

Correspondence

Fat metabolism during propofol infusion

Editor,—Tsubokawa and colleagues¹ suggest that their finding of hypertriglyceridaemia in rabbits receiving infusions of propofol may provide an explanation for the adverse events reported after prolonged propofol infusion in children receiving intensive care.² The case report of fat overload syndrome³ to which they refer describes an infant receiving long-term parenteral nutrition, including fat emulsion 5 g kg⁻¹ day⁻¹, who developed tachycardia, fever, liver dysfunction, coagulopathy and hyperlipidaemia. These abnormalities were thought to be caused by fat overload and resolved after discontinuation of the i.v. lipid solution. In contrast, one of the striking features described in reports of possible propofol toxicity in children^{2,4–6} is the occurrence of bradycardia with abnormal atrioventricular conduction. In addition, the lipid load these children received (<2.4 g kg⁻¹ day⁻¹) was below the maximum recommended for parenteral nutrition.

Propofol for prolonged sedation in humans appears to have been introduced without prior animal studies and there remains a paucity of laboratory data. Infusions of propofol of 8 h duration have been studied in the rabbit undergoing mechanical ventilation.⁷ Only light planes of anaesthesia were obtained with a mean propofol infusion rate of 876 µg kg⁻¹ min⁻¹. Anaesthesia was complicated by a high incidence of hypotension and hypoxaemia. Four of 10 rabbits died during the study. No adverse effects were seen in two control rabbits that received infusions of lipid alone.

It is unlikely that the fat overload syndrome is the cause of the adverse reactions described in children receiving prolonged propofol infusions. An animal model of prolonged high-dose propofol infusion would further our understanding of these events.

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Editor,—We thank Dr Cray for his interest in our article. He points out that the adverse reactions induced by prolonged propofol infusion in children are pathologically different from fat overload syndrome, because the former causes bradycardia with abnormal atrioventricular conduction but the latter causes tachycardia. We believe this is caused by a difference in plasma propofol concentration.

All of the patients described by Parke and colleagues¹ were undergoing mechanical ventilation which suggests they were suffering from respiratory dysfunction. As propofol is metabolized more slowly under hypoxic compared with normoxic conditions,² plasma propofol concentrations may be higher in patients suffering from respiratory dysfunction, and as propofol is a negative inotrope, high concentrations may cause bradycardia.

In contrast, Dr Cray suggested that it is unusual to develop fat overload syndrome when the propofol infusion rate is <2.4 g kg⁻¹ day⁻¹. We do not agree with this point. Intralipid is frequently infused in critically ill patients. Lindholm demonstrated that fat elimination was slower in such patients compared with healthy subjects.³ When propofol is infused in critically ill patients for prolonged periods, there is a possibility that the fat overload syndrome can occur, even if propofol is infused below the maximum recommended rate.

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Adrenocortical function and steroid therapy in critical illness

Editor,—The editorial by Masterson and Mostafa¹ made interesting reading, particularly as it coincided with the 50th anniversary of the discovery of the anti-inflammatory effects of cortisone in rheumatoid arthritis. Readers may be interested to refer to a recent article by Glyn² on the discovery of cortisone by Philip Hench. This discovery earned Hench the Nobel prize for medicine in 1950. However, steroids seemed destined for controversy from the start, because in 1954 a multicentre study showed no difference between the effects of cortisone and aspirin in rheumatoid arthritis, and Glyn notes that the clinical usefulness of cortisone in rheumatology remains controversial to this day. Glyn also maintains that the significance of cortisone 'in general medicine remains beyond dispute'. If only that were true for steroids in intensive care medicine!

Masterson and Mostafa mention the controversy regarding the relationship between relative adrenocortical insufficiency and outcome. We agree that there is doubt that adrenocortical insufficiency is associated with increased mortality in the critically ill, but disagree that the study by Schein and colleagues³ 'failed to find a relationship between low plasma cortisol concentrations and increased mortality'. While it is true that there was no significant difference between cortisol concentrations of survivors and non-survivors, the number of subjects was small, no ACTH stimulation tests were performed and none of the patients had a blood cortisol concentration below the 'normal' range (10–20 µg dl⁻¹). Therefore, while there was no evidence of adrenal hypofunction, the study was unable to support conclusions about the relationship between adrenal hypofunction and mortality.

