Low-dose dopamine: there is a scientific rationale

Sir,—Regarding the recent editorial “Low-dose dopamine: will there ever be a scientific rationale?”, I do not question its content, but rather that what should have been included.

It is expressed clearly and well justified that low-dose dopamine probably does not save lives in intensive care units. The authors briefly mention that dopamine “…limits adenosine triphosphate utilization and oxygen requirements in nephron segments, at least for ischemic injury…”.

This point is important for the justification of the use of dopamine in the protection of the kidney during a relatively short-lasting (hours) or severe ischemic insult. This idea is derived from some anatomical and physiological characteristics of the medulla. Within the medulla, oxygen diffuses from arterial to venous vasa recta which predisposes the outer medulla to a degree of oxygen deprivation. In this region the medullary thick ascending limb of Henle’s loop (mTAL) is responsible for the creation of an osmotic gradient by reabsorption of sodium. This process demands and consumes a significant amount of energy and oxygen. The rate of reabsorption at the level of mTAL is the main determinant of renal oxygen demand, and suppression of reabsorption is associated with a significant increase in medullary oxygen tension. A well documented, dopamine-induced anti-aldosterone effect and inhibition of Na⁺–K⁺-ATPase results in a decrease in solute reabsorption, and subsequently a decrease in oxygen demand in the tubules, particularly in the mTAL, the most vulnerable part of the nephron to ischemic insult. In addition, dopamine increases the formation and release of prostaglandin E₂ which dilates medullary vessels and also inhibits oxygen consumption in tubular cells.

An increase in renal blood flow resulting from activation of DA-1 receptors might improve renal function (renal blood flow, glomerular filtration rate (GFR), sodium and water excretion) in patients with acute renal insufficiency, however, the increase in GFR per se, which represents an “improvement in renal function”, might be detrimental for the viability of the kidney undergoing a short but severe ischemic insult (e.g. supraparenchymal acute cross-clamping). An increase in renal cortical blood flow and GFR would be associated with an increase in transport of the solute to the tubules, an increase in reabsorption and oxygen demand.

This scientific rationale for the use of dopamine (in conjunction with other drugs decreasing reabsorption) has not enjoyed overwhelming confirmation by clinical data. There are probably many reasons for this. One may be that there is a narrow window of opportunity where any therapeutic intervention can be proved by outcome studies. In other words, the majority of patients would not need any treatment and their renal function would be preserved after a relatively short ischemic insult; or, for some patients, the ischemic insult would be so severe that none of the treatments could be effective. The situation can be aggravated by the different baseline status of renal function and reserves. One study of the prophylactic use of dopamine demonstrated a significant decrease in the incidence of renal insufficiency in patients undergoing angiography with impaired baseline renal function, while there was a difference in patients with relatively normal renal function. Thus the lack of clinical data, present scientific literature seems to justify the rationale that low-dose dopamine in addition to (or in conjunction with) some other loop diuretics might protect the kidneys during ischemic insult.

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External cooling in critically ill febrile ICU patients

Sir,—The findings of Poblete and colleagues indicate that external cooling is more effective than antipyretic agents in the treatment of febrile ICU patients. As the authors noted, application of ice sponges in critically ill febrile ICU patients is relatively inconvenient and the method of external cooling used in the first instance by many ICU is the rotary fan. However, an extensive literature search has revealed no studies on the efficacy of this method in these circumstances. In addition, increased risk of airborne infection is a potential concern. Fans are unlikely to act as a source of infection in the way that contaminated air conditioning systems can, but they might enhance transmission of airborne pathogens between adjacent patients. Environmental contamination of the ICU with pathogenic bacteria is well known and in one ICU inadvertent circulation of air from an isolation room back into the main unit led to an outbreak of methicillin-resistant Staphylococcus aureus. Given the ineffectiveness of antipyretic drugs demonstrated by Poblete and colleagues, further studies on the efficacy and risks of other antipyrexic therapies used in the ICU seem warranted.

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**Inhaled nitric oxide**

Sir,—The Intensive Care Society recently published recommended safety precautions for the therapeutic use of inhaled nitric oxide (Winter 1996 newsletter). Included in these was a suggestion that when high concentrations of nitric oxide are used in areas of limited ventilation, a scavenging system should be used. A footnote added that activated charcoal absorbers were ineffective scavengers of nitric oxide. This information seems to have come from an article by Squire, Kightley and Petros1 where the authors stated “using activated charcoal...no reduction in exhaust gas concentration was detected at any time”.

