Pharmacodynamics of intravenous frusemide bolus in critically ill patients

Agnes Huang, Nora Luethi, Johan Mårtensson, Rinaldo Bellomo and Luca Cioccari

ABSTRACT

Objective: To assess the physiological, biochemical and haemodynamic response to a single intravenous (IV) dose of frusemide in critically patients.

Design, setting and patients: A prospective observational study of 21 critically ill patients in a tertiary intensive care unit in Australia.

Interventions: We collected information on urine output (UO), fluid balance, serum and urinary electrolyte levels, serum biochemical levels and haemodynamics. We compared data from the 6-hour period before administration of a single IV bolus of frusemide 40 mg with data from the 6-hour period after administration.

Results: We studied 21 patients (12 of whom were women) with a median age of 73 years (interquartile range [IQR], 64–80 years). The IV bolus induced a > 1000 mL increase in UO in six patients (28.6%); a 500–1000 mL increase in six patients (28.6%) and a < 500 mL increase in nine patients (42.8%). The median difference in UO before and after frusemide was 590 mL (IQR, 290–1111 mL). The 6-hour fluid balance became negative in 15 patients (71.4%) and positive in six patients (28.6%), with a median change of –595 mL (IQR, –880 to 98 mL). Frusemide significantly increased urinary sodium, potassium and chloride losses and decreased blood chloride levels. There were no detectable changes in haemodynamics. On linear regression analysis, sodium excretion and UO correlated with higher mean arterial pressure (MAP) and age, and with lower albumin and creatinine levels.

Conclusions: In a cohort of critically ill patients without chronic renal impairment, frusemide increased UO and urinary sodium, potassium and chloride losses, and induced hypochloraemia and metabolic alkalosis. However, its diuretic effects were extremely variable and were modified by age, MAP and creatinine and albumin levels.

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Loop diuretics are commonly prescribed to critically ill patients as an intravenous (IV) bolus to increase urine output (UO) and induce a negative fluid balance.[1-3] The pharmacokinetic and pharmacodynamic effects of loop diuretics have been described in patients with congestive cardiac failure, chronic kidney disease and acute kidney injury.[4-6] However, no systematic, quantitative assessment of such effects has yet been conducted in a heterogeneous population of critically ill patients. A more detailed, quantitative appreciation of the effects of loop diuretics would help inform clinicians about the likely effects of such therapy and assist them in choosing dose and frequency, and estimating potential side effects.

We aimed to determine the effect of an IV bolus of a loop diuretic agent (frusemide) at one of the most commonly prescribed doses (40 mg)[7] on UO, fluid balance, circulating electrolyte levels, urinary electrolyte excretion and haemodynamic parameters in a cohort of patients in the intensive care unit.

Methods

Our study was approved by the institutional human research ethics committee (LNR/15/Austin/304) with a waiver for informed consent, because regular blood gas analyses are part of routine care in our ICU and no additional blood was drawn solely for study purposes.

Patients and data collection

We prospectively recruited a convenience sample of patients admitted to a single tertiary ICU between August 2015 and January 2016 and for whom the attending physician had decided to administer an IV bolus of frusemide 40 mg. We instructed medical and nursing staff daily to report to a member of the research team any planned administration of IV frusemide. The team member screened the patient for eligibility. We enrolled patients in the study if they met the following criteria: age 18 years or older, planned administration of an IV bolus of frusemide 40 mg, anticipated ICU length of stay of at least 24 hours after frusemide administration, existing intra-arterial cannula for blood sampling and an indwelling urinary catheter for urine sampling. Exclusion criteria were known chronic kidney disease, frusemide allergy, additional IV frusemide administration within 6 hours before or after the 40 mg bolus, and need for renal replacement therapy.

We collected demographic data, ICU admission diagnoses and Acute Physiology and Chronic Health Evaluation (APACHE) III scores. We recorded the cumulative fluid balance at the time of frusemide injection and 6 hours after the injection. We also recorded hourly mean arterial pressure (MAP), heart rate, central venous pressure (CVP),

norepinephrine infusion rate, fluid input and UO during the 6 hours before and until 6 hours after the frusemide injection. We calculated the UO response to frusemide injection as:

(total UO during 6 hours after frusemide injection) – (total UO during 6 hours before frusemide injection)

We considered patients to be "frusemide responders" if the UO in the 6 hours after frusemide administration was more than twice the UO in the 6 hours before,[8] or if their total UO after frusemide injection was greater than 100 mL/h for at least 2 hours.[9]

Blood and urine sample collection and analysis

We collected arterial blood samples for arterial blood gas (ABG) and electrolyte analysis immediately before frusemide injection and 6 hours after injection. ABG samples were analysed using the Radiometer ABL 825 blood gas analyser (Radiometer Medical). We repeated these measurements in spot urine samples before frusemide injection and in the urine collected during the 6 hours after the frusemide bolus. Urinary electrolyte and creatinine concentrations were measured at the hospital laboratory. We calculated mass excretion (ME) of electrolytes as:

urine concentration × urine volume

Electrolyte-free water clearance was calculated as described elsewhere.[10]

