loop diuretic (torasemide or frusemide) vs *placebo*

Table 3 shows the outcome of treatment with loop diuretic or placebo. Patients given torasemide or frusemide had a significant increase in urine output and fractional excretion of sodium in the first 24 h compared to placebo. These patients did not receive any more mannitol than those in the placebo group. However, there was no significant difference in the final outcome (recovery, dialysis, or death) at day 21. Twenty three per cent of placebo patients recovered full renal function without requiring haemodialysis compared to 17% and 28% for patients given torasemide and frusemide respectively ($P=0.56$).

The proportion of patients requiring dialysis were not different in the three groups. The time to dialysis in each group was torasemide 5 ± 5 days, frusemide 5.4 ± 5.7 days, and placebo 2.8 ± 1.2 days ($P=0.35$). Loop diuretics had no effect on the duration of dialysis (torasemide 5.6 ± 4 days, frusemide 13.4 ± 13.7 days, placebo 13.2 ± 10.7 days, $P=0.16$).

The number of patients who died by day 21 without requiring dialysis was 47% and 41% in the torasemide and frusemide groups respectively and 37% in the placebo group ($P=0.73$). The total number of deaths by day 21 (dialysis and non-dialysis dependent patients) was 70% in the torasemide group, 66% in the frusemide group and 50% in the placebo group ($P=0.24$).

Table 4 shows the final outcome of all patients who required dialysis. There was no significant difference between the groups. All patients still alive at day 56 were no longer dialysis-dependent.

The day the serum creatinine started to fall spontaneously was taken as an indication of renal recovery and there is no significant difference between the groups (torasemide day 6.9 ± 6.8, frusemide day 4.5 ± 5, placebo day 7.6 ± 6.7, $P=0.46$).

Actuarial survival curves for the three groups are shown in Figure 1. This is continued up to day 56, since all of the patients who died as a result of their primary illness had done so by then. At day 56 survival between placebo (43%), frusemide(38%), and torasemide (30%) was not significantly different.

Daily median values for serum creatinine, sodium, potassium, calcium and CRP over the 21-day study period were calculated. There was no significant difference in these between the three groups.

Table 3. Outcome of acute renal failure at day 21

	Torasemide (%)	Frusemide (%)	Placebo (%)	*P**
Increase in urine flow	57	48	23	0.02
Renal recovery	17	28	23	0.56
Dialysis	36	31	40	0.87
Death by 21 days (no dialysis)	47	41	37	0.73
Total death by 21 days	70	66	50	0.24

*Chi-square test, placebo *vs* torasemide or frusemide.

Table 4. Final outcome (day 56) of patients requiring dialysis

	Torasemide (%)	Frusemide (%)	Placebo (%)
Death	64	60	42

*Chi-square test, placebo *vs* frusemide or torasemide, $P=0.52$.

Oliguric vs non-oliguric patients

The patients were divided into two groups—oliguric and non-oliguric—based on their urine output during the first 24 h after starting medication. Those patients whose urine volume in the first 24 h averaged $\geqslant 50$ ml/h were termed non-oliguric. Conversely those patients with hourly urine volumes <50 ml/h were termed oliguric. One patient has been excluded from statistical analysis because he died prior to the first urine collection after entry into the study. Therefore $n=91$.

Fifty-one patients remained oliguric during the first 24 h of the study while 40 were non-oliguric either spontaneously or because of diuretic treatment. By day fifty-six, 35 (69%) of the oliguric patients had died compared to 17 (43%) of the non-oliguric patients ($P=0.01$). The pre-study APACHE II score was better in the group who became non-oliguric (17.2 ± 5.9 *vs* 20.6 ± 5.5, $P=0.008$), as was the pre-study creatinine clearance (14 ± 11 ml/min *vs* 4 ± 4 ml/min, $P<0.0001$).

In the group of patients who were non-oliguric, 8 (20%) were on placebo and 32 (80%) were on a diuretic. In the non-oliguric placebo group ($n=8$) two patients (25%) had died by day 56. In the non-oliguric diuretic group ($n=32$), 15 (47%) had died by day 56 ($P=0.3$).

Side-effects

There was a non-significant increase in the incidence of seizures in the patients given loop diuretic—torasemide 6, frusemide 6, placebo 1 ($P=0.1$). One patient on frusemide became acutely deaf but recovered when the drug was stopped.

Torasemide caused a significant rise in γGT, an effect that is reversible and given as a warning on the international data sheet.

Only 22% of patients continued on mannitol for 3 days. The reasons for stopping mannitol are as follows: severe oliguria/anuria ($n=27$), death before day 3 ($n=24$), hyperosmolality ($n=15$), acute pulmonary oedema ($n=1$), renal recovery ($n=2$), withdrawn from study ($n=2$). The patient who developed pulmonary oedema was not hyperosmolar. Only one of the patients who became hyperosmolar had any symptoms (confusion).