We recently had reason to test if “Aldasorber” (Shirley Aldred and Co. Ltd, Bradford, UK) activated charcoal scavenging units absorb nitric oxide. A nitric oxide mixture containing 40 ppm of nitric oxide was passed through an Aldasorber unit at 10 litre min⁻¹, and the effluent nitric oxide concentration was recorded with a chemiluminescence analyser linked to a personal computer recording at 6-s intervals. The analyser has a limit of detection of 0.05 ppm and a display resolution of 0.1 ppm in the range used. When the carrier gas was nitrogen alone, nitric oxide appeared at the outlet of the absorber almost immediately, and reached a maximum of approximately one-third of the inlet concentration (fig. 1). When the carrier gas was air, nitric oxide was detected in the effluent gas only after 13.2 h, and at 24 h the effluent concentration was only 0.1 ppm. When 40 ppm of nitrogen dioxide in nitrogen were passed at 10 litre min⁻¹ through an absorber, no nitrogen dioxide was detected in the effluent gas over the 1-h period of the experiment.

**Figure 1** Effluent nitric oxide (NO) concentration when an NO mixture containing NO 40 ppm was passed through an Aldasorber activated charcoal scavenging unit.

The discrepancy between these results and those of Squire, Kightley and Petros1 is difficult to explain. They used Carbomix (Penna Pharmaceuticals Ltd, Gwent, UK) as an absorber, a charcoal designed to be mixed into a slurry and instilled into the stomach to absorb drugs in the aqueous phase. This formulation is approximately 80% charcoal; the remainder is citric acid, acacia gum and glycerine. This presumably alters the gas absorbing properties of the charcoal. Aldasorber units are designed to remove organic anaesthetic agents in the gas phase.

Our results suggest that nitric oxide is scavenged by activated charcoal, but only in the presence of oxygen. As nitrogen dioxide is scavenged even without oxygen, it is possible that the charcoal catalysts the oxidation of nitric oxide to nitrogen dioxide which is then absorbed. Whatever the mechanism, activated charcoal would appear to be an effective scavenger of nitric oxide at concentrations used in clinical practice.

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**Predominant involvement of motor fibres in patients with critical illness polyneuropathy**

Sir,—Hund and colleagues demonstrated that critically ill patients may suffer from an acute axonal motor polyneuropathy which is related to sepsis, and not to the use of neuromuscular blocking agents.1 This result has important nosological implications because the reduction in compound motor action potential (CMAP) with preserved sensory action potential has until now been taken as evidence in favour of neuromuscular blocking agent-related neuropathy (or myopathy) and against critical illness polyneuropathy (CIP).2 However, three aspects of this study need clarification.

First, seven of 20 patients with grade 2-3 denervations were found to have CIP and normal CMAP amplitude (fig. 1). This was a strange result. In axonal neuropathy the total number of nerve fibres is reduced, while myelination of surviving fibres is maintained. Therefore, CMAP amplitude (which is the sum of the action potentials of all nerve fibres) decreases while nerve conduction velocity remains normal or nearly normal. CMAP, an energy-requiring event, may be reduced at an early stage of sepsis and critical illness. In contrast, signs of denervation take several days or weeks to become evident.3 Therefore, it would be theoretically justifiable to have reduced CMAP without signs of denervation, but the opposite situation would not be possible. In the discussion the authors stated that “these 20 patients had abnormal CMAP”.

Second, it was suggested that mild CIP is unlikely to cause weaning failure. However, mild CIP of the limbs does not necessarily imply mild CIP of the diaphragm and respiratory muscles, and it would be worrying for intensive care physicians to assume that neuromuscular problems are not ongoing without carefully assessing respiratory muscles and nerves.3

Finally, the authors stated that myopathy was an unlikely diagnosis in their patients because creatine kinase concentration (CK) was mostly normal and asthma was not a cause of admission. Diagnosis of myopathy in critically ill unconscious patients requires muscle biopsy for confirmation. CK may remain normal, but the muscle may be electrically inexcitable.4 An electrophysiological study is not conclusive in itself. In fact, CMAP may be reduced because of motor neuropathy, myopathy or both. Furthermore, denervation signs may be seen also in myopathy when the necrotic process disconnects the end-plate zone from the active membrane.5 We have shown that many septic patients with an electrophysiological diagnosis of CIP had a myopathy at biopsy.6

Sepsis does not spare muscle and critical illness myopathy is at least as frequent as CIP,7 provided the correct investigations are used. If biopsy is not planned, diagnosis of neuromuscular disorder would be more appropriate.

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Although CMAP amplitudes are usually reduced, we encountered patients who had normal CMAP amplitudes despite severe denervation activity on EMG. For example, in patient No. 14, who had severe sepsis after major abdominal surgery, median nerve CMAP amplitude was 8.1 mV and SNAP 22 μV at the time of grade 3 denervation activity in all muscles examined. Patient No. 17, with polytrauma and severe head injury, had a median nerve CMAP of 6.0 mV and SNAP of 84.9 μV (sic) shortly before death. In this patient, grade 3 denervation was present for 2.5 weeks. The reason for this finding is unