Pharmacodynamics of intravenous frusemide bolus in critically ill patients

Frank Shann

To the Editor: Huang and colleagues[1] report the effects of an intravenous bolus of frusemide 40 mg. However, they do not tell us how rapidly the bolus was given.

Rapid injection of frusemide causes ototoxicity which is related to the peak level.[2-4] It is exacerbated by renal failure and co-administration of aminoglycosides; toxicity of aminoglycosides is related to total area under the concentration–time curve and not the peak level, as shown in an elegant experiment in cats.[5] In 2001, we noticed a high prevalence of hearing impairment among children who had received extracorporeal membrane oxygenation in intensive care at the Royal Children's Hospital, Melbourne, and we realised that they had been given bolus doses of frusemide. Since 2001, the hospital policy has been that frusemide is never given as a bolus, and that the maximum rate of intravenous administration is 0.05 mg/kg/minute — so that a 1.0 mg/kg dose is infused over at least 20 minutes.[6] Whenever possible, high doses are given by continuous infusion, which often requires another intravenous cannula because frusemide is incompatible with many other drugs; solutions infused over more than 12 hours need to be protected from light.

It would be interesting to know how quickly Huang and colleagues gave the 40 mg frusemide boluses, and whether they tested for ototoxicity.

Frank Shann[1,2]

1 Royal Children's Hospital, Melbourne, VIC, Australia.

2 The University of Melbourne, VIC, Australia.

frank.shann@rch.org.au

1 Huang A, Luethi N, Mårtensson J, Bellomo R, Cioccari L. Pharmacodynamics of intravenous frusemide bolus in critically ill patients. *Crit Care Resusc* 2017; 19: 142-9.

2 Rybak LP. Furosemide ototoxicity: clinical and experimental aspects. *Laryngoscope* 1985; 95 (Suppl 38): 1-14.

3 Rybak LP. Pathophysiology of furosemide ototoxicity. *J Otolaryngol* 1982; 11: 127-33.

4 Heidland A, Wigand ME. The effect of furosemide at high doses on auditory sensitivity in patients with uremia. *Klin Wochenschr* 1970; 48: 1052-6.

5 Waitz JA, Moss EL, Weinstein MJ. Aspects of the chronic toxicity of gentamicin sulfate in cats. *J Infect Dis* 1971; 124 (Suppl): S125-9.

6 Shann F. *Drug doses*. 17th ed. Melbourne: Collective; 2017.

Luca Cioccari and Rinaldo Bellomo

In reply: We thank Shann for his constructive comments on our recent article.[1] To our knowledge, in adults, frusemide ototoxicity has only been described with high-dose intravenous (IV) therapy (> 240 mg/hour) or at lower doses (equivalent of 80–160 mg/hour) in patients with renal failure[2] or concurrent aminoglycoside therapy. We are not aware of reports of ototoxicity in adult patients for a dose of 40 mg IV as typically given by intensivists in Australia and New Zealand[3] and in accordance with the manufacturer's recommendations.[4] Moreover, in our unit (and probably in most other units), frusemide boluses of up to 80 mg are administered over 3–5 minutes by protocol.

We acknowledge that the risk of ototoxicity may be reduced by a continuous infusion of frusemide rather than bolus therapy. However, in a recent study of critically ill patients with acute kidney injury, no significant side effects were reported after a bolus dose of up to 80 mg IV of frusemide.[5]

As explicitly stated in our article, we excluded patients with chronic renal failure, and additional IV frusemide administration within 6 hours before or after the 40 mg bolus was not permitted, thus minimising risk. Nevertheless, we agree that caution is warranted when IV frusemide is administered to high-risk patients and that slow administration may be wise.

Luca Cioccari[1,2]

Rinaldo Bellomo[1,3]

1 Austin Health, The University of Melbourne, Melbourne, VIC, Australia.

2 Department of Intensive Care Medicine, University Hospital, University of Bern, Switzerland

3 The University of Melbourne, Melbourne, VIC, Australia.

luca.cioccari@austin.org.au

1 Huang A, Luethi N, Mårtensson J, Bellomo R, Cioccari L. Pharmacodynamics of intravenous frusemide bolus in critically ill patients. *Crit Care Resusc* 2017; 19: 142-9.

2 Brown CB, Ogg CS, Cameron JS. High dose frusemide in acute renal failure: a controlled trial. *Clin Nephrol* 1981; 15: 90-6.

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

4 Sanofi Australia. Lasix (frusemide): information for health professionals.. http://www.guildlink.com.au/gc/ws/sw/pi.cfm?product=swplasix10816 (accessed Sept 2017).

5 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.