A pilot randomised controlled trial evaluating the pharmacodynamic effects of furosemide versus acetazolamide in critically ill patients

Alastair JW Brown, Salvatore L Cutuli, Glenn M Eastwood, Laurent Bitker, Philip Marsh and Rinaldo Bellomo

Diuretics are commonly used in the intensive care unit (ICU) with the aim of achieving a negative fluid balance; yet remarkably little is known about their pharmacodynamic properties in critically ill patients. The most frequently used class of diuretic drugs are the loop diuretics, and furosemide is the most commonly used loop diuretic. However, loop diuretics may have a number of undesirable side effects, including electrolyte derangements and metabolic alkalosis.

The carbonic anhydrase inhibitor acetazolamide has a diuretic effect, and is increasingly being investigated as an adjunctive therapy in patients with decompensated heart failure deemed resistant to loop diuretics by increasing the presentation of sodium to the loop of Henle. Furthermore, acetazolamide has been recently evaluated in an ICU population as a method of treating metabolic alkalosis. Despite such use, little controlled information based on randomised studies exists about the pharmacodynamics of acetazolamide in critically ill patients. In particular, although a number of studies have been published recently to quantify the pharmacodynamic effects of an intravenous bolus of furosemide in the ICU, no similar studies have been published to quantify the pharmacodynamic effects of acetazolamide in this population. Finally, no study has directly compared the effects of these two drugs when used in the clinical environment in a general ICU population.

We aimed to perform a pragmatic pilot randomised pharmacodynamic study comparing the effects of acetazolamide and furosemide at commonly administered doses (furosemide 40 mg intravenous and acetazolamide 500 mg intravenous) in ICU patients deemed to require diuretic therapy by the treating clinicians. Specifically, we sought to identify and compare changes in urine output, urinary electrolyte excretion, and serum electrolyte levels. We hypothesised that acetazolamide would have a different chloriuretic effect to acetazolamide. Furthermore, we sought to evaluate a number of secondary outcomes; in particular, we sought to compare the change in urine output, fluid balance, natriuresis, and plasma pH.

ABSTRACT

Objective: To compare the physiological and biochemical effects of a single intravenous dose of furosemide or acetazolamide in critically ill patients.

Design: Single centre, pilot randomised controlled trial.

Setting: Large tertiary adult intensive care unit (ICU).

Participants: Twenty-six adult ICU patients deemed to require diuretic therapy.

Intervention: Single dose of intravenous 40 mg furosemide or 500 mg acetazolamide.

Main outcome measures: Data were collected on urine output, cumulative fluid balance, and serum and urine biochemistry for 6 hours before and 6 hours after diuretic administration.

Results: Study patients had a median age of 55 years (IQR, 50–66) and median APACHE III score of 44 (IQR, 37–52). Furosemide caused a much greater increase in urine output and much greater median mass chloride excretion (121.7 mmol [IQR, 81.1–144.6] v 23.3 mmol [IQR, 20.4–57.3]; P < 0.01) than acetazolamide. Furosemide also resulted in a progressively more negative fluid balance while acetazolamide resulted in greater alkalinisation of the urine (change in median urinary pH, +2 [IQR, 1.75–2.12] v 0 [IQR, 0–0.5]; P = 0.02). In keeping with this effect, furosemide alkalinised and acetazolamide acidified plasma (change in median serum pH, +0.03 [IQR, 0.01–0.04] v −0.01 [IQR, −0.04 to 0]; P = 0.01; change in median serum HCO$_3^-$, +1.5 mmol/L [IQR, 0.75–2] v −2 mmol/L [IQR, −3 to 0]; P < 0.01).

Conclusions: Furosemide is a more potent diuretic and chloriuretic agent than acetazolamide in critically ill patients, and achieves a threefold greater negative fluid balance. Compared with acetazolamide, furosemide acidifies urine and alkalinises plasma. Our findings imply that combination therapy might be a more physiological approach to diuresis in critically ill patients.
Methods

Our study was approved the institutional human research ethics committee (HREC/17/Austin/75), with the option for deferred consent due to the need to provide treatment as part of emergency care. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR identification number: 1261700566336).

Patient selection and randomisation

We prospectively enrolled 26 patients admitted to one tertiary ICU between May and December 2017 for whom the attending physician had made a decision to administer a dose of intravenous diuretic. Patients who were to be administered a diuretic within the ICU were screened for eligibility by a member of the study team.