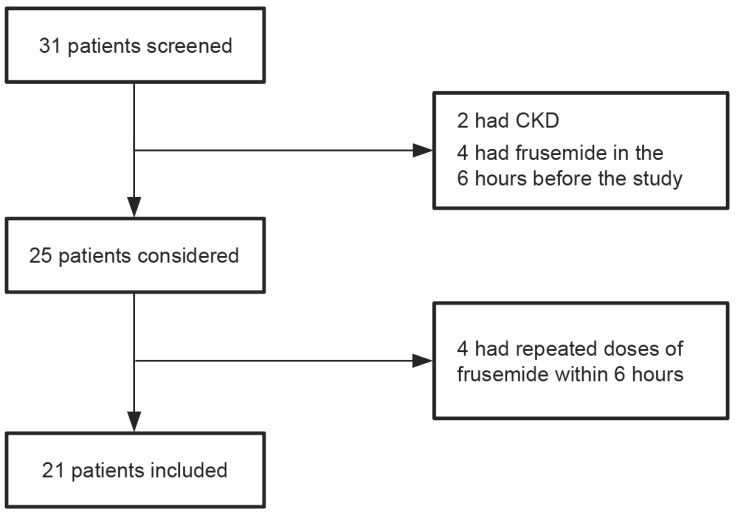
Statistical analysis

We analysed data using Stata, version 13.1 (StataCorp). Continuous variables are expressed as medians with interquartile ranges (IQRs), and categorical variables as frequencies with percentages. We compared data obtained before and after frusemide injection using the Wilcoxon signed-rank test. We used multivariable linear regression analysis to assess the association between a change in UO after frusemide injection with the following predetermined variables: age, MAP and baseline serum albumin and creatinine levels. Statistical significance was defined as $P < 0.05$.

Results

Thirty-one patients met our eligibility criteria. Two patients had chronic kidney disease and eight patients were excluded because they received additional doses of frusemide during the 6 hours before or after the frusemide injection. The remaining 21 patients (including 12 women [57.1%]) were included in the final analysis (Figure 1). Patient characteristics are summarised in Table 1. Six patients (28.6%) were receiving diuretic medication before ICU admission. Four patients (19.0%) were admitted after cardiac surgery. The median time spent in the ICU before the IV frusemide bolus was 44 hours overall (IQR, 25–88 hours), 23 hours (IQR, 18–49 hours) for patients who had had cardiac surgery and 33 hours (IQR, 25–158 hours) for patients who had been receiving chronic diuretic medication. Five patients (23.8%) had acute kidney injury and nine patients (42.9%) were receiving vasopressors at the time of the study.

Figure 1. Patient selection path



CKD = chronic kidney disease.

Changes in urine output

The observed frusemide-induced diuresis varied markedly among patients (Figure 2). The IV frusemide bolus induced an increase in UO of > 1000 mL in six patients (28.6%), a 500–1000 mL increase in six patients (28.6%) and a < 500 mL increase in nine patients (42.8%). Eighteen patients (85.7%) had a UO of > 100 mL for at least 2 hours after the bolus, and 15 patients (71.4%) doubled their UO after frusemide. Two patients (9.5%) were non-responders. The median total UO during the 6 hours preceding frusemide injection was 280 mL (IQR, 235–420 mL), and it increased to 995 mL (IQR, 645–1510 mL) during the 6 hours after frusemide injection, for a median difference in diuresis of 590 mL (IQR, 290–1111 mL) ($P < 0.001$). In patients receiving vasopressors ($n = 9$), the median difference in UO was 417 mL (IQR, 290–810 mL) ($P = 0.004$), and, in patients receiving long-term diuretic medication, UO increased by 623 mL (IQR, 117–1111 mL) ($P = 0.031$) (Table 2).

On multivariable linear regression analysis, higher MAP was independently associated with a greater increase in UO over 6 hours after frusemide injection (38.5 mL increase [95% CI, 21.3–55.8 mL] per mmHg increase in

Table 1. Patient demographic data

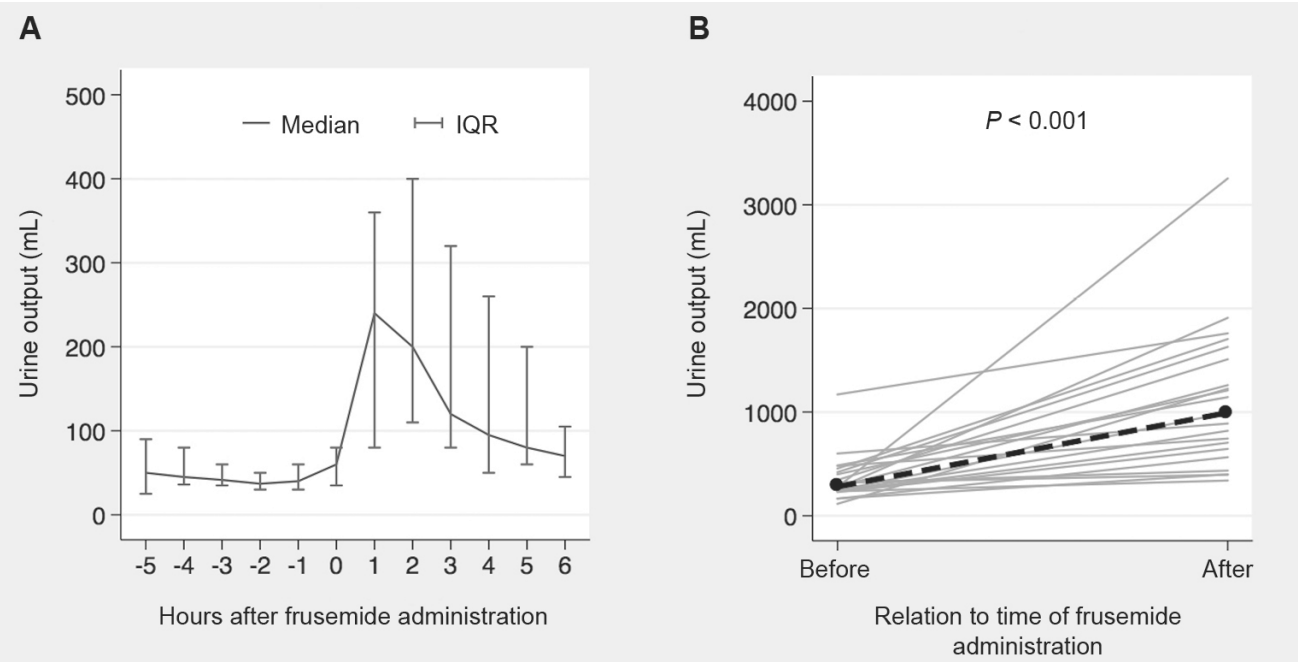
Variable	All patients (*n* = 21)
Median age, years (IQR)	73 (64–80)
Female, *n* (%)	12 (57.1%)
Median weight, kg (IQR)	79 (68–94)
Median APACHE III score (IQR)	64 (48–75)
Admission diagnosis	
Cardiac surgery, *n* (%)	4 (19.0%)
Non-cardiac surgery, *n* (%)	6 (28.6%)
Cardiovascular disease, *n* (%)	2 (9.5%)
Respiratory disease, *n* (%)	5 (23.8%)
Sepsis, *n* (%)	2 (9.5%)
Metabolic disease, *n* (%)	1 (4.8%)
Gastrointestinal disease, *n* (%)	1 (4.8%)
Median baseline creatinine level, µmol/L (IQR)	82 (58–103)
Median serum albumin level, g/L (IQR)	24 (20–27)

Variable	All patients (*n* = 21)
Chronic diuretic intake, *n* (%)	6 (28.6%)
Frusemide	3 (14.3%)
Frusemide + spironolactone	1 (4.8%)
Hydrochlorothiazide	2 (9.5%)
Spironolactone	3 (14.3%)
AKIN stage, *n* (%)	
0	16 (76.2%)
1	3 (14.3%)
2	1 (4.8%)
3	1 (4.8%)
Positive fluid balance before frusemide, *n* (%)	13 (61.9%)
Vasoactive agents at time of frusemide bolus, *n* (%)	9 (42.9%)
Norepinephrine	7 (33.3%)
Milrinone	4 (19.0%)
Nitroglycerine	1 (4.8%)
Median time in ICU, hours (IQR)	44 (25–88)

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation. AKIN = Acute Kidney Injury Network. ICU = intensive care unit.

MAP). In contrast, higher serum albumin and creatinine levels were independently associated with a negative UO response (40.0 mL decrease [95% CI, 15.2–64.8 mL] per g/L increase in albumin level, and 2.7 mL decrease [95% CI, 0.5–4.9 mL] per µmol/L increase in creatinine level). Finally, we also observed a significant association between age and a greater UO response to frusemide (20.1 mL increase [95% CI, 5.5–34.8 mL] per year of age) (Table 3).

Figure 2. Urine output before and after a bolus of intravenous frusemide 40 mg



A. Hourly urine output. B. Cumulative urine output. IQR = interquartile range.

Table 2. Haemodynamic and fluid balance data, before and after an intravenous bolus of frusemide 40 mg

Variable	Before frusemide	After frusemide	Difference	*P*
6-Hour urine output, mL				
All patients (*n* = 21)	280 (235–420)	995 (645–1510)	590 (290–1111)	< 0.001
Patients receiving vasopressors (*n* = 9)	280 (235–400)	820 (565–1210)	417 (290–810)	0.004
Patients receiving long-term diuretics (*n* = 6)	278 (235–318)	986 (435–1260)	623 (117–1111)	0.031
Cumulative fluid balance, mL	305 (–363 to 1235)	–88 (–1078 to 239)	–595 (–880 to 98)	0.078
Cumulative fluid input, mL	180 (0–350)*	110 (0–390)†	0 (–220 to 0)	0.424
Mean arterial pressure, mmHg	80 (70–88)	82 (75–90)	2 (–2 to 4)	0.383
Central venous pressure,‡ mmHg	11 (10–13)	12 (8–16)	0 (–1 to 1)	0.774
Heart rate, beats/min	85 (77–88)	88 (81–94)	2 (–1 to 6)	0.664
Norepinephrine, µg/min	0 (0–1.1)	0 (0–2.2)	0 (0–0)	0.688
Creatinine clearance, mL/min	69 (39–132)§	65 (49–95)	0.5 (–13 to 22)	1.0

* At the time of frusemide administration, since midnight. † At 6 hours after frusemide administration, since midnight. ‡ Data available for 18 of 21 patients before, and 15 of 21 patients after, frusemide administration. § Data available for 16 of 21 patients before frusemide administration.

Table 3. Multivariate linear regression analysis of the effect of an intravenous bolus of frusemide 40 mg on urine output in the 6 hours after administration

	Univariate analysis		Multivariate analysis	
Variable	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Age (per year)	–2.2 (–23.1 to 18.8)	0.832	20.1 (5.5 to 34.8)	0.010
MAP (per mmHg)	30.3 (9.4 to 51.2)	0.007	38.5 (21.3 to 55.8)	< 0.001
Albumin (per g/L)	–32.7 (–71.2 to 5.7)	0.091	–40.0 (–64.8 to –15.2)	0.003
Creatinine (per µmol/L)	–2.9 (–6.1 to 0.3)	0.076	–2.7 (–4.9 to –0.5)	0.020

MAP = mean arterial pressure

Table 4. Serum and urine electrolyte changes and blood gas analysis, before and after intravenous frusemide bolus 40 mg (median [interquartile range])*

Variable	Before frusemide	After frusemide	Difference	*P*
Urine electrolyte, mmol/L				
Sodium	31 (10–64)	106 (71–110)	46 (11–62)	< 0.001
Chloride	30 (30–30)	102 (83–120)	69 (47–88)	< 0.001
Potassium	43 (36–85)	24 (19–40)	–22 (–44 to –6.6)	< 0.001
SID‡	68 (35–112)	27 (14–38)	–38 (–83 to –6.4)	0.002
Magnesium	8.4 (5.5–15)	4.6 (2.7–5.7)	–4.9 (–10 to –1.7)	0.007
Creatinine	8.3 (5.4–16)†	2.2 (1.4–4.1)	–6 (–12 to –3)	< 0.001
Arterial blood gas variable				
Sodium, mmol/L	137 (134–141)	137 (134–143)	0 (–1 to 1)	0.629
Chloride, mmol/L	105 (100–107)	102 (100–105)	–2 (–3 to –1)	0.001
Potassium, mmol/L	4.0 (3.8–4.1)	3.9 (3.7–4.2)	–0.1 (–0.2 to 0.2)	0.648
SID,‡ mmol/L	36 (34–39)	40 (36–41)	1.8 (0.5–3.5)	0.007
Calcium, mmol/L	1.1 (1.1–1.2)	1.1 (1.1–1.1)	–0.02 (–0.04 to 0.01)	0.115
Creatinine, mmol/L	82 (58–103)	83 (61–107)	2 (–3 to 5)	0.263
Bicarbonate, mmol/L	25 (24–28)	28 (26–30)	1 (1–3)	0.001
Base excess, mmol/L	2 (0–4)	4 (2–5)	1 (1–2)	0.001
pH	7.4 (7.4–7.5)	7.4 (7.4–7.5)	0.01 (0–0.02)	0.210
Lactate, mmol/L	1.8 (1.3–2.3)	1.7 (1.1–1.9)	–0.4 (–0.5 to 0.3)	0.189
Glucose, mmol/L	8.6 (6.6–9.9)	7.9 (5.8–9.2)	–0.3 (–0.8 to 0.6)	1.0

SID = strong ion difference. * Using two-sided Wilcoxon signed-rank test. † Abbreviated SID = Na + K – Cl. ‡ Baseline measurement available for 16 of 21 patients.

Effect on fluid balance

The cumulative fluid balance from the time of ICU admission to the time of frusemide administration was positive in 13 patients (61.9%) and negative in eight patients (38.1%). The 6-hour fluid balance after frusemide administration became negative in 15 patients (71.4%) and positive in six patients (28.6%), with a median change of –595 mL (IQR, –880 mL to 98 mL) (Table 2). After IV frusemide 40 mg, the cumulative fluid balance was positive in 10 patients (47.6%) and negative in 11 patients (52.4%).

Clearance and excretion of electrolytes

Six-hour creatinine clearance was measured at 69 mL/min (IQR, 39–132 mL/min) before, and 65 mL/min (IQR, 49–95 mL/min) after, administration of frusemide ($P = 1.0$). We observed a significant increase in urinary sodium and chloride concentrations and a drop in urinary potassium concentrations over the 6 hours after frusemide injection (Table 4). However, ME of sodium, potassium and chloride increased after frusemide administration. Similarly, fractional excretion of sodium, potassium and chloride increased (Table 5). Free water clearance, plasma and urine tonicity were not affected by a single IV bolus of frusemide 40 mg (Figure 3).

Changes in serum electrolytes

Frusemide administration resulted in a significant decrease in serum chloride levels, but sodium and potassium levels remained unchanged. Consequently, the strong ion difference increased, which led to metabolic alkalosis with a significant rise in measured bicarbonate concentration and base excess. These effects did not significantly affect blood pH (Table 4). Nine patients (42.6%) received IV potassium or magnesium supplementation (at a 10 mmol/h infusion rate) during the 6-hour observation period, when blood sampling had revealed hypokalaemia and hypomagnesaemia, respectively. Potassium was administered on 11 occasions to eight patients (38.1%), with a median dose of 20 mmol per episode (IQR, 15–30 mmol). Magnesium was administered to three patients (14.3%), with a median dose of 20 mmol per episode (IQR, 10–20 mmol). However, the observed alterations in serum electrolyte and biochemical levels were unchanged after we excluded patients who received additional IV electrolyte supplementation.

Effect on haemodynamics

A single bolus of frusemide 40 mg had no significant effect on MAP, heart rate, CVP or norepinephrine requirements in the 6 hours before and 6 hours after frusemide injection (Table 2).

Discussion

Key findings

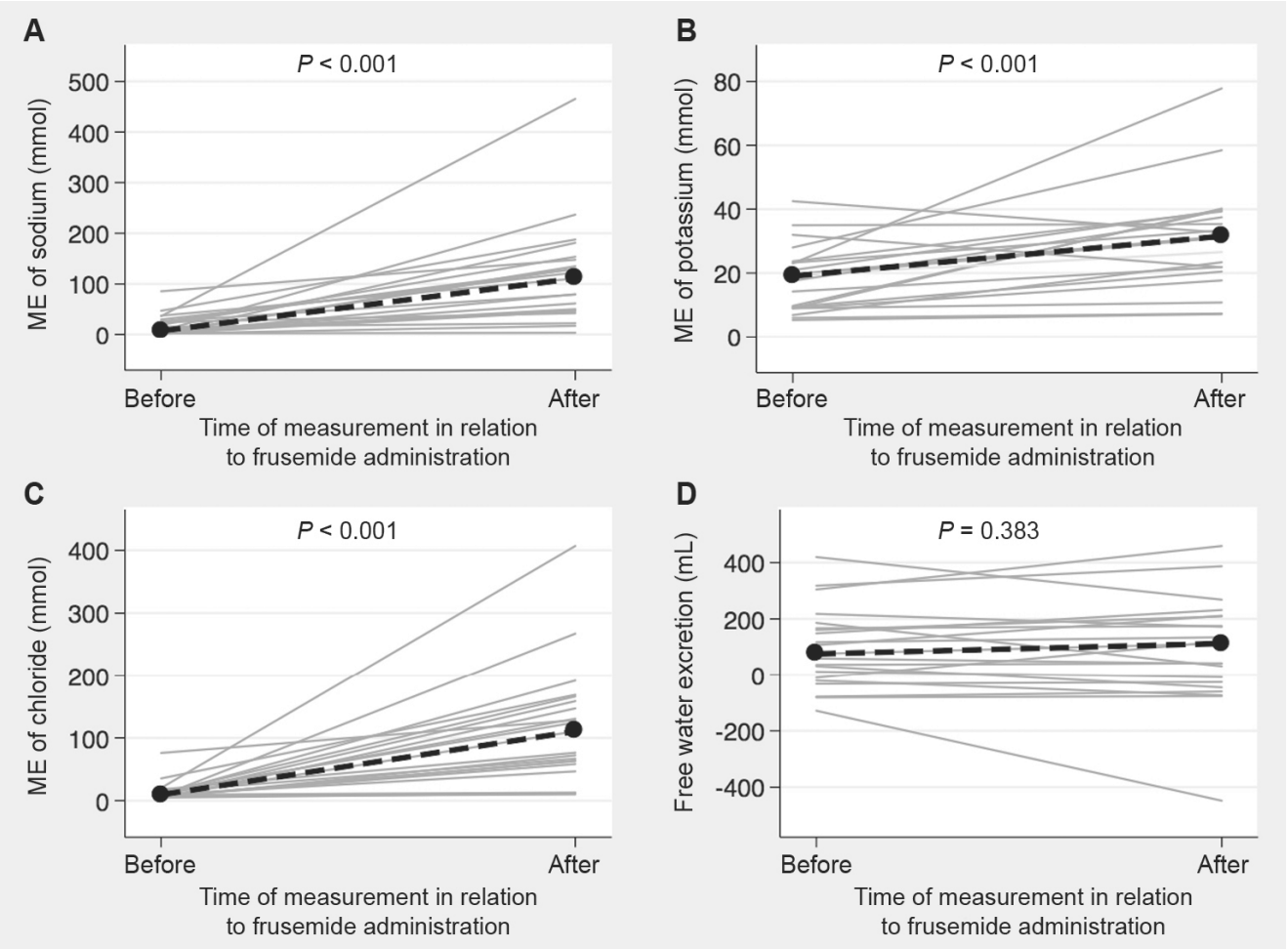
We assessed the physiological, biochemical and haemodynamic response to an IV bolus of frusemide 40 mg in critically patients. UO response to this intervention was highly variable, ranging from 340 mL to more than 3 L over the first 6 hours after administration. There was a greater response associated with higher MAP, increasing age and lower serum albumin and creatinine levels. However, despite increasing UO in all patients, the change in median cumulative fluid balance failed to reach significance. Frusemide injection caused a marked increase in sodium,