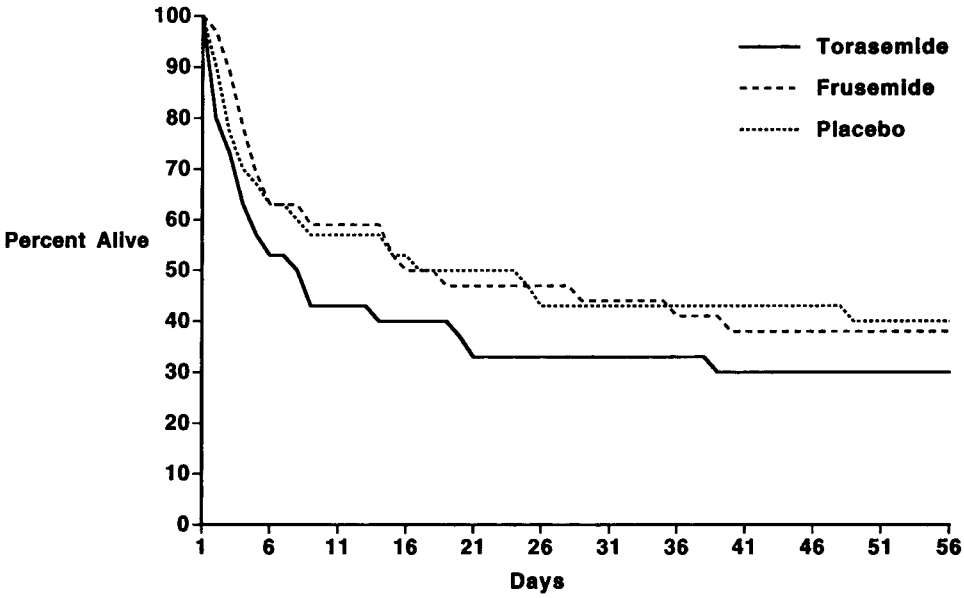

Fig. 1. Actuarial survival for the three groups of study patients, placebo, frusemide, and torasemide up to day 56.

Discussion

Can loop diuretics convert oliguric ARF to non-oliguric ARF?

The use of high-dose loop diuretics in patients with incipient ARF can significantly improve urine output. Thus 57% of patients given torasemide and 48% of patients given frusemide had a significant increase in urine volume in the first 24 h compared to placebo (23%).

Patients who became non-oliguric had a lower mortality than those patients who remained oliguric (43% *vs* 69% $P=0.01$). However, patients who became non-oliguric were less ill as evidenced by a significantly lower APACHE II score. They may also have had less severe renal failure as their creatinine clearance was higher. However, this is an imprecise measurement of renal function in these patients. On this evidence we cannot attribute a 'beneficial' effect on mortality solely to the use of loop diuretics.

Of more significance would have been a significant improvement in mortality between those patients who became spontaneously non-oliguric with placebo and those whose diuresis was induced by the use of loop diuretics. There was no difference in mortality at day 56 between the non-oliguric group who had placebo (spontaneously non-oliguric) and the non-oliguric group given loop diuretic. However, the number of patients in this subgroup analysis is small and larger numbers of patients are required for statistical analysis.

It has been suggested that continuous low-dose infusions of frusemide might be preferable to high-dose bolus injections [15]. It is possible, therefore, that we might have achieved an even greater diuretic effect by the continuous infusion of the loop diuretic.

In 1976 Kleinknecht *et al.* [1] studied 55 patients with established oliguric ARF. Thirty-three were given a variable dose of frusemide while 33 were given only intravenous fluids. There was no significant reduction in the duration of oliguria in the group given loop diuretic. Minuth and colleagues [2] found a sustained diuresis in 22% of 104 patients given a variable does (40–500 mg) of frusemide. Other groups however, have shown that intravenous frusemide modifies ARF by causing sustained polyuria [3–9].

Can loop diuretics shorten the period of renal dysfunction and reduce the need for dialysis

Renal recovery was considered to begin when the serum creatinine started to fall spontaneously, without dialysis. There was no significant difference in the time to renal recovery between the three groups. The need for dialysis was also not different. These findings agree with the studies of Brown *et al.* [5] and Borirakchanyavat *et al.* [9].

Minuth and colleagues [2], however, found a reduction in the need for dialysis in patients given loop diuretic. Cantarovich *et al.* [3] showed that a progressive doses of frusemide (100–3200mg/day in geometric progression on continuous days) shortened the period of renal dysfunction, presumably because of the high average daily dose of frusemide (1.24 g/day) received by the progressive dose group compared to the fixed dose group (600 mg/day). We gave a maximum dose of loop diuretic 1.2 g/day.

Can loop diuretics decrease mortality in ARF?

Our prospective randomized double-blind study failed to demonstrate an improved mortality in patients treated with loop diuretics, a finding in keeping with most previous less well-controlled studies. [1,2,5,6]. Only Anderson *et al.* [8] showed a reduction in mortality in the subgroup of patients given frusemide and

who were non-oliguric. This subgroup also had a lower fractional excretion of sodium and lower urinary sodium than those who did not respond to the diuretic, implying they had less severe renal failure as renal tubular sodium reabsorption continued. This is in keeping with our observation that the patients who became non-oliguric after loop diuretics had significantly less severe organ failure and better renal function on presentation

All of the patients in this study received both low-dose dopamine and mannitol. It is therefore unlikely that the differences seen between placebo and diuretic groups were due their presence. The decision to use low-dose dopamine and mannitol was taken in 1990. Today these drugs are less likely to be used in ARF since there is no proven beneficial effect on renal function and clinical outcome [16]. They may even be harmful and should probably be avoided in patients with ARF [17,18].

In conclusion, this prospective, placebo-controlled, double-blind, randomized study has shown that loop diuretics have no beneficial effect on the duration of renal dysfunction, the need for dialysis, or on mortality in ARF. Patients who become non-oliguric (with or without a loop diuretic) have a better survival but are less ill and have less severe renal failure than patients who remain oliguric.

In very ill patients many insults contribute to the onset of ARF; most patients suffer from multiple-organ failure. Perhaps it is a naive to suppose that a drug acting primarily on the kidneys would have a beneficial effect on a multisystem disorder and so improve survival. Our study has shown that loop diuretics have little effect on the natural history of ARF apart from a small increase in urine output in the less-ill group. The conversion of oliguric into non-oliguric ARF, however, could be an indication for their use in order to improve fluid balance, despite their lack of influence on outcome. If we are to significantly improve mortality in these patients we suggest that attention should be focused on the early detection and management of all aspects of multi-organ failure.

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