Also mentioned in Masterson and Mostafa's editorial were the problems in the diagnosis of relative adrenocortical insufficiency because of the lack of consensus on interpretation of the ACTH stimulation test.¹ In the conclusion of a review of ACTH stimulation tests in 1985, May and Carey stated: 'survey of the literature reveals a bewildering variety of criteria for normalcy of rapid ACTH test results'.⁴ They proposed that a peak cortisol concentration greater than 550 nmol litre⁻¹ was a satisfactory single criterion for normal adrenal function. Not all workers have accepted this value and there remains a confusing array of criteria. Some, such as Patel, Selby and Jeffcoate, have proposed higher peak concentrations.⁵ Others support the use of the cortisol increment.⁶

We feel that many of these controversies exist because, as mentioned by Masterson and Mostafa, it is not yet clear what constitutes normal adrenal function in the critically ill. On the subject of adrenal insufficiency in the critically ill, it seems the scientific community have put the cart before the horse, with the driver carrying the horse! We are

using a test (the ACTH stimulation test) without being sure of how to interpret the result, to diagnose a condition which may not even exist, without even knowing what constitutes normal function.

Thus while we wholeheartedly agree with Masterson and Mostafa that a consensus on the definition of adrenal insufficiency in critical illness is needed, we feel that this should wait while vigorous efforts are made to establish what constitutes 'normal' adrenocortical function in these patients.

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Editor,—The recent editorial by Masterson and Mostafa on adrenocortical function in critical illness again draws attention to this important area.¹ However, a few points are perhaps worthy of discussion.

Inclusion of the reports by Finlay and McKee of June 1982² and McKee and Finlay of February 1983³ from the Western Infirmary, Glasgow is fallacious, as these patients were receiving etomidate infusions. This oversight, which first appeared 11 yr ago,⁴ has been repeated by numerous authors since.^{5–13} In fact, in June 1983, Ledingham and Watt found that after the introduction of etomidate, mortality in the ICU of the Western Infirmary among trauma patients increased from 25% in 1979–80 to 44% in 1981–82.¹⁴ Ledingham, Finlay, Watt and McKee reported the effect of stopping etomidate.¹⁵ Of 21 subsequent patients, none had low plasma cortisol concentrations compared with 27% of the previous 133 patients. The rest is history.¹⁶ The Glasgow reports are important, not for indicating an incidence of adrenocortical hypofunction in critical illness (which they clearly do not) but rather that if adrenal function is iatrogenically depressed, mortality increases.^{2,3} Subsequent exogenous cortisol (hydrocortisone) replacement, not

surprisingly, improves mortality.³ The June 1982 report did not find that 27% of critically ill patients had low plasma cortisol concentrations,² as quoted by Masterson and Mostafa,¹ rather it was the second article published in February 1983 that included this finding.³ Interestingly, the same error was made by Journey and colleagues in 1987.⁴

Premorbid Addison's or pituitary disease is rare in critically ill patients and adrenal function usually returns to normal in survivors.⁴⁻⁶ What is more common and what is the issue in critical illness is reversible adrenal suppression, especially in the face of prolonged sepsis. Despite the suggestion to the contrary,¹ thyroid function tests are of little help as a marker of secondary adrenal insufficiency in critical illness.¹⁰⁻¹³ Masterson and Mostafa correctly point out the association between inotrope requirements and suspicion of adrenal insufficiency. However, it is not the rapidity of the increase that is the clue, rather it is the resistance to inappropriately high doses for the clinical condition.⁶⁻¹⁷ Furthermore, although not generally recognized, we have found high cardiac output and low systemic vascular resistance to be recurrent features in these patients.⁶⁻¹⁸

Schein and colleagues' study examined unstimulated plasma cortisol concentrations 11 ± 2 h after septic shock.¹⁹ All patients had concentrations greater than 0.5 µmol litre⁻¹. Therefore, by the criteria of basal plasma cortisol concentrations, they did not find adrenal insufficiency.¹ Masterson and Mostafa's second reference to this study, casting doubt on the association between adrenocortical insufficiency and outcome, would therefore seem illogical.

Using unstimulated plasma cortisol concentrations, Cook and colleagues found evidence of adrenal insufficiency in septic patients.⁹ Three ACTH stimulation studies in septic patients found an incidence of adrenal insufficiency of 19%, 41% and 24%, respectively.⁷⁻¹³⁻²⁰ It is of note that the time of testing was within 24 h of the diagnosis of sepsis for two of these studies and the morning after diagnosis in the other. Contrary to Duggan, Browne and Flynn's assertion,¹⁷ in the case reports that prompted the editorial, Bouachour and colleagues did not find that the incidence of adrenal insufficiency ranged from 6.25% to 75% depending on the population studied, rather it depended on the different criteria used to interpret the ACTH stimulation test.¹² Journey and colleagues' report showing a 2% incidence deserves further analysis.⁴ Although 70 patients were included, only 13 were septic, nine of whom died. All patients were studied within 3 h of admission. One patient who had low post-ACTH cortisol concentrations was given hydrocortisone and survived.

Masterson and Mostafa's views on the role of ACTH stimulation tests and cortisol assays in guiding treatment are overly dismissive.¹⁷ An ACTH test takes 1 h or less. If treatment is imperative, hydrocortisone may be started before laboratory confirmation. If the situation is desperate, dexamethasone 4 mg (not detected by the plasma cortisol assay) may be given with equal or greater effect than

hydrocortisone 100 mg. Subsequent ACTH stimulation testing may confirm or refute the diagnosis later.

Indeed, physiological doses of corticosteroids may improve outcome but Schneider and Voerman used cortisol 300 mg (hydrocortisone) daily,²¹ not the 30 mg quoted¹ (which is certainly not physiological in critically ill patients). Even this is not the whole story as Sainsbury, Stoddart and Watson demonstrated that plasma cortisol concentrations 180 min after hydrocortisone 100 mg ranged from 1.22 to 4.660 µmol litre⁻¹ depending on the patient's weight.²² The dose should be individualized.²³

A final point: the reference given by Masterson and Mostafa for the study by Rothwell, Udwardia and Lawler⁷ is the same as the one cited by Bouachour and colleagues in 1995 and is incorrect.¹² The correct reference is included below.

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Editor,—Thank you for the opportunity to reply to Dr McAllister and Drs Absalom and Scott. We are grateful to Dr McAllister for pointing out the typing error of the dose of hydrocortisone (300 mg day⁻¹) recommended by Schneider and Voerman¹ in critically ill patients, and giving us the correct reference for Rothwell, Udwardia and Lawler.²

Unlike Knighton, Woodcock and Hough,³ and Absalom and Scott, Dr McAllister may have missed the message of the editorial. Apart from highlighting the problem and causes of adrenocortical insufficiency in the critically ill, the message is that patients who have low basal plasma cortisol concentrations probably have adrenocortical insufficiency. However, some critically ill patients appear to have 'normal' or even markedly increased plasma cortisol concentrations and/or may or may not respond 'normally' to a short tetracosactrin (Synacthen) test. Also, occasionally in such patients, circulatory collapse which does not respond to inotropic support appears to respond to 'physiological' hydrocortisone administration, as Knighton, Woodcock and Hough described.³ Do these patients have adrenocortical insufficiency or is there another explanation? Although the patients appear to behave as such, our current state of knowledge and the literature do not easily provide the answer.

We were aware that many of the patients described in the reports from the Western Infirmary, Glasgow^{4,5} received etomidate. It was not, therefore, an oversight that we included their findings. We also agree with the conclusions of Ledingham and colleagues on the association between etomidate, low cortisol concentrations and mortality.^{6,7} If we understood his letter, McAllister appears to lay *all* the Glasgow findings at the door of etomidate. This interpretation does not allow for the degree of clinical and scientific prudence that these authors showed in their reports.

First, although 21 patients were admitted to their unit after stopping etomidate, only 15 were considered critically ill.⁶ The authors stated that 'low serum cortisol values in critically ill patients *may* have been associated with etomidate infusion' and 'increased mortality amongst multiple trauma patients receiving etomidate infusion could, *at least in part*, be explained by adrenocortical suppression'.⁶ They also stated in a previous letter⁷ that sedation in 1981–92 was *predominantly* (not wholly) morphine and etomidate. High doses of opioid alone can suppress adrenocortical function.⁸ Furthermore, compared with their February 1983 report⁵ in which 27% of critically ill patients had low plasma cortisol, Finlay and McKee first reported⁴ that 18 of 57 patients (31.6%) had cortisol concentrations <350 nmol litre⁻¹ and 13 of 57 patients (22.8%) concentrations <260 nmol litre⁻¹ (lower limit of 'normal'). Therefore, it would appear that adrenocortical insufficiency in some of the patients in the Glasgow reports may have been a result of causes other than etomidate. Rydvall and colleagues⁹ recently reported in a group of patients similar to those described by the Glasgow group but who did not receive etomidate, that in 36% of their patients, plasma cortisol was <400 nmol litre⁻¹. Also, there was a significantly increased probability ($P < 0.05$) for plasma cortisol to be <400 nmol litre⁻¹ in patients admitted to the ICU as a result of trauma, a cerebral disorder or those receiving ventilator therapy. Moreover, patients treated with mannitol had an increased probability ($P = 0.008$) of having a plasma cortisol concentration <400 nmol litre⁻¹. If we accept these data, it can be concluded that there are many variables in the causation of adrenocortical insufficiency which we do not know. Therefore, the inclusion of the Glasgow reports in our editorial appears reasonable.

As for the diagnosis of secondary adrenocortical insufficiency, McAllister should have quoted our entire sentence and not focused only on 'thyroid function tests' (*which always include thyrotrophin concentration*). We did not suggest the use of such tests as a 'marker' for secondary adrenocortical insufficiency. When secondary adrenocortical insufficiency is suspected, others have advised that 'investigations should include testing for thyrotrophin concentrations'.¹⁰ The same authors also stressed that when interpreted rigidly and in isolation, the Synacthen test can be unreliable. Moreover, it is doubtful that the references quoted^{11,12} can support his argument. Neither investigation used a long tetracosactrin test which may distinguish between secondary and primary adrenocortical insufficiency.¹³ Also, Soni and colleagues¹¹ did not report the results for thyrotrophin or comment on the adrenocorticotrophic hormone (ACTH) values among the groups, which appeared to be within the normal range. The study by Jarek and colleagues¹² was an outcome prediction investigation which contained only 12 patients who had sepsis or septic shock, and some of their endocrine tests were not performed. Many of their patients were receiving hormone therapy.

Conflicting advice for routine screening of adrenocortical

function has been given. It is considered superfluous by Span and colleagues.¹⁴ Others¹⁵ are in favour of screening critically ill patients for adrenocortical insufficiency, particularly those with prolonged stay and those aged >55 yr. Unnecessary delay in diagnosis or treatment, especially by waiting until there is no response to inappropriately high doses of inotropes in critically ill patients, would be unwise. We deliberately suggested that rapidly escalating inotropic requirements in association with a poor haemodynamic response should prompt the clinician to consider and hence establish the diagnosis of adrenocortical insufficiency sufficiently early. While we do not refute the presence of high cardiac output and low systemic vascular resistance in patients with adrenocortical insufficiency, these features parallel those seen in septic shock.¹⁶ The latter can occur despite culture-negative microbiology. Furthermore, the diagnosis of patients in the report by Gleadle and colleagues¹⁷ included a wide range of pathologies, such as acute haemorrhagic pancreatitis, shotgun wound involving the bowels, complicated by an episode of septic shock, and chicken pox. Anticipation of the more common condition, sepsis, may prevent early recognition of acute adrenocortical insufficiency.¹⁶ Hence, such clinical features may not be helpful in these cases.

We agree with Absalom and Scott that the number of subjects in the study by Schein and colleagues¹⁸ was small and no ACTH stimulation test was performed. Not all patients in that study had plasma cortisol concentrations >0.5 $\mu\text{mol litre}^{-1}$. Patient No. 33 had a plasma cortisol concentration of 15.2 $\mu\text{g dl}^{-1}$ (0.43 $\mu\text{mol litre}^{-1}$) and the cortisol concentration of patient No. 17 was 19.2 $\mu\text{g dl}^{-1}$ (approximately 0.52 $\mu\text{mol litre}^{-1}$). The authors also questioned "what is a 'normal' value for plasma cortisol in septic shock"? They, and others,¹³ considered a concentration >20 $\mu\text{g dl}^{-1}$ (0.55 $\mu\text{mol litre}^{-1}$) as 'normal' or appropriate and adequate for critically ill or stressed patients. They were unable to confirm a statistically significant difference between cortisol concentrations in patients who survived and those who did not. They concluded that there was no indication that plasma cortisol concentrations may be used in the prediction of patient outcome.

We do not believe that we were dismissive about the role of the Synacthen test. Our last statement was a testimony to that. We would however caution the interpretation of its results. McAllister's comments on such tests confirm what we stated, that the wide variation in the reported incidence of adrenocortical insufficiency may be caused by the variation in the criteria used to diagnose it. He also restates what we clearly said about the administration of hydrocortisone before laboratory confirmation of adrenocortical insufficiency. More importantly, there is an ongoing debate in the clinical biochemistry literature not only about the interpretation of cortisol response to tetracosactrin but also about the dose used and the timing for measurement of plasma cortisol.¹⁹⁻²¹ The standard 250 μg Synacthen test is thought to be an unphysiological

high stimulus which may overestimate adrenocortical reserve.²⁰ Also, the use of an incremental response in the interpretation of the Synacthen test may be misleading.¹⁹ A 1 μg Synacthen test has been suggested and measurement of the cortisol response at 30 min after tetracosactrin was thought preferable.¹⁹⁻²¹

It is not commonly appreciated that plasma cortisol concentrations in the healthy resting state overlap with those in adrenocortical insufficiency (primary or secondary) and in cortisol excess syndromes.¹³ Furthermore, in common with all laboratory measurements, in particular those made by complex immunoassays, the assay of plasma cortisol is subject to imprecision. All methods for measurements of plasma cortisol do not produce the same results. The UK National External Quality Assessment Scheme (UK NEQAS) distributes aliquots of six plasma pools to some 250 laboratories each month for assessment of the concentration of cortisol in these samples. At least 12 different methods are recorded as being used for measurement of cortisol. Typical examples of the range of concentrations of cortisol measured on samples containing a mean concentration of 257 nmol litre^{-1} were from 150 nmol litre^{-1} to 400 nmol litre^{-1} , a mean level of 117 nmol litre^{-1} were from 50 nmol litre^{-1} to 185 nmol litre^{-1} , and a mean value of 588 nmol litre^{-1} were from 340 nmol litre^{-1} to 900 nmol litre^{-1} . Laboratories using the same fully automated machine can report concentrations, at the 95% confidence level, varying by 30% at 257 nmol litre^{-1} , 44% at 117 nmol litre^{-1} and 16% at 588 nmol litre^{-1} . It is essential that physicians are aware that the concentration of plasma cortisol produced by their individual laboratory cannot be compared directly with those from another laboratory unless they measure the hormone with the same degree of bias.

Reference to high plasma cortisol concentrations, as reported by Sainsbury, Stoddart and Watson²² is inappropriate. Only seven volunteers were studied, and *all* were *healthy!* Indeed, if we assume that these results apply to critically ill patients then the use of hydrocortisone 30 mg, perhaps as an initial test dose, may be physiological! After all, such a dose is used as replacement therapy in adrenocortical insufficiency. As for individualization of the dose of hydrocortisone according to patient weight, it is very difficult to accurately weigh critically ill patients.

Lastly, it would appear that McAllister has mis-cited his references 19 and 20. We need to define what constitutes both 'normal' and adrenocortical insufficiency in the critically ill patient. We do not know all the answers. This is why, in our editorial, we called for consensus not dogma.

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- 1 Schneider AJ, Voerman HJ. Abrupt haemodynamic improvement in late septic shock with physiological doses of glucocorticoids. *Intensive Care Med* 1991; **17**: 436–7
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Blind intubation via the ILMA: what about accidental oesophageal intubation?

Editor,—We read with interest the study by Chan and colleagues¹ on blind intubation via the intubating laryngeal mask airway (ILMA). We noted that in their results there was

no discussion of the possibility of accidental oesophageal intubation. However, several studies have demonstrated that the oesophageal inlet may be included in the bowl of the standard laryngeal mask airway (LMA) at a frequency of up to 9%.^{2,3} Additionally, in a recent article, ILMA position was graded fibroscopically and accidental oesophageal intubation was reported in three of 100 patients,⁴ while in a limited series of data concerning the use of ILMA in patients with difficult airways, it was reported in one of 30 patients.⁵

We would like to convey our experience concerning the incidence of accidental oesophageal intubation via the ILMA. After obtaining institutional approval and patient consent, we studied 100 ASA I or II patients presenting for elective surgery. Patients were excluded if they were at risk of regurgitation or aspiration. Two senior anaesthetists experienced in the placement of the LMA studied 50 patients each. After induction of anaesthesia with fentanyl 1 µg kg⁻¹ and propofol 2.5–3.0 mg kg⁻¹, neuromuscular block was achieved with cisatracurium 0.15 mg kg⁻¹. Patients' lungs were ventilated for 3 min with 100% oxygen supplemented with 2% sevoflurane and then an ILMA of the size appropriate to patient weight was introduced according to the manufacturer's guidelines.⁶ Successful placement was judged by chest wall movement and capnography, in addition to the ability to deliver a tidal volume of 7 ml kg⁻¹ without a leak, at an airway pressure ≤20 cm H₂O. Blind intubation was attempted via the ILMA using a silicone 7.0–8.0 mm tracheal tube. If the first intubating attempt failed, a sequence of adjusting manoeuvres was performed according to the inventor's guidelines.⁶ Successful tracheal intubation was determined by capnography. The ILMA was inserted successfully at the first attempt in all patients. The overall success rate for intubation was 91% (45 of 50 (90%) and 46 of 50 (92%) for each investigator), 48% on the first attempt, 20% on the second attempt while 23% required 3–5 attempts. Oesophageal intubation occurred in eight patients (8%) during the first attempt (5 of 50 (10%) and 3 of 50 (6%) for each investigator). We noticed that in five of these eight patients, intubation was finally successful after applying the appropriate adjusting manoeuvres.⁶

In summary, we consider that tracheal intubation via the ILMA, being a blind technique, has a risk of accidental oesophageal intubation as the oesophageal inlet may be included in the bowl of the ILMA. This event is not necessarily associated either with inability to ventilate the patient's lungs through the ILMA or with failure in achieving successful intubation via the ILMA. Thereafter, capnography and/or any other oesophageal detector device should always be available whenever blind intubation via the ILMA is performed.

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Editor,—Thank you for the opportunity to reply to Dimitriou and Voyagis. We agree fully that oesophageal intubation is a hazard of any blind intubation technique. Indeed, although in our short communication¹ we did not record the incidence of oesophageal intubation, it is our experience that it forms a substantial proportion of those failures with increasing risk as further attempts are made. Our study was completed before the original articles were published, hence we did not have the benefit of their experiences.^{2–4} It is possible that the incidence of oesophageal intubation may be reduced if tracheal intubation is abandoned at any slight resistance and multiple manipulations (up to eight) are attempted before the tracheal tube is finally passed.⁵

Interestingly, Dimitriou and Voyagis recorded a substantially lower success rate of 91% compared with 97% in our series, despite allowing up to five attempts (maximum three attempts in our patients). This is the same success rate achieved by 10 medical officers with no previous experience of anaesthesia in a study we have just completed.

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Myelopathy after hyperbaric local anaesthetics used for continuous spinal anaesthesia is iatrogenic

Editor,—In the review article on continuous spinal anaesthesia, Denny and Selander¹ discussed cases of cauda equina syndrome (CES) after continuous (intermittent) spinal anaesthesia (CSA) associated with hyperbaric lidocaine and tetracaine.^{2,3} Anaesthetists should be cognizant that these myelopathies had little, if anything, to do with the aetiologies they enumerated. (*Myelopathy* is a general term denoting functional disturbances and/or pathological changes in the spinal cord. *Dorland's Medical Dictionary*, 28th edition, D.M. Anderson, Chief Lexicographer 1994; 1090.) Evidently, Denny and Selander¹ and those who 'reintroduced' CSA^{2,3} are unaware that CES occurred in these patients because they were in the *supine horizontal position* while attempting to establish anaesthesia!^{2,3} The *position* used resulted in exorbitant, unrecommended doses of lidocaine (175–300 mg) and tetracaine (37 mg) being administered in an attempt to establish anaesthesia.^{2,3} Because of *this position*, these solutions did not spread cephalad but pooled in the terminal portion of the dural sac resulting in CES.

It is *essential* when such solutions are administered for CSA that to avoid pooling resulting in CES, patients must be in the 5–10° Trendelenburg position during injection and until the desired level of anaesthesia is obtained. This was stated by Lemmon and colleagues,^{4,5} the originators of CSA, and by others who used it.^{6–8} With patients preferably in the 10° Trendelenburg position,⁷ local anaesthetics with a specific gravity of approximately 1.035 do: (1) not pool on the caudad (sacral) side of the lordotic hump (L3); (2) spread cephalad; (3) produce the desired anaesthesia from the first or *reduced* second dose of the local anaesthetic; and (4) avoid CES.^{4–8}

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Editor,—We thank Dr Moore for his comments on our review article on continuous spinal anaesthesia (CSA).¹ Regarding the mechanism behind the cauda equina syndrome (CES), we agree with Dr Moore that the supine, horizontal position could increase the risk of sacral pooling of a poorly diluted local anaesthetic. A prerequisite for such pooling is that the spinal catheter has not reached above (cranial to) the lordotic hump, that the anaesthetic solution is hyperbaric and that it was injected very slowly (e.g. through a microcatheter), minimizing mixing with the CSF. A slight head-down position would most likely reduce the risk of sacral pooling, especially when hyperbaric local anaesthetic solutions are used.

However, the main factor in causing the CES (which is not a myelopathy) in connection with CSA seems to be the use of highly concentrated local anaesthetic solutions such as 5% lidocaine. The neurotoxic potency of 5% lidocaine has been well documented,^{2,3} and one might also anticipate similar neurotoxicity with the use of any other high-concentration local anaesthetic, if it is allowed to remain insufficiently diluted around the thinly protected nerve roots for long enough. As pointed out, the ignorant anaesthetist may respond to the resultant restrictive spread of the spinal anaesthesia by injecting more of the local anaesthetic, and thus increase the risk of neurotoxic damage.

We remember that Dr Moore in the early 1980s expressed concern about the potential neurotoxicity of highly concentrated local anaesthetics, and that in his opinion, no short-acting, amide local anaesthetic should be used clinically in concentrations greater than 2%. It is well documented that excellent spinal anaesthesia can be achieved with 1.5% or 2% lidocaine,^{4,5} so why use higher concentrations for spinal anaesthesia?

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Is tramadol an antidepressant?

Editor,—Tramadol, an atypical centrally acting analgesic, with relatively weak opioid receptor affinity, has been used extensively in the management of mild to moderate pain, in both the acute and chronic setting.¹ There is a large body of evidence to suggest that the analgesic actions of tramadol are unrelated to opioid receptors and are instead mediated via central noradrenergic and/or serotonergic mechanisms. For instance, tramadol-induced analgesia may be antagonized by the α_2 adrenoceptor antagonist yohimbine.² In particular, it has been shown that tramadol is an effective norepinephrine and serotonin uptake blocker.^{3,4} Moreover, these actions are demonstrable at clinically relevant plasma concentrations.

Blockade of norepinephrine and/or serotonergic uptake systems is a common feature of many if not all clinically used antidepressants and one would therefore be surprised if tramadol did not exhibit antidepressant properties itself. Interestingly, a recent animal study showed that tramadol, in common with many antidepressants, exhibited activity in the 'forced swim' test,⁵ an established predictor of antidepressant efficacy. Despite extensive clinical use, tramadol has not to our knowledge been examined explicitly for antidepressant potential. It would be interesting to see if tramadol exhibited antidepressant actions in a context removed from its use as an analgesic.

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Methodological problems arising from ‘serial publishing’ on the effectiveness of granisetron in PONV

Editor,—We read with interest the dose finding study on granisetron by Fujii and co-workers¹ and would like to comment on problems we see with this and other studies by the same author(s). First, we are not surprised about the reported dose of granisetron 40 µg kg⁻¹ being safe and effective in reducing postoperative nausea and vomiting (PONV).¹ This has been reported previously by the same authors in five dose-finding studies in patients undergoing various other types of surgery.^{2–6} Although the type of operation was generally assumed to be a key factor in PONV,^{7–8} recent studies have shown that the relative impact of surgery is low, as the different incidences of PONV after various operations are caused mainly by patient-related risk factors.^{9–10} To the best of our knowledge, there is no strong evidence to support the assumption that the effectiveness of granisetron is influenced by the type of operation. In addition, the previously mentioned studies by Fujii and co-workers suggest that efficacy does not depend on the surgical procedure.^{2–6} Therefore, we would like to question the value of serial publishing of results in different types of surgery.

Second, it is well accepted^{7–11} and confirmed by recent analyses^{10–12–13} that a positive history of PONV or motion sickness increases the risk of nausea and vomiting for subsequent procedures. As patients at very high risk are more likely to profit from antiemetic prophylactic treatment when the number-needed-to-treat is considered,¹⁴ it is difficult to understand why patients with a previous history of PONV or motion sickness were excluded from the study.¹

Third, Fujii and co-workers have reported in 20 studies with almost 2000 patients that granisetron is superior to placebo.^{1–6–15–27} In accordance with other colleagues^{28–29} we wonder if such comparisons with placebo are still ethically justified if there seems to be such an overwhelming body of evidence suggesting the superiority of granisetron.

Fourth, Fujii and colleagues reported in a dose-finding study that granisetron 20 µg kg⁻¹ was not sufficient to reduce PONV.² However, this dose regimen was used

1 yr later in a subsequent study for comparison with a combined granisetron–dexamethasone regimen in the same type of operation.¹⁷ We were not surprised that the combined regimen proved to be significantly better than a suboptimal dose of granisetron alone.²

Fifth, numerous studies have shown that droperidol is more effective than placebo in the prevention of PONV³⁰ although this was not demonstrated by Fujii and colleagues.^{21–22–25–27} However, their results^{21–22–25–27} are questionable as group sizes were generally too small to provide sufficient statistical evidence for a lack of effect. To calculate appropriate group sizes a power analysis is necessary. From meta-analyses we know that a reduction in the incidence of PONV is normally no more than 50% of placebo.¹⁴ Thus assuming an incidence of PONV of 60% with placebo and a possible reduction to 30% with an antiemetic, this would require a minimal group size of 49 patients if a type I error of 0.05 and type II error of 0.2 is accepted (Instat 2.0, Graphpad). For this reason, the results of the study by Fujii and colleagues seem statistically questionable which may lead to wrong conclusions.¹ This also applies to other studies by the same authors.^{21–22–25–27}

In summary, we feel obliged to criticize this type of ‘serial publishing’ by Fujii and co-workers because of inappropriate group sizes and the neglect of previously acquired results.

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Editor,—As demonstrated in several reports,^{1–5} we have studied previously the effective antiemetic dose of granisetron, a selective 5-hydroxytryptamine type-3 (5-HT₃) receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) after various types of surgery. However, no study has investigated the efficacy of granisetron for preventing PONV in patients undergoing thyroidectomy. The incidence of PONV after this surgical procedure is relatively high (60–65%) when no prophylactic antiemetic is given.^{6,7} Therefore, we studied the efficacy of granisetron in the prevention of PONV in this population. In addition, we have found no report investigating the minimum effective dose for the prevention of PONV after thyroidectomy. Even if the effective dose is the same (40 µg kg⁻¹) in patients undergoing several types of surgery, it remains uncertain that this dose is effective for preventing PONV after thyroidectomy.

It is well known that a positive history of motion sickness and/or previous PONV predisposes to an increased incidence of PONV.⁸ Therefore, we excluded patients with a relatively high risk of PONV from our clinical trials.^{1–5} Several investigators have compared the antiemetic efficacy of new agents, such as ondansetron, granisetron, tropisetron and dolasetron, with placebo for preventing PONV.^{9–12} Similarly, we compared the efficacy of granisetron and placebo for preventing PONV after thyroidectomy.

McKenzine and colleagues¹³ demonstrated that an ondansetron–dexamethasone combination was more effective than ondansetron alone in the prevention of PONV in patients undergoing major gynaecological surgery. They reported that the prophylactic use of ondansetron was superior to placebo for the prevention of PONV in women undergoing ambulatory gynaecological surgery.¹⁴ Similarly, we compared the efficacy of granisetron and dexamethasone with granisetron alone for the prevention of PONV.¹⁵ We would like to find a more effective pharmacological approach for reducing the incidence of PONV.

As in our other recent reports,^{16,17} we performed a power analysis for statistics. In this clinical study,¹⁸ it was documented that 25 patients per group were sufficient to detect a difference of $\alpha=0.05$ and power $(1-\beta)=0.8$.

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