Table 5. Electrolyte and water excretion, before and after intravenous frusemide bolus 40 mg (median [interquartile range])*

Variable	Before frusemide	After frusemide	Difference	*P*
Mass excretion,† mmol				
Sodium	7.2 (3.6–25)	111 (49–148)	74 (44–131)	< 0.001
Potassium	19 (9–23)	32 (22–39)	11 (1.9–19)	< 0.001
Chloride	9.5 (7.1–14)	110 (63–159)	67 (52–144)	< 0.001
Magnesium	2.5 (1.4–5.1)	3.7 (2.7–5.8)	1.2 (–0.9 to 2.1)	0.078
Fractional excretion, %				
Sodium	0.22 (0.09–0.77)	2.4 (1.8–3.7)	2.0 (1.6–2.7)	< 0.001
Potassium	13 (8.4–27)	31 (20–42)	11 (5.9–22)	< 0.001
Chloride	0.24 (0.11–0.7)	3.3 (1.9–5.4)	2.9 (1.4–4.4)	< 0.001
Plasma tonicity, mOsmol/L	283 (275–291)	283 (276–292)	1 (–1.6 to 2.6)	0.664
Urine tonicity, mOsmol/L	202 (129–292)	257 (209–300)	30 (–13 to 77)	0.189
Free water clearance,‡ mL	76 (–10 to 167)	113 (–26 to 209)	6.5 (–46 to 48)	0.383

* Compared using two-sided Wilcoxon signed-rank test. † Calculated as urine concentration × urine volume.
‡ Calculated as urine volume × (1 – [2 × (urine Na + urine K)] ÷ [2 × (Na + K)]).

Figure 3. Mass excretion of sodium (A), potassium (B) and chloride (C) and free water clearance (D), before and after an intravenous bolus of frusemide 40 mg



ME = mass excretion.

potassium and chloride excretion, which contributed to metabolic alkalosis.

Relationship to previous studies

We are among the first to systematically explore and quantify the physiological, biochemical and fluid balance-related response to a standardised dose of frusemide in critically ill adults without chronic renal impairment. In a recent prospective cohort of 30 critically ill patients, the diuretic effect of a single bolus dose of IV frusemide was best predicted by the measured creatinine clearance.[6] However, that study population was very different from ours, in that all patients had acute kidney injury, 73% had sepsis, 47% required norepinephrine and 53% were mechanically ventilated. The frusemide dose was also variable, ranging from 20 to 80 mg. The renal response to frusemide has been shown to be influenced by several factors, such as age,[11] level of dehydration,[12] underlying renal disease[4] and serum albumin concentration.[13] However, in studies of other populations, no detailed analysis of the effects of frusemide on multiple related variables has been reported.

In a study of 27 trauma patients, frusemide (dose range, 20–610 mg) resulted in a 45% increase in 24-hour UO and less 24-hour net fluid gain, without any significant change in haemodynamic parameters or creatinine or potassium levels.[14] A single-centre study of 43 patients in a respiratory ICU, treated with frusemide (10 mg bolus plus 5 mg/h infusion), reported negative fluid balances, ranging from a mean of –878 mL/day to –1908 mL/day. That study also reported multiple episodes of hypotension, hypokalaemia and, in almost one-quarter of patients, a glomerular filtration rate decline of more than 20 mL/min/1.73 m^2.[15] In a medical ICU, 22 patients with pulmonary oedema or fluid overload were randomised to frusemide therapy by either continuous infusion or intermittent boluses.[16] The two regimens were equally effective in achieving negative

fluid balance and decreasing CVP, but the MAP gradually declined.

In our study, we did not observe significant changes in haemodynamic parameters or serum potassium levels after a single dose of frusemide, even after excluding patients who received potassium supplementation. However, it is logical to expect greater effects on haemodynamic parameters and electrolyte balance with repeated boluses of frusemide.[17,18]

Our finding that low albumin level predicts a greater UO response is unexpected. In two randomised controlled trials (RCTs) (n = 37 and n = 40), infusions of albumin and frusemide versus double-placebo,[19] and the addition of albumin to frusemide versus frusemide-placebo,[20] significantly improved oxygenation, fluid balance and haemodynamic stability in hypoproteinaemic patients with acute respiratory distress syndrome treated for 5 and 3 days, respectively. However, the combination of albumin and frusemide did not significantly increase UO; the effect on fluid balance was due to administration of higher volumes of crystalloid in the non-albumin group.

Lower albumin levels lead to a reduction in glomerular plasma oncotic pressure, increasing net ultrafiltration pressure.[21] This could explain our finding of lower albumin levels being associated with higher UO.

In a study of 475 patients with decompensated heart failure,[22] the UO produced by frusemide 40 mg equivalents was affected by renal function, haemodynamic status, degree of volume overload and fluid intake. In our cohort of critically ill patients, MAP proved the strongest predictor of diuretic response. Such a relationship between increased blood pressure and diuresis[23] has been previously reported by some studies,[24,25] but not all.[26,27]

Implications of study findings

Our findings suggest that to achieve a greater diuretic and natriuretic response, increasing the patient's blood pressure may be important. They also imply that a single bolus of frusemide 40 mg is unlikely to significantly alter haemodynamic parameters or vasopressor requirements or to lower an elevated CVP. Our study further implies that frusemide-induced chloride losses contribute to metabolic alkalosis and that diuresis is highly variable in critically ill patients. In future studies, it is therefore important to identify non-responders, who are unlikely to increase their UO after frusemide administration, as this may help to reduce unnecessary drug administration and potentially harmful effects.[28,29]

Strengths and limitations

Our study has several strengths. We analysed the pharmacodynamic effects of a commonly prescribed dose of frusemide using a prospective study design and minimising the risk of incomplete data collection. We included patients with an indwelling arterial catheter, central venous line and urinary catheter, thus ensuring the invasive measurements of all relevant variables. By calculating the effect on UO, fluid balance, ME and fractional excretion of electrolytes, electrolyte supplementation and free water clearance, we provide a comprehensive analysis of the physiological and biochemical effects of an IV frusemide bolus in critically ill patients. In our multivariable regression analysis, we used the *change* in UO relative to baseline, rather than the actual UO, as the dependent variable, which is a more sensitive way to identify predictors of UO response.

We also adjusted for several important determinants of frusemide response, such as serum albumin levels, kidney function and MAP.

Our study has some limitations. It was not an RCT, which means that we were not able to establish causality, only association. Randomising patients to placebo when diuretic therapy is clinically warranted is ethically problematic, so we were not able to use an RCT study design. We did not standardise the criteria for frusemide administration, and no such criteria exist in the literature. We studied a specific bolus dose without considering the effects of a continuous infusion, which may limit the generalisability of our findings. However, a bolus of frusemide 40 mg IV is a typical dose given by intensivists[7] and, therefore, our results are likely to reflect everyday practice in the ICU.

We analysed effects over only 6 hours after a single frusemide dose and did not report long-term outcomes or side effects. However, our study was explicitly designed to provide information on the acute physiological effects of a single frusemide bolus. Finally, the small sample size and the single-centre study design may have limited external validity. Nevertheless, our findings provide important novel quantitative information on the effect of frusemide on electrolyte losses, levels and diuresis in critically ill patients; information that was not previously available.

Conclusions

In a cohort of critically ill patients without known renal impairment, frusemide increased UO and urinary sodium, potassium and chloride losses, and induced hypochloraemia and metabolic alkalosis with a negative fluid balance of about 600 mL. However, such effects were extremely variable and were modified by MAP, age and serum albumin and creatinine levels.

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Competing interests

None declared.

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References

1 Bagshaw SM, Delaney A, Jones D, et al. Diuretics in the management of acute kidney injury: a multinational survey. *Contrib Nephrol* 2007; 156: 236-49.

2 Mehta RL, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA* 2002; 288: 2547-53.

3 Uchino S, Doig GS, Bellomo R, et al. Diuretics and mortality in acute renal failure. *Crit Care Med* 2004; 32: 1669-77.

4 Kühnel HJ, Günther K, Stein G, Hoffmann-Traeger A. Pharmacokinetics and pharmacodynamics of high dose furosemide in patients with chronic renal failure or nephrotic syndrome. *Int J Clin Pharmacol Ther Toxicol* 1987; 25: 616-21.

5 Finkelstein Y, Adler Y, Nussinovitch M, Shoenfeld Y. Continuous infusion versus intermittent administration of furosemide in pediatric and adult patients with severe congestive heart failure. *Pediatrics Related Topics* 1997; 36: 181-4.

6 Silbert BI, Ho KM, Lipman J, et al. Determinants of urinary output response to IV furosemide in acute kidney injury: a pharmacokinetic/pharmacodynamic study. *Crit Care Med* 2016; 44: e923-9.

7 Jones SL, Martensson J, Glassford NJ, et al. Loop diuretic therapy in the critically ill: a survey. *Crit Care Resusc* 2015; 17: 223-6.

8 Ho KM, Walters S, Faulke D, Liang J. Clinical predictors of acute renal replacement therapy in critically ill patients with acute renal impairment. *Crit Care Resusc* 2003; 5: 97-102.

9 Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. *Crit Care* 2013; 17: R207.

10 Mallie JP, Bichet DG, Halperin ML. Effective water clearance and tonicity balance: the excretion of water revisited. *Clin Invest Med* 1997; 20: 16-24.

11 Muhlberg W, Platt D, Neubig E. Pharmacokinetics and pharmacodynamics of furosemide in geriatric patients. *Arch Gerontol Geriatr* 1986; 5: 249-63.

12 Sjöström PA. Mechanisms of reduced effects of loop diuretics in healthy volunteers and in patients with renal disease. *Scand J Urol Nephrol Suppl* 1988; 111: 1-66.

13 Sjöström PA, Kron BG, Odlind BG. Determinants of furosemide delivery to its site of action. *Clin Nephrol* 1995; 43 Suppl 1: S38-41.

14 Yeh DD, Tang JF, Chang Y. The use of furosemide in critically ill trauma patients: a retrospective review. *J Emerg Trauma Shock* 2014; 7: 83-7.

15 Thomsen G, Bezdjian L, Rodriguez L, Hopkins RO. Clinical outcomes of a furosemide infusion protocol in edematous patients in the intensive care unit. *Crit Care Nurse* 2012; 32: 25-34.

16 Mojtahedzadeh M, Salehifar E, Vazin A, et al. Comparison of hemodynamic and biochemical effects of furosemide by continuous infusion and intermittent bolus in critically ill patients. *J Infusion Nursing* 2004; 27: 255-61.

17 Luciani GB, Nichani S, Chang AC, et al. Continuous versus intermittent furosemide infusion in critically ill infants after open heart operations. *Ann Thorac Surg* 1997; 64: 1133-9.

18 Martin SJ, Danziger LH. Continuous infusion of loop diuretics in the critically ill: a review of the literature. *Crit Care Med* 1994; 22: 1323-9.

19 Martin GS, Mangialardi RJ, Wheeler AP, et al. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2002; 30: 2175-82.

20 Martin GS, Moss M, Wheeler AP, et al. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2005; 33: 1681-7.

21 Brenner BM, Humes HD. Mechanics of glomerular ultrafiltration. *N Engl J Med* 1977; 297: 148-54.

22 Aronson D, Burger AJ. Diuretic response: clinical and hemodynamic predictors and relation to clinical outcome. *J Card Fail* 2016; 22: 193-200.

23 Evans RG, Majid DS, Eppel GA. Mechanisms mediating pressure natriuresis: what we know and what we need to find out. *Clin Exp Pharmacol Physiol* 2005; 32: 400-9.

24 Martin C, Eon B, Saux P, et al. Renal effects of norepinephrine used to treat septic shock patients. *Crit Care Med* 1990; 18: 282-5.

25 Piva J, Alquati T, Garcia PC, et al. Norepinephrine infusion increases urine output in children under sedative and analgesic infusion. *Rev Assoc Med Bras (1992)* 2014; 60: 208-15.

26 Albanese J, Leone M, Garnier F, et al. Renal effects of norepinephrine in septic and nonseptic patients. *Chest* 2004; 126: 534-9.

27 Bourgoin A, Leone M, Delmas A, et al. Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. *Crit Care Med* 2005; 33: 780-6.

28 Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. *BMJ* 2006; 333: 420.

29 Lassnigg A, Donner E, Grubhofer G, et al. Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol* 2000; 11: 97-104. ❑