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EDITORIAL

Some is good and more is bad: getting the dose right in the critically ill

Critically ill patients are the sickest patients in the hospital. The patient's attendants naturally feel that if they are giving a drug or using a technique to improve the patient's condition, then giving them as much as possible has to be good. But is this really so? Clearly, for some drugs, this is wrong. Usually these drugs have easy laboratory measurements or clinical measures of effect. For example, heparin and insulin have simple, quantitative analyses of their effects: thrombin time and blood glucose concentration. Given in excess, both drugs can cause the life-threatening complications of haemorrhage and hypoglycaemia. Not all drugs have the same easy methods of monitoring nor the potential life threatening complications. The antibiotics vancomycin and gentamicin may cause deafness with high concentrations over time. Their assays should be available in every hospital in which they are prescribed, but they are more difficult than the measurements of blood glucose concentration and thrombin time.

We may not know fully the relationship between dose, plasma concentration and the physiological change, for example digoxin. Similarly, corticosteroids have been used in pharmacological doses in the treatment of shock [1]. Such doses have been shown to be associated with an increased mortality, especially in those patients with renal failure [2]. More recently, the use of lower doses of corticosteroids has been shown to improve outcome of survival from septic shock [3]. Dopexamine is the synthetic analogue of the naturally occurring catecholamine, dopamine. It produces changes in cardiac output, arterial pressure, systemic vascular resistance, oxygen transport and other haemodynamic variables. The role of dopexamine has been studied in the preoperative 'optimization' of the high-risk surgical patient, using these variables. A large multicentre study was performed in which a placebo group was compared with a low-dose dopexamine ($0.5\,\mu g\,kg^{-1}\,min^{-1}$) group and a high-dose dopexamine ($2.0\,\mu g\,kg^{-1}\,min^{-1}$) group [4]. At 28 days, there was no significant difference in mortality between the three groups. However, posthoc analysis has shown that the low-dose dopexamine group had a reduced mortality in the cohort of emergency surgical patients. Accepting the difficulty with posthoc analysis, it is surprising that the lower dose, with limited cardiovascular effects, should have this favourable outcome.

Improving patient comfort (reducing anxiety and agitation, inducing sleep) is one of the major concerns of those looking after critically ill patients. However, there is no easy measure that encompasses all aspects of patient comfort. Sedation scores tend to be monitors of conscious level, while plasma concentrations of drug are difficult, and correlate poorly with effect. Even when sedation scales are used as part of protocol-driven treatment, they tend to be poorly or inappropriately used. Over-sedation is common [5–7]. This makes patients easier to look after; they stay still, do not extubate their tracheal tubes, or pull out their intravascular cannulae, or 'fight' the ventilator. All of these may be good; however, the overall risks to the patient of over-sedation are considerable [8]. Failure to wake up results in an increased rate of ventilator-associated pneumonia and cranial computerized tomography scans. Other more subtle risks include changes in the immune system, critical care neuropathy, muscle wasting and pressure sores [9]. Neuromuscular-blocking agents may be essential in a few selected patients. Their use by continuous infusion, but without monitoring (either electrostimulatory or by intermittently stopping), may lead to an increased risk of postintensive care weakness, although this has been disputed [10,11].

Feeding is life-saving treatment. Once again, there is an often held belief that the more the better. An excessive intake of carbohydrates leads to an increase in carbon dioxide production. This may then be responsible for prolonged weaning from mechanical ventilation [12,13]. In addition, the increase in meta-

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bolism can result in fever. Fats are also an essential component of enteral and parenteral nutrition. The adverse effects of administering too much have been well reported. Pancreatitis, cholestasis and hepatic dysfunction are not uncommon. These conditions may be also inadvertently caused when drugs, solubilized in fat, are given along with total parenteral nutrition. For example, the fat load given to a patient receiving total parenteral nutrition and sedated with propofol can be far in excess of requirements [14].

It is not just drugs, which may be given in excess. Humidification of the artificial airway is another area where there is often little consideration and adjustment of the treatment to the patient's needs. The problems of over and under humidification of mechanically ventilated patients have been well documented [15,16]. These may be a reflection of the difficulties of monitoring effect. The Sputum Scoring System has been developed to standardize the amount and consistency of sputum [17]. There may be a change from a heat and moisture exchange (HME) to a hot water bath humidifier when the secretions become sticky and viscous. In our experience, the reversion back to HME when the secretions become watery is rare. Perhaps a change in practice would come about if a more reliable method of monitoring humidification became commonplace. Alternatively, new technology may be able to self-regulate according to the patient's requirement [18].

High values of positive end-expiratory pressure (PEEP) and other intrapulmonary pressures in a patient whose lungs are being mechanically ventilated may result in the detrimental effects of barotrauma and volume trauma [19]. Originally, large ($>12\,mL\,kg^{-1}$) tidal volumes were thought to increase recruitment of alveoli and improve gas exchange. However, this is now known to be hazardous in most patients. Ventilation strategies using tidal volumes of $6-8\,mL\,kg^{-1}$ along with higher positive end-expiratory pressures of 10–15 cmH_2O have been associated with a reduced mortality [20,21]. This has been called the 'open lung' approach [22]. In addition, Ranieri and his colleagues [23] showed in a randomized controlled trial of patients with acute respiratory distress syndrome that the cytokine response to mechanical ventilation may be attenuated by minimizing overdistension of the lungs.

There have been many debates in recent years over the correction of low plasma concentrations, even to normal physiological values. There is some evidence that indeed such attempts at correction may be hazardous to the patient. The administration of albumin to correct hypoalbuminaemia is, at best, ineffective at altering the outcome, and at worst, it may increase mortality (although this remains contentious) [24–26]. Similarly in sepsis, plasma iron concentrations decrease because of redistribution but total body iron stores remain normal. By withholding iron supplementation, micro-organisms are depleted of an essential growth factor. Therefore, giving iron may increase host susceptibility to infection [27,28]. Zinc is another trace element that has a decrease in plasma concentration during acute critical illness. If supplementation is provided to patients with catheter sepsis or pancreatitis, fever is increased [29].

Traditionally in the UK, in patients needing mechanical ventilation of the lungs, haemoglobin concentration has been kept at around $10\,g\,dL^{-1}$. This value was thought to be the best balance between viscosity and oxygen delivery, to improve arterial pressure and outcome. However, the Canadian Transfusion Study showed that a lower haemoglobin concentration ($7–8\,g\,dL^{-1}$) is associated with reduced mortality in this group of critically ill patients [30].

There is still much for us to learn and appreciate about the use of drugs and techniques in the critically ill population. Therapeutic failure is usually easy to recognize. For a few drugs, overdose is easy to recognize either in the laboratory or clinically, for example the opioids and the catecholamines. As time passes and more sophisticated modes of monitoring become incorporated into clinical practice, then many of the concerns about over-treatment may be alleviated. The introduction of the bispectral index monitor (BIS) may be of benefit, in conjunction with other monitoring systems, in the prevention of over sedation [31]. For many drugs, however, the clinician's scepticism about the safety of drugs and therapy in large doses remains the best defence for the patient against toxicity, morbidity and potentially mortality.

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References

1 Kass EH. High-dose corticosteroids for septic shock. *N Engl J Med* 1984; **311**: 1178–1179.

2 Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; **317**: 653–658.

3 Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; **26**: 645–650.

4 Takala J, Meier-Hellmann A, Eddleston J, Hulstaert P, Sramek V. Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. *Crit Care Med* 2000; **28**: 3417–3423.

5 Shelly MP, Sultan MA, Bodenham A, Park GR. Midazolam infusions in critically ill patients. *Eur J Anaesthesiol* 1991; **8**: 21–27.

6 Detriche O, Berre J, Massaut J, Vincent JL. The Brussels sedation scale: use of a simple clinical sedation scale can avoid excessive sedation in patients undergoing mechanical ventilation in the intensive care unit. *Br J Anaesth* 1999; **83**: 698–701.

7 McCollam JS, O'Neil MG, Norcross ED, Byrne TK, Reeves ST. Continuous infusions of lorazepam, midazolam, and propofol for sedation of the critically ill surgery trauma patient: a prospective, randomized comparison. *Crit Care Med* 1999; **27**: 2454–2458.

8 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *Engl J Med* 2000; **342**: 1471–1477.

9 Prielipp RC, Coursin DB, Wood KE, Murray MJ. Complications associated with sedative and neuromuscular blocking drugs in critically ill patients. *Crit Care Clin* 1995; **11**: 983–1003.

10 Meyer KC, Prielipp RC, Grossman JE, Coursin DB. Prolonged weakness after infusion of atracurium in two intensive care unit patients. *Anesth Analg* 1994; **78**: 772–774.

11 Prielipp RC, Coursin DB, Scuderi PE *et al.* Comparison of the infusion requirements and recovery profiles of vecuronium and cisatracurium 51W89 in intensive care unit patients. *Anesth Analg* 1995; **81**: 3–12.

12 Herve P, Simonneau G, Girard P, Cerrina J, Mathieu M, Duroux P. Hypercapnic acidosis induced by nutrition in mechanically ventilated patients: glucose versus fat. *Crit Care Med* 1985; **13**: 537–540.

13 al Saady NM, Blackmore CM, Bennett ED. High fat, low carbohydrate, enteral feeding lowers $PaCO_2$ and reduces the period of ventilation in artificially ventilated patients. *Intensive Care Med* 1989; **15**: 290–295.

14 Eddleston JM, Shelly MP. The effect on serum lipid concentrations of a prolonged infusion of propofol – hypertriglyceridaemia associated with propofol administration. *Intens Care Med* 1991; **17**: 424–426.

15 Branson RD, Campbell RS. Humidification in the intensive care unit. *Respir Care Clin N Am* 1998; **4**: 305–320.

16 Shelly MP, Lloyd GM, Park GR. A review of the mechanisms and methods of humidification of inspired gases. *Intens Care Med* 1988; **14**: 1–9.

17 Suzukawa M, Usuda Y, Numata K. The effect of sputum characteristics of combining an unheated humidifier with a heat-moisture exchanging filter. *Respir Care* 1989; **34**: 976–984.

18 Kapadia F, Shelly MP, Anthony JM, Park GR. An active heat and moisture exchanger. *Br J Anaesth* 1992; **69**: 640–642.

19 Gammon RB, Shin MS, Buchalter SE. Pulmonary barotrauma in mechanical ventilation. Patterns and risk factors. *Chest* 1992; **102**: 568–572.

20 Artigas A, Bernard GR, Carlet J *et al.* The American-European Consensus Conference on ARDS, Part 2. Ventilatory, pharmacologic, supportive therapy, study design strategies and issues related to recovery and remodeling. *Intensive Care Med* 1998; **24**: 378–398.

21 Marini JJ. Tidal volume, PEEP, and barotrauma. An open and shut case? *Chest* 1996; **109**: 302–304.

22 Kirby RR. Round and round we go, and where we stop, nobody knows: the open lung concept and high-level positive end-expiratory pressure (revisited). *Crit Care Med* 2000; **28**: 1672–1673.

23 Ranieri VM, Suter PM, Tortorella C *et al.* Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999; **282**: 54–61.

24 Nicholson J, Woolmarans M, Park GR. The role of albumin in critical illness. *Br J Anaesth* 2000; **85**: 599–610.

25 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *Br Med J* 1998; **317**: 235–240.

26 Cook D, Choi P. Review: albumin does not reduce death in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia: Commentary. *Evidence Based Med* 1999; **4**: 19.

27 Fishbane S. Review of issues relating to iron and infection. *Am J Kidney Dis* 1999; **34**: S47–S52.

28 Hoen B. Iron and infection: clinical experience. *Am J Kidney Dis* 1999; **34**: S30–S34.

29 Lindahl M, Leanderson P, Tagesson C. Novel aspect on metal fume fever: zinc stimulates oxygen radical formation in human neutrophils. *Hum Exp Toxicol* 1998; **17**: 105–110.

30 Hebert PC, Wells G, Blajchman MA *et al.* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; **340**: 409–417.

31 De Deyne C, Struys M, Decruyenaere J, Creupelandt J, Hoste E, Colardyn F. Use of continuous bispectral EEG monitoring to assess depth of sedation in ICU patients. *Intensive Care Med* 1998; **24**: 1294–1298.