Patients were enrolled if they met the following criteria:
- age more than 18 years;
- physician decision to administer an intravenous diuretic;
- anticipated length of stay of more than 24 hours after administration of study drug; and
- existing intra-arterial or central venous catheter and indwelling urinary catheter.

The exclusion criteria included:
- known allergy to furosemide or acetazolamide or other sulphonamides;
- known end-stage renal failure;
- long-standing use of diuretics;
- dose of any diuretic in the preceding 12 hours;
- significant acid-base disturbance at time of enrolment (pH < 7.3 or > 7.5); and
- treatment with renal replacement therapy.

Eligible patients were then allocated to either treatment arm using sealed opaque envelopes to ensure blinded allocation. The allocation sequence was generated using a computer-generated block randomisation pattern in blocks of two, four and six in a 1:1 ratio. This was an open label trial and all members of the clinical team were aware of the treatment allocation.

Intervention

Patients received either a single bolus of 40 mg furosemide or 50 mg acetazolamide. No other diuretics were administered to patients during the 6-hour study period. At the end of the study period, patients continued with standard care.

Data collection

We collected demographic data, ICU admission diagnosis and patient comorbidities from the hospital electronic patient record. We recorded hourly urine output, fluid balance and cumulative fluid balance at the time of the diuretic bolus and for the 6 hours before and after the bolus from the electronic fluid balance chart.

We calculated the change in fluid balance as the cumulative fluid balance 6 hours after diuretic medication minus the cumulative fluid balance at the time of study drug administration. We also calculated the change in cumulative urine output as the cumulative urine output for 6 hours after diuretic administration minus the cumulative urine output 6 hours before diuretic administration.

Urine and blood collection

We obtained serum samples and arterial blood gas samples immediately before the administration of the study medication and 6 hours after the drug was administered. The blood gas samples were analysed using the Radiometer ABL 825 blood gas analyser (Radiometer Medical). Serum samples were analysed in the hospital laboratory. Paired urine samples were taken at the same time as blood samples. A spot urine sample of the urine produced during the preceding hour by the patient was taken immediately before administration of study drug and all of the urine produced during the 6 hours after diuretic administration was collected. Urine samples were analysed in the hospital laboratory. The lower limit of the hospital laboratory assays for urine sodium and chloride measurements were 20 mmol/L and 60 mmol/L, respectively, as such any value below these levels was taken to be 19 mmol/L and 59 mmol/L, respectively, for the purposes of data analysis. We calculated mass excretion of electrolytes and during the study period as urine concentration × urine volume, we also calculated the changes in urine electrolytes and pH (Δ variable) as urine concentration after diuretic minus spot urine sample concentration.

Statistical analysis

We assumed that using $\alpha = 0.05$ for significance, a study of 24 patients would have an 80% power to detect a difference in 6-hourly chloride excretion of 60 mmol with acetazolamide and 90 mmol with furosemide, assuming a standard deviation (SD) of 30 mmol in each group. We randomly allocated 26 patients to account for possible withdrawal of consent.

Data were analysed using the R Software, version 3.3.1 (R Foundation for Statistical Computing), with the package lme4 and lsmeans. A $P < 0.05$ was considered as statistically significant. Continuous variables are reported as median with interquartile range (IQR) in brackets; categorical variables are reported as count with percentage in parenthesis.

Comparisons between study arms were performed using Fisher exact test for categorical variables, and the Wilcoxon–Mann–Whitney rank-sum test for continuous variables. To assess the effects of each study drug on serum and urinary electrolytes, we compared their value at 6 hours of drug administration, and their change from
baseline, using the Wilcoxon–Mann–Whitney test. We also compared the effects of study drugs on hourly urine output and cumulative fluid balance over 6 hours, using the linear mixed effects regression model, accounting for the repetition and the interdependence of hourly assessments in a given individual. When relevant, we completed this analysis by performing a pairwise comparison of hourly urine output and cumulative fluid balance at each time point between study groups, using the Tukey adjusting method.

**Results**

**Baseline characteristics**

We enrolled 26 patients from May to December 2017. One patient subsequently withdrew consent, leaving 12 patients in the acetazolamide arm and 13 patients in the furosemide arm. Patients had a median age of 55 years (IQR, 50–66) and Acute Physiology and Chronic Health Evaluation (APACHE) III score of 44 (IQR, 37–52). There were no significant differences between groups at baseline for type of admission, comorbidity, illness severity, use of mechanical ventilation and baseline biochemistry (Table 1).

