

## Commentary

# Recently published papers: Topical issues in pharmacology

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The use of pharmacological agents in intensive care units (ICUs) is ever on the increase, with novel therapies appearing in the literature regularly. The complexities of polypharmacy are a challenge to the intensivist, and any guidance as to which drugs to use, when to use them and how much to use is always welcome. Happily, therefore, over the past 2 months a number of interesting papers and articles have appeared covering drugs both new and old.

Cardiac arrest in the community is associated with a very high mortality rate. Ventricular fibrillation (VF) is both the most common mode of arrest and carries the best prognosis if early defibrillation is available [1]. However, a subgroup of patients with VF are resistant to direct current defibrillation, in which case an antiarrhythmic agent is required, but very few randomized controlled trials (RCTs) have been conducted to verify the efficacy of any particular agent.

Dorian and colleagues [2] compared lidocaine with amiodarone in the management of out-of-hospital, shock-resistant VF. In a double-blind RCT, 347 patients were randomly assigned to either lidocaine 1.5 mg/kg or amiodarone 5 mg/kg as an initial dose. In addition, a further 1.5 and 2.5 mg/kg, respectively, were given if required. The primary end-point was survival to hospital. A total of 41 patients (22.8%) in the amiodarone group and 20 patients (12.0%) in the lidocaine group survived to hospital ( $P=0.009$ ; odds ratio 2.17, 95% confidence interval 1.21–3.83). However, only nine patients in the amiodarone and five in the lidocaine group survived to hospital discharge.

In this population, receiving amiodarone increased the chances of an individual arriving at hospital alive. Time to paramedic intervention (i.e. drug administration), however, was an equally important factor. Interestingly, time interval to first attempted defibrillation was not associated with a survival benefit, which is presumably a reflection of the

refractory nature of the VF. Sadly, the survival rate to discharge – a more relevant outcome – between the groups was not significantly different, with overall survival to discharge being a dismal 4%. This low survival is consistent with out-of-hospital cardiac arrest. However, it seems reasonable to extrapolate these findings to the in-patient population, in which case administration of amiodarone as the first-line agent for shock-resistant VF may result in improved survival in the hospital setting.

Staying with matters cardiac, an RCT that considered the management of acute exacerbations of chronic heart failure was published in March 2002 in the *Journal of the American Medical Association* [3]. The precise role of the selective phosphodiesterase inhibitor milrinone in intensive care remains obscure, with no survival benefit demonstrated. Acute exacerbation of chronic heart failure is a relatively common indication for admission into a critical care setting, but with few randomized outcome trials to guide our management. This study investigated whether a short course of milrinone could improve clinical outcomes. Patients were randomly assigned to a 48-hour infusion of milrinone (0.5 µg/kg per min initially) or placebo. The number of hospital days for management of cardiovascular problems 60 days after randomization did not differ between the two groups, and no difference was found for in-hospital or 60-day mortality. The milrinone group suffered higher incidences of hypotension requiring intervention and new atrial arrhythmias. The study adds weight to the feeling that the selective phosphodiesterase inhibitors contribute little to the general intensivists pharmacological arsenal.

Singer and colleagues [4] reported on eight patients with septic shock refractory to fluid, catecholamine, corticosteroid and methylene blue therapy who were salvaged with the long-acting vasopressin analogue terlipressin. The use of vasopressin has previously been described in resistant

hypotension secondary to sepsis, but is associated with troublesome rebound hypotension on withdrawal [5,6]. An intravenous bolus of terlipressin (1–2 mg) was given to each of eight patients demonstrating profound and resistant vascular hyporeactivity. Bolus terlipressin resulted in a progressive increase in mean arterial pressure, allowing withdrawal of noradrenaline (norepinephrine) in seven of the eight patients. This improvement in mean arterial pressure was maintained for 5 hours; one patient required a repeat bolus. Four patients went on to ICU discharge and three to hospital discharge. No negative sequelae were noted. The authors concluded that, although the mechanism of increased vasomotor sensitivity to terlipressin is not known, it offers a promising alternative for management of life-threatening and intractable hypotension in septic shock. Although such reports are somewhat anecdotal, the results are promising for a condition that is known to carry a high mortality rate, and it may be that the time for a larger outcome trial approaches.

The March/April edition of *Intensive Care Monitor* [7] comments on a paper that examined the immunomodulatory effects of high-dose hydrocortisone in septic shock [8]. It is known that cortisol has permissive and suppressive effects on the immune response, and it has been reported that supraphysiological doses can reverse septic shock [9]. However, little is known regarding the cytokine response to high-dose hydrocortisone. In a small, double-blind, placebo-controlled RCT, 24 patients with septic shock were randomly assigned to either high-dose hydrocortisone or placebo [8]. End-points included time to shock reversal and effect on serum cytokine concentration. By day 3 the Sequential Organ Failure Assessment score was lower in the hydrocortisone group than in the placebo group ( $P < 0.05$ ). No difference in mortality was found. Interleukin-6 and interleukin-8 were both significantly reduced in the treatment group, whereas interleukin-10 and tumour necrosis factor- $\alpha$  were similar between the two groups.

The observed reduction in interleukin-6 levels is of significance because this proinflammatory cytokine has been correlated with severity of septic shock, and this may explain the quicker resolution of organ-related morbidity in the treatment group. This is consistent with findings reported in a more recent paper on the effects of methylprednisolone in unresolving acute respiratory distress syndrome [10], and may account for a therapeutic modality by which high-dose steroid therapy works. It is difficult to conclude a great deal more from this study, but it positively contributes towards a rationale for the use of steroids in management of the inflammatory response.

Thromboembolic disease is a frequent cause of morbidity and mortality in ICU patients, and it often goes undetected. Low-molecular-weight heparins have been shown to reduce significantly the incidence of thromboembolic complications [11] and are now considered standard therapy, but the

incidence remains high in critically ill patients when compared with that in other patient populations. A group from Amsterdam postulated in *The Lancet* that this may be partly due to lowered bioavailability resulting from vasopressor use in critically ill patients. They considered three groups of patients: ICU patients on vasopressors, ICU patients not on vasopressors and postoperative ward patients. Each patient had received at least three doses of nadroparin 2850 IU. Serial concentrations of factor Xa activity (do the authors mean anti-factor Xa activity?) were compared between the groups. The biological action of the low-molecular-weight heparin was found to be significantly less in ICU patients on vasopressors than in ICU patients not on vasopressors and in postoperative ward patients.

This lower heparin activity may contribute to the observed high incidence of thromboembolism in the critically ill population. It is suggested that vasopressor therapy reduces the uptake of subcutaneously administered drug as a result of impaired peripheral perfusion, and therefore these patients should be given greater doses. In the absence of routine anti-factor Xa activity assays, some caution may be required before instituting blind dose increases for a group of patients who are at risk of occult bleeding and for a drug with effects that are difficult to reverse.

## Competing interests

None declared.

## References

- Eisenberg MS, Mengert TJ: **Cardiac resuscitation.** *N Engl J Med* 2001, **344**:1304-1313.
- Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A: **Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation.** *N Engl J Med* 2002, **346**:884-890.
- Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghide M: **Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial.** *JAMA* 2002, **287**:1541-1547.
- O'Brien A, Clapp L, Singer M: **Terlipressin for norepinephrine-resistant septic shock.** *Lancet* 2002, **359**:1209-1210.
- Malay MB, Ashton RC Jr, Landry DW, Townsend RN: **Low-dose vasopressin in the treatment of vasodilatory septic shock.** *J Trauma* 1999, **47**:699-703.
- Tsuneyoshi I, Yamada H, Kakihana Y, Nakamura M, Nakano Y, Boyle WA III: **Hemodynamic and metabolic effects of low-dose vasopressin infusions in vasodilatory septic shock.** *Crit Care Med* 2001, **29**:487-493.
- Jenkins IR: **Immunomodulation in septic shock: hydrocortisone differentially regulates cytokine response.** *Intensive Care Monitor* 2002, **9**:32-33.
- Briegel J, Jochum M, Gippner-Steppert C, Thiel M: **Immunomodulation in septic shock: hydrocortisone differentially regulates cytokine responses.** *J Am Soc Nephrol* 2001, **12**(suppl 17):S70-S74.
- Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcen A: **Reversal of late septic shock with supraphysiologic doses of hydrocortisone.** *Crit Care Med* 1998, **26**:645-650.
- Umberto Meduri G, Tolley AE, Chrousos GP, Stentz F: **Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome.** *Am J Respir Crit Care Med* 2002, **165**:983-991.
- Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH: **Deep vein thrombosis and its prevention in critically ill adults.** *Arch Intern Med* 2001, **161**:1268-1279.