BMJ

Meta-analysis of frusemide to prevent or treat acute renal failure

Kwok M Ho and David J Sheridan

Updated information and services can be found at:
http://bmj.com/cgi/content/full/333/7565/420

These include:

Data supplement	"References w1 - w22" **http://bmj.com/cgi/content/full/bmj.38902.605347.7C/DC1**
References	This article cites 13 articles, 4 of which can be accessed free at: **http://bmj.com/cgi/content/full/333/7565/420#BIBL**
	9 online articles that cite this article can be accessed at: **http://bmj.com/cgi/content/full/333/7565/420#otherarticles**
Rapid responses	6 rapid responses have been posted to this article, which you can access for free at: **http://bmj.com/cgi/content/full/333/7565/420#responses**
	You can respond to this article at: **http://bmj.com/cgi/eletter-submit/333/7565/420**
Email alerting service	Receive free email alerts when new articles cite this article - sign up in the box at the top left of the article

Topic collections	Articles on similar topics can be found in the following collections

Urology (1196 articles)
Clinical trials (epidemiology) (3895 articles)
Epidemiologic studies (6991 articles)
Disability (772 articles)
Acute renal failure (70 articles)
Urological surgery (2241 articles)
Ear, nose and throat/otolaryngology (751 articles)
Internet (971 articles)

Notes

To order reprints follow the "Request Permissions" link in the navigation box

To subscribe to *BMJ* go to:
http://resources.bmj.com/bmj/subscribers

Meta-analysis of frusemide to prevent or treat acute renal failure

Kwok M Ho, David J Sheridan

Editorial by
Bennett-Jones

Intensive Care Unit,
Royal Perth
Hospital, Perth,
Western Australia
6000
Kwok M Ho
consultant
David J Sheridan
*resident medical
officer*

Correspondence to:
K M Ho kwok.ho@
health.wa.gov.au

Abstract

Objective To investigate the potential beneficial and adverse effects of frusemide to prevent or treat acute renal failure in adults.

Design Meta-analysis of randomised controlled trials.

Data sources Cochrane controlled trials register (2005 issue 4), Embase, and Medline (1966 to 1 February 2006), without language restrictions.

Review methods Two reviewers checked the quality of the studies and independently extracted data.

Results Nine randomised controlled trials totalling 849 patients with or at risk of acute renal failure were included. Outcome measures not significantly different after frusemide treatment were in-hospital mortality (relative risk 1.11, 95% confidence interval 0.92 to 1.33), risk for requiring renal replacement therapy or dialysis (0.99, 0.80 to 1.22), number of dialysis sessions required (weight mean difference −0.48 sessions, −1.45 to 0.50), and proportion of patients with persistent oliguria (urine output <500 ml/day: 0.54, 0.18 to 1.61). Stratifying studies that used frusemide to prevent or treat acute renal failure did not change the results on mortality (relative risk ratio 2.10, 95% confidence interval 0.67 to 6.63) and the risk for requiring dialysis (4.12, 0.46 to 37.2). Evidence suggested an increased risk of temporary deafness and tinnitus in patients treated with high doses of frusemide (relative risk 3.97, 95% confidence interval 1.00 to 15.78).

Conclusions Frusemide is not associated with any significant clinical benefits in the prevention and treatment of acute renal failure in adults. High doses may be associated with an increased risk of ototoxicity.

Introduction

Several small randomised controlled studies evaluating the use of frusemide to either prevent or treat acute renal failure have produced negative results.[w1-w4] Frusemide is frequently used to facilitate fluid and electrolyte management of acute renal failure,[1] yet its potential benefits, adverse effects, and cost effectiveness to prevent or treat this condition remain uncertain. We carried out a meta-analysis to assess the potential beneficial and harmful effects of frusemide in acute renal failure and whether effects differ when used to prevent or to treat acute renal failure.

Methods

We searched the Cochrane controlled trials register, Embase, and Medline for randomised controlled clinical trials comparing frusemide with placebo in adults (see bmj.com for exploded MeSH terms). We also included studies of single dose frusemide compared with prolonged continuous infusion (see bmj.com for exclusions).

Two reviewers independently recorded the trial characteristics, outcomes, and quality of identified studies (Jadad score), using a predesigned data abstraction. Grading of allocation concealment was based on the Cochrane approach. One study that published data in two publications[2] [w5] was combined to represent one trial.

We chose in-hospital mortality and the proportion of patients requiring renal dialysis or replacement therapy as the main outcomes because they are the most relevant clinical outcomes in patients with acute renal failure. Other outcomes were the proportion of patients remaining oliguric (urine output <400-500 ml/day), proportion of patients who developed ototoxicity, number of dialysis sessions required until recovery, and length of hospital stay.

Statistical analyses

Using a random effect model we report the differences in categorical outcomes between the treatment and placebo or control groups as relative risks with 95% confidence intervals. We further stratified the effects of frusemide on mortality and the need for dialysis after frusemide treatment into studies using frusemide to prevent or to treat acute renal failure, and we tested this interaction by relative risk ratio.[3] Using a random effect model we report the differences in length of hospital stay and the number of dialysis sessions required as weighted mean differences. We used the χ^2 statistic to assess heterogeneity between trials and the I^2 statistic to assess the extent of inconsistency.[4] One study reported tinnitus and deafness in several patients after frusemide treatment but did not specify the number.[w5] We therefore estimated that at least three patients would have tinnitus or deafness in the frusemide group. One study reported the duration of continuous renal replacement therapy until recovery.[w4] We pooled the results of this study with others that reported the total number of dialysis sessions required until recovery of renal function. We carried out sensitivity analyses by excluding one study that compared a single dose of frusemide with prolonged continuous infusion[w6] or by including only studies that had adequate allocation concealment.[w1-w3] [w7] Publication bias was assessed by funnel plot using mortality as an end point. We considered a P value less than 0.05 as significant.

Results

Nine of 23 potentially eligible studies,[w1-w9] totalling 849 patients, were included (see bmj.com). Three used frusemide to prevent acute renal failure[w1-w3] and six used frusemide to treat acute renal failure.[w4-w9] The

Study or subcategory	No with event/No in group		Relative risk (random effect) (95% CI)	Weight (%)	Relative risk (random effect) (95% CI)
	Frusemide	Placebo			
Inhospital mortality					
Frusemide to prevent acute deterioration in renal function					
Hager[w2]	6/62	3/59		1.92	1.90 (0.50 to 7.26)
Lassnigg[w1]	4/41	1/40		0.75	3.90 (0.46 to 33.42)
Subtotal (95% CI)	103	99		2.67	2.33 (0.75 to 7.25)
Total events: 10 (frusemide), 4 (placebo)					
Test for heterogeneity: χ^2=0.31, df=1, P=0.58, I^2=0%					
Test for overall effect: z=1.46, P=0.15					
Frusemide to treat acute renal failure					
Brown[w6]	18/28	16/28		19.25	1.13 (0.74 to 1.72)
Cantarovich[w7]	59/166	50/164		36.16	1.17 (0.86 to 1.59)
Cantarovich[w9]	9/19	7/13		7.22	0.88 (0.44 to 1.76)
Cantarovich[w9]	6/15	7/13		5.41	0.74 (0.33 to 1.65)
Kleinknecht[w5]	13/33	12/33		9.01	1.08 (0.58 to 2.01)
Shilliday[w4]	20/32	17/30		20.29	1.10 (0.73 to 1.67)
Subtotal (95% CI)	293	281		97.33	1.09 (0.90 to 1.31)
Total events: 125 (frusemide), 109 (placebo)					
Test for heterogeneity: χ^2=1.46, df=5, P=0.92, I^2=0%					
Test for overall effect: z=0.85, P=0.39					
Total (95% CI)	396	380		100.00	1.11 (0.92 to 1.33)
Total events: 135 (frusemide), 113 (placebo)					
Test for heterogeneity: χ^2=3.53, df=7, P=0.83, I^2=0%					
Test for overall effect: z=1.08, P=0.28					
Requirement for renal replacement therapy or dialysis					
Frusemide to prevent acute deterioration in renal function					
Hager[w2]	0/62	0/59			Not estimable
Lassnigg[w1]	2/41	0/40		0.47	4.88 (0.24 to 98.60)
Solomon[w3]	1/25	0/28		0.43	3.35 (0.14 to 78.60)
Subtotal (95% CI)	128	127		0.90	4.08 (0.46 to 35.96)
Total events: 3 (frusemide), 0 (placebo)					
Test for heterogeneity: χ^2=0.03, df=1, P=0.86, I^2=0%					
Test for overall effect: z=1.27, P=0.21					
Frusemide to treat acute renal failure					
Brown[w6]	28/28	27/28		47.31	1.04 (0.97 to 1.11)
Karayannopoulos[w9]	1/10	7/10		1.16	0.14 (0.02 to 0.96)
Kleinknecht[w5]	31/33	31/33		42.66	1.00 (0.88 to 1.13)
Shilliday[w4]	10/32	12/30		7.96	0.78 (0.40 to 1.54)
Subtotal (95% CI)	103	101		99.10	0.94 (0.71 to 1.26)
Total events: 70 (frusemide), 77 (placebo)					
Test for heterogeneity: χ^2=21.68, df=3, P<0.0001, I^2=86.2%					
Test for overall effect: z=0.39, P=0.69					
Total (95% CI)	231	228		100.00	0.99 (0.80 to 1.22)
Total events: 73 (frusemide), 77 (placebo)					
Test for heterogeneity: χ^2=13.95, df=5, P=0.02, I^2=64.2%					
Test for overall effect: z=0.12, P=0.91					

0.01 0.1 1 10 100
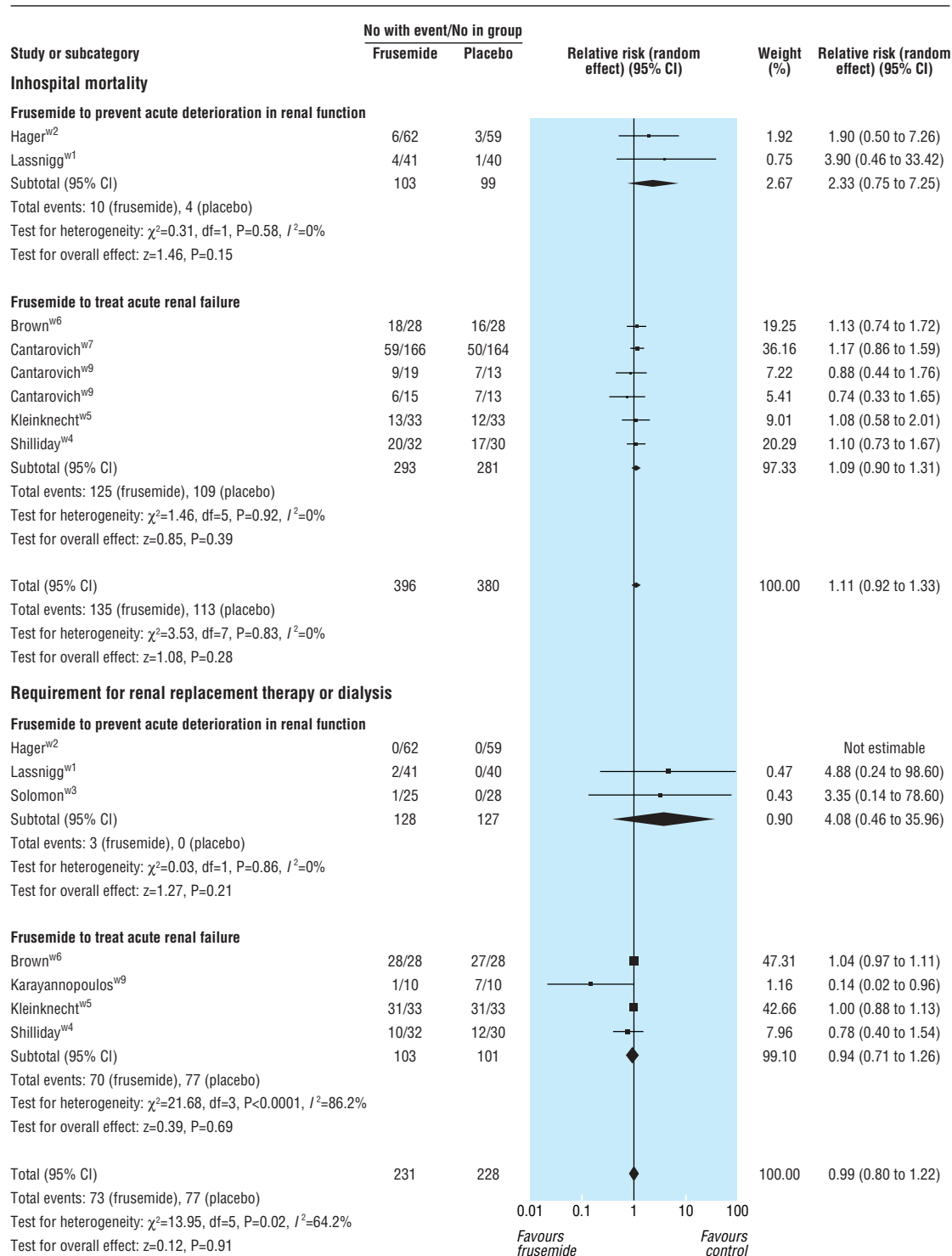Favours frusemide — Favours control

Fig 1 Effect of frusemide on in-hospital mortality and proportion of patients requiring renal replacement therapy or dialysis

three preventive studies included patients who underwent cardiac surgery, cardiac angiography, and major general or vascular surgery. In two of these studies all participants had mild pre-existing renal impairment.[w1] [w2] Five of the six treatment studies included patients with acute renal failure without chronic renal failure and one study included patients who had either acute renal failure or acute on chronic renal failure.[w9]

Doses of frusemide used to prevent acute renal failure were 1 mg/h or 2.5 mg/h by intravenous infusion[w1] [w2] or a single intravenous bolus dose of 80 mg.[w3] In the treatment group doses ranged from 600-3400 mg/day in studies of established acute renal failure. In one of these[w6] the control group also received one dose of frusemide (1 g) while the treatment group received prolonged frusemide infusion (3.4 g/day) until the serum creatinine level fell to less than 300 µmol/l. Two different doses of frusemide were assessed in two separate treatment groups in one study.[w8] The criteria for dialysis were described in three
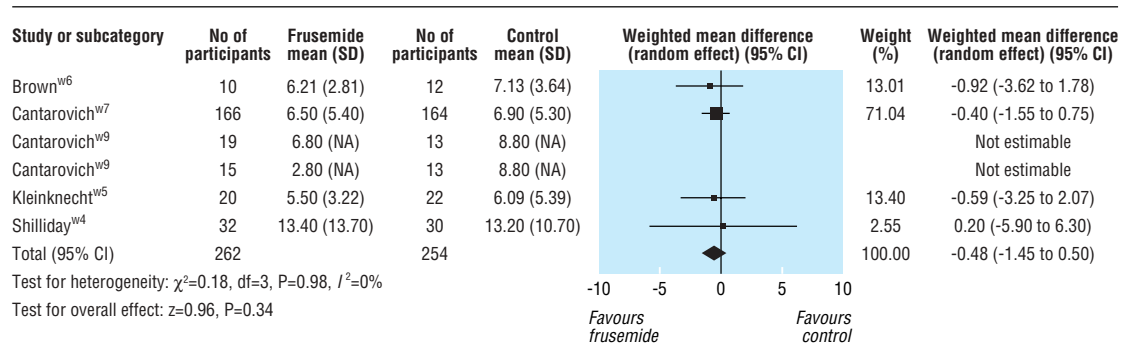
Study or subcategory	No of participants	Frusemide mean (SD)	No of participants	Control mean (SD)	Weighted mean difference (random effect) (95% CI)	Weight (%)	Weighted mean difference (random effect) (95% CI)
Brown[w6]	10	6.21 (2.81)	12	7.13 (3.64)		13.01	-0.92 (-3.62 to 1.78)
Cantarovich[w7]	166	6.50 (5.40)	164	6.90 (5.30)		71.04	-0.40 (-1.55 to 0.75)
Cantarovich[w9]	19	6.80 (NA)	13	8.80 (NA)			Not estimable
Cantarovich[w9]	15	2.80 (NA)	13	8.80 (NA)			Not estimable
Kleinknecht[w5]	20	5.50 (3.22)	22	6.09 (5.39)		13.40	-0.59 (-3.25 to 2.07)
Shilliday[w4]	32	13.40 (13.70)	30	13.20 (10.70)		2.55	0.20 (-5.90 to 6.30)
Total (95% CI)	262		254			100.00	-0.48 (-1.45 to 0.50)

Test for heterogeneity: $\chi^2=0.18$, df=3, P=0.98, $I^2=0\%$

Test for overall effect: z=0.96, P=0.34

-10   -5   0   5   10

Favours frusemide   *Favours control*

Fig 2 Number of dialysis sessions required after frusemide or control treatments

studies.[w5-w7] Jadad scores ranged from 1 to 5 (mean 2.6). Allocation concealment was adequate in four studies.[w1-w3 w7] Double blinding was used in four studies.[w1 w2 w4 w7] Three studies reported the proportion of patients who were randomised but lost to follow-up. (See bmj.com for characteristics of included studies.)

No significant heterogeneity was found for in-hospital mortality and ototoxicity but heterogeneity was significant for other outcomes. No significant reduction after frusemide treatment was found for in-hospital mortality (relative risk 1.11, 95% confidence interval 0.92 to 1.33, P=0.28, $I^2=0\%$; fig 1), risk for requiring renal replacement therapy or dialysis (0.99, 0.80 to 1.22, P=0.91, $I^2=64.2\%$; fig 1), number of dialysis sessions required (weighted mean difference −0.48 sessions, −1.45 to 0.50, P=0.34, $I^2=0\%$; fig 2), or proportion of patients with persistent oliguria (urine output <400-500 ml/day; 0.54, 0.18 to 1.61, P=0.27, $I^2=90.8\%$; fig 3). Regardless of whether frusemide was used to prevent or to treat acute renal failure no significant difference was found on mortality (relative risk ratio 2.10, 95 confidence interval 0.67 to 6.63, P=0.20) and the proportion of patients requiring dialysis (4.12, 0.46 to 37.2, P=0.21). High dose

frusemide (1-3.4 g daily) was associated with a suggestion of an increased risk of temporary deafness and tinnitus (relative risk 3.97, 95% confidence interval 1.00 to 15.78, P=0.05, $I^2=0\%$; fig 3). The length of hospital stay was reported in two preventive studies.[w1 w2] Frusemide was associated with an increase in hospital stay (weighted mean difference 3.57 days, 95% confidence interval 0.02 to 7.12, P=0.049, $I^2=0\%$). None of the studies reported a formal cost effectiveness analysis. The funnel plot showed a small possibility of publication bias, with absence of small studies showing a reduction in mortality after frusemide treatment (see bmj.com).

Sensitivity analyses

The magnitude and significance of the results was not changed after excluding one study that used a single bolus of frusemide in the control group[w6] or studies without adequate allocation concealment.[w4-w6 w8 w9]

Discussion

Meta-analysis showed that frusemide is not effective in the prevention and treatment of acute renal failure in

Study or subcategory	No with event/No in group		Relative risk (random effect) (95% CI)	Weight (%)	Relative risk (random effect) (95% CI)
	Frusemide	Control			
Patients who remained oliguric					
Brown[w6]	4/28	26/28		23.85	0.15 (0.06 to 0.38)
Cantarovich[w8]	8/19	6/13		24.89	0.91 (0.41 to 2.01)
Cantarovich[w8]	4/15	6/13		22.88	0.58 (0.21 to 1.61)
Kleinknecht[w5]	28/33	31/33		28.38	0.90 (0.76 to 1.07)
Total (95% CI)	95	87		100.00	0.54 (0.18 to 1.61)

Total events: 44 (treatment), 69 (control)

Test for heterogeneity: $\chi^2=32.63$, df=3, P<0.0001, $I^2=90.8\%$

Test for overall effect: z=1.11, P=0.27

Patients who mentioned deafness or tinnitus					
Brown[w6]	2/28	0/28		21.25	5.00 (0.25 to 99.67)
Cantarovich[w8]	3/166	1/164		37.49	2.96 (0.31 to 28.20)
Kleinknecht[w5]	3/33	0/33		22.24	7.00 (0.38 to 130.41)
Shilliday[w4]	1/32	0/30		19.02	2.82 (0.12 to 66.62)
Total (95% CI)	259	255		100.00	3.97 (1.00 to 15.78)

Total events: 9 (treatment), 1 (control)

0.01   0.1   1   10   100

Test for heterogeneity: $\chi^2=0.28$, df=3, P=0.96, $I^2=0\%$

Test for overall effect: z=1.96, P=0.05

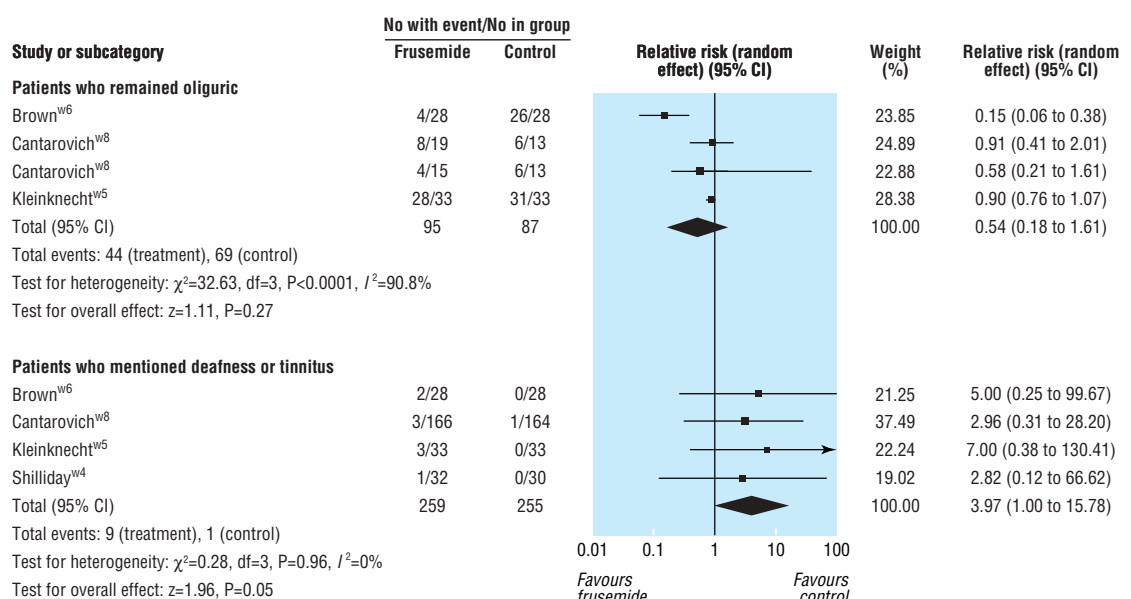*Favours frusemide*   *Favours control*

Fig 3 Proportion of patients remaining oliguric (urine output <400-500 ml/day) after frusemide or control treatments and those mentioning tinnitus or deafness

adults. It did not reduce in-hospital mortality, the requirement for dialysis, the number of dialysis sessions required until recovery of renal function, the proportion of patients remaining oliguric (urine output <400-500 ml/day), and the length of hospital stay. Furthermore, high doses may be associated with an increased risk of ototoxicity.

It has been argued that, especially at high doses, frusemide may convert oliguric acute renal failure to non-oliguric acute renal failure and thus reduce the requirement for dialysis.[w7 w14] We found no such potential benefits. As frusemide is largely excreted unchanged in the urine, it is the urinary excretion of the drug, not its plasma concentration, that determines the efficacy of its diuretic action.[5 6] Non-oliguric acute renal failure is in general associated with a better prognosis than oliguric acute renal failure.[7] Studies have shown that patients who have diuretic responses to frusemide have less severe acute renal failure.[w4] Therefore, a positive diuretic response to frusemide may indicate that patients have a milder form of acute renal failure rather than frusemide being capable of converting a more severe form of acute renal failure to a less severe form and improve the outcome.[w4 8] Our results agree with this hypothesis.

We did not find any significant increase in mortality after frusemide treatment. High doses (1-3.4 g daily) may, however, be associated with an increased risk of ototoxicity. Frusemide is primarily excreted by the kidneys and high doses can increase its serum concentration substantially in acute renal failure,[6 w8] hence the higher risk of ototoxicity.

Limitations of the study

In the pooled studies only four trials had adequate allocation concealment[w1-w3 w7] and four had a Jadad score of 3 or more.[w1 w2 w4 w7] The magnitude and direction of the results were not changed in sensitivity analysis by including only the studies with adequate allocation concealment. Furthermore, the number of patients we included may be inadequate to exclude small but significant clinical benefits of frusemide. With the sample size of this meta-analysis, a positive protective effect of frusemide on the risk for requiring dialysis can only be shown if the associated relative risk reduction exceeds 30%. If frusemide can reduce the relative risk for requiring dialysis by only 20%, a sample size of 400 patients would show such an effect if the

---

What is already known on this topic

Frusemide, a potent loop diuretic, can induce diuresis in some patients with acute renal impairment

What this study adds

Frusemide is not associated with any clinical benefits when used to prevent and treat acute renal failure in adults

High doses of frusemide may be associated with an increased risk of ototoxicity

---

baseline risk for requiring dialysis is 70% in the control group. Secondly, with the absence of small studies showing a reduction in mortality after frusemide treatment small publication bias was possible (see bmj.com). The asymmetrical shape of the funnel plot could be the result of the small number of included studies rather than to true publication bias.[9] Finally, although our results were largely consistent across the included studies, significant differences were found in how frusemide was given. The benefits of a particular dose or mode of administration remain uncertain.

1 Uchino S, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Diuretics and mortality in acute renal failure. *Crit Care Med* 2004;32:1669-77.
2 Ganeval D, Kleinknecht D, Gonzales-Duque LA. High-dose frusemide in renal failure. [Letter.] *BMJ* 1974;290:244-5.
3 Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;326:219.
4 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
5 Wittner M, Di Stefano A, Wangemann P, Greger R. How do loop diuretics act? *Drugs* 1991;41(suppl 3):1-13.
6 Miyazaki H, Hirai J, Taneike T. The pharmacokinetics and pharmacodynamics of furosemide in anesthetized dogs with normal and experimentally decreased renal function. *Nippon Juigaku Zasshi* 1990;52:265-73.
7 Frankel MC, Weinstein AM, Stenzel KH. Prognostic patterns in acute renal failure: the New York Hospital, 1981-1982. *Clin Exp Dial Apheresis* 1983;7:145-67.
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 Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *J Clin Epidemiol* 2005;58:894-901.

(Accepted 12 June 2006)

doi 10.1136/bmj.38902.605347.7C

The hazards of being an unemployed SHO

Being an unemployed senior house officer can lead to feelings of frustration, anxiety, and poor self worth. But by far the greatest hazard is in the constant search for adrenaline rushes alternative to those provided when carrying the crash bleep or learning a new clinical skill.

Last Sunday a friend took me to try an extreme sport called dirt surfing. This involves standing on a metal frame similar in shape to a giant skateboard with a BMX cycle wheel at the front and back and hurtling down a steep downhill dirt track. If you can build up enough speed the contraption becomes surprisingly stable, and you can practise using your body weight to steer while enjoying the incredible rush of hurtling downhill at speed on a sunny day. What a glorious activity.

Unfortunately, as far as I can gather, the only way to stop at the end of your ride is to fall off, and that's how I ended up with dirt in my hair, a bruise on my bottom, and a broken ankle.

The following day I had a previously arranged appointment for an unrelated medical problem, and I hobbled into the clinic in my newly acquired cast below the knee with my newly acquired crutches. The consultant saw me arrive and understood immediately the implications of my situation. He looked me up, down, then square in the eye, and said, "You really need to get yourself a job."

Belinda Hirsh *unemployed SHO, Borehamwood*
(binihirsh@unforgettable.com)