**Urinary biochemistry**

There were significant changes in urinary biochemistry after administration of the two study drugs (Table 2). Absolute urine chloride concentration was greater with furosemide administration (median, 97 mmol/L [IQR, 87–120]) vs 59 mmol/L [IQR, 59–59]; \( P < 0.01 \). Thus, the median mass excretion of chloride over 6 hours in the furosemide arm was significantly greater than in the acetazolamide arm (median, 16 mmol/L [IQR, 9.8–20.5] vs 4 mmol/L [IQR, 1–4]; \( P < 0.01 \)).
group increased significantly (22.9 mmol [IQR, 15.6–29.8] v 121.7 mmol [IQR, 81.1–144.6]; P < 0.01), but there was no change following acetazolamide (median, 23.8 mmol [IQR, 15.0–34.4] v 23.3 mmol [IQR, 20.4–57.3]; P = 0.26). The fractional excretion of chloride also increased only in the furosemide group and was unchanged in the acetazolamide group (Table 2).

The fractional excretion of sodium increased after administration of acetazolamide (median, 0% [IQR, 0–0%] v 1% [IQR, 0–1]) and also after administration of furosemide (median, 0% [IQR, 0–0%] v 2% [IQR, 1.75–4.25%]), but the effect on mass excretion was about fivefold greater in the furosemide group (Table 2). The fractional excretion of potassium and its mass excretion increased in both groups from baseline, with no difference in the magnitude of effect between groups (Table 2). The fractional excretion of magnesium was also greater with furosemide. There was a divergent effect on the urine anion gap (Table 2). Thus, urinary pH increased in the acetazolamide group but was unchanged in the furosemide group (Table 2). There was no change in creatinine clearance in either group compared with baseline (Table 2).

### Serum biochemistry

Serum sodium, potassium and chloride did not change significantly in either group (Table 2). However, there was significantly different effect on plasma pH, which rose in the furosemide group but fell in the acetazolamide group (Table 2). There was also a significant difference in the effect on bicarbonate, which increased with furosemide and fell with acetazolamide (Table 2).

### Urine output and fluid balance

There were significant differences in the effects of the two diuretics on fluid balance and urine output. Furosemide induced a significant increase in urinary output that was

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**Table 2. Electrolyte excretion and changes from baseline in urine and serum biochemistry**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acetazolamide</th>
<th>Furosemide</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>13</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td><strong>Urine biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine pH, median (IQR)</td>
<td>+2 (1.75–2.12)*</td>
<td>0 (0–0.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>FeNa*,† median (IQR)</td>
<td>+1% (0–1%)*</td>
<td>+2% (1.75–3.25%)*</td>
<td>0.01</td>
</tr>
<tr>
<td>FeK*,† median (IQR)</td>
<td>+16% (10.25–23.5%)*</td>
<td>+20% (16–24.5%)*</td>
<td>0.58</td>
</tr>
<tr>
<td>FeCl−,† median (IQR)</td>
<td>0% (0–1%)</td>
<td>+3% (2.0–5.5%)*</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FeMg2+,† median (IQR)</td>
<td>0% (–0.7% to 2.0%)</td>
<td>+9.0% (5.6–9.8%)*</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Urine Mg2+ (mEq/L), median (IQR)</td>
<td>−1.73 (−3.28 to −0.76)</td>
<td>−2.48 (−9 to 1.36)</td>
<td>0.55</td>
</tr>
<tr>
<td>Mass excretion Na+ (mmol),‡ median (IQR)</td>
<td>+17.5 (3.5–55.5)</td>
<td>+80.6 (46.3–116.8)*</td>
<td>0.12</td>
</tr>
<tr>
<td>Mass excretion K+ (mmol),‡ median (IQR)</td>
<td>+21 (14–33.0)*</td>
<td>+35.5 (26.0–43.7)*</td>
<td>0.41</td>
</tr>
<tr>
<td>Mass excretion Cl− (mmol),‡ median (IQR)</td>
<td>+23.3 (20.4–57.3)</td>
<td>+121.7 (81.1–144.6)*</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mass excretion Mg2+ (mmol),‡ median (IQR)</td>
<td>−0.2 (−0.8 to 0.3)</td>
<td>+1.9 (0.7–2.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min),‡ median (IQR)</td>
<td>−8.9 (−56.4 to 18.2)</td>
<td>−14.4 (−73.88 to 2.05)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Serum biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma pH, median (IQR)</td>
<td>−0.01 (−0.04 to 0)</td>
<td>+0.03 (0.01–0.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum HCO3− (mmol/L), median (IQR)</td>
<td>−2 (−3 to 0)</td>
<td>+1.5 (0.75–2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Serum Na+ (mmol/L), median (IQR)</td>
<td>0 (−1 to 1)</td>
<td>1 (0–1.25)</td>
<td>0.27</td>
</tr>
<tr>
<td>Serum K+ (mmol/L), median (IQR)</td>
<td>−0.2 (−0.3 to 0)</td>
<td>−0.15 (−0.45 to 0)</td>
<td>0.72</td>
</tr>
<tr>
<td>Serum Cl− (mmol/L), median (IQR)</td>
<td>1 (−1 to 2)</td>
<td>−1 (−2 to 0.25)</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L), median (IQR)</td>
<td>+5 (1–8)</td>
<td>+5 (1.75–9.5)</td>
<td>0.85</td>
</tr>
<tr>
<td>Serum anion gap (mEq/L), median (IQR)</td>
<td>1.2 (−2.3 to 2.0)</td>
<td>−0.7 (−1.2 to 0.1)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Cl− = chloride; Fe = fractional excretion; HCO3− = bicarbonate; IQR = interquartile range; K+ = potassium; Mg2+ = magnesium; Na+ = sodium.

* Represents a statistically significant change from baseline within the treatment group. † Fe calculated as 100 × (urine concentration × serum creatinine × 1000) ÷ (serum concentration × urine creatinine × 1000). ‡ Mass excretion calculated as urine concentration × urine volume.
sustained for 3 hours and returned to baseline by 6 hours (Figure 1). In contrast, the administration of acetazolamide did not result in a significantly increased urine output over 6 hours (median, 0.81 mL/kg per hour [IQR, 0.45–0.93] v 0.95 mL/kg per hour [IQR, 0.58–1.63]; \( P = 0.16 \)). These changes were reflected in an increasingly negative fluid balance over the study period in the furosemide group, but there was no significant change in fluid balance after administration of acetazolamide (Figure 2).

Discussion

Key findings
We tested the hypothesis that acetazolamide would lead to a degree of diuresis and natriuresis similar to that achieved with furosemide, but with a significantly lower urinary chloride excretion and less metabolic alkalosis than furosemide. In keeping with our hypothesis, we found a greater chloriuresis in the furosemide group than in the acetazolamide group. We also found a difference in urine pH between the two groups and alkalinisation of the urine with acetazolamide but not furosemide, leading to acidification of plasma in the acetazolamide group and alkalinisation of plasma in furosemide group. However, contrary to our hypothesis, we found much greater diuresis, natriuresis and negative fluid balance in the furosemide group and only limited changes in urine output, fluid balance and natriuresis in the acetazolamide group.

Relationship to previous literature
We are the first group to directly compare the biochemical and physiological effects of furosemide and acetazolamide in a randomised controlled study in critically ill patients. However, a few recent studies have evaluated the pharmacodynamic effects of a bolus of furosemide in critically ill patients.\(^\text{10–12}\) One study selected a cohort of patients with acute kidney injury (Acute Kidney Injury Network criteria stage 1–3) and found this group to have a varied response to furosemide, with 67% of patients showing a median increase in urine output of 200% (IQR, 140–650%), but with 27% of patients being non-responders, with a median increase of only 30% (IQR, –30% to 70%). This suggests that there is heterogeneity of response to furosemide. However, this study population was different to ours as all patients had acute kidney injury and the furosemide ranged from 20 mg to 40 mg.
compared with our patients who received a standard dose of 40 mg regardless of whether the patient had acute kidney injury, as this is the most commonly used dose in the ICU.1

A retrospective study sought to analyse the urinary electrolyte response to single and multiple boluses of furosemide10 in patients without acute or chronic kidney disease with a lower dose of diuretic (mean, 12 mg; SD, 5). Similar to our study, they found that there was an increased natriuresis and chloriuresis. They also found a decrease in the urine anion gap following the administration of furosemide. A further study prospectively enrolled patients to receive a bolus of 40 mg furosemide.12 These investigators found a median change in fluid balance 6 hours after the administration of furosemide of 595 mL (IQR, –880 to 98 mL), which is very similar to the median change of 513 mL (IQR, –1322 to –154) seen in our study. This group also found an increase in serum anion gap and a decrease in urine anion gap. However, this study involved some patients receiving long term diuretic therapy who were excluded in the present trial. We excluded patients receiving long term therapy due to concerns it may have created diuretic resistance, but it appears this may not be the case.

To our knowledge, our study is the first to quantify the diuretic, electrolyte and acid-base effect of acetazolamide in critically ill patients. A case–control study had demonstrated that in the context of ventilated critically ill patients, acetazolamide was effective in reversing metabolic alkalosis.9 However, this research exclusively studied patients with chronic obstructive pulmonary disease (COPD) undergoing mechanical ventilation. Nonetheless, it found a similar reduction in serum bicarbonate to our study. A further large multicentre randomised controlled trial again demonstrated a reversal of metabolic alkalosis with acetazolamide.8 This trial evaluated only patients with COPD and did not collect data regarding changes in fluid balance or the administration of other diuretics.

The diuretic effects of acetazolamide were first quantified in healthy humans in 1956.13 This study found that acetazolamide had only a modest effect on urine output. A 2017 pilot investigation of acetazolamide versus placebo in addition to loop diuretics found that there was no increase in urine output compared with controls, but that patients achieved a more negative fluid balance in the acetazolamide group compared with placebo.5 These findings are consistent with the minimal diuretic effect of acetazolamide seen in our study.

**Study implications**

Our findings imply that loop diuretics induce a significantly greater diuresis, natriuresis and negative fluid balance than acetazolamide and that acetazolamide has little if any diuretic effect in critically ill patients. Moreover, they imply that, in critically ill patients, these two drugs have opposing actions on urine and plasma biochemistry and acid-base status. Finally, they logically imply that co-administration of acetazolamide with furosemide may allow the achievement of furosemide-associated diuresis without its associated acid-base side effects.

**Strengths and limitations**

Our study has several strengths. It was randomised and controlled in design with concealed allocation, which would minimise bias. We compared the pharmacodynamic effects of two diuretics at commonly used doses using a prospective randomised controlled trial design to minimise incomplete data collection and to establish causality. We included patients with an indwelling catheter and arterial line to ensure that we were able to accurately measure all of our variables. By collecting data on urine output, fluid balance, mass excretion and fractional excretion of electrolytes, in addition to serum electrolytes, we were able to provide a comprehensive assessment of the physiological and biochemical changes arising from the uses of the two study drugs.

Our study has some limitations. We did not standardise the indication for which the diuretic had to be administered, as no such indication exists within the literature. As a pilot study, this investigation was open label, which increased the risk of bias. However, the endpoints were physiological and biochemical variables rather than clinical outcomes, so the risk of this bias was reduced. We undertook multiple comparisons and did not adjust for multiplicity choosing $P < 0.05$ as our threshold for significance. We believe that this is a reasonable approach for a pilot study, as it was intended only to be hypothesis-generating; nevertheless, the values for most significant changes were $P < 0.01$. We used a standard dose of furosemide and acetazolamide that did not account for body weight, age, or renal function. Nevertheless, we know that 40 mg of furosemide is the most commonly used dose in the ICU and, therefore, our results should reflect everyday practice. There are no data to suggest which factors determine the diuretic response to acetazolamide and, therefore, it is not possible to know if our dosing could have been optimised for different patients.

Our study investigated patients only over 6 hours after the administration of the study drugs. It is therefore not possible to draw any conclusions over the clinical outcomes associated with the administration of these two drugs and their long term effects. Our study was designed as a pragmatic pharmacodynamics investigation of the acute effects of the two drugs. We used a small sample size and
the study was performed in a single centre, which may limit its external validity. However, overall, our findings provide relevant and quantitative data on the effect of furosemide and acetazolamide on urine biochemistry and fluid balance in critically ill patients which had not been previously studied.

Conclusion
In a single centre, pilot randomised controlled trial of critically ill patients, furosemide had a significantly greater diuretic, natriuretic and chloriuretic effect than acetazolamide, and was associated with metabolic alkalosis. Acetazolamide had a very weak diuretic and natriuretic effect, a weaker chloriuretic effect and induced metabolic acidosis. Our findings imply that co-administration of acetazolamide with furosemide may logically allow the achievement of furosemide-associated diuresis, natriuresis and negative fluid balance without its associated acid-base side effects. Further studies would be required to evaluate this in clinical practice.

Competing interests
None declared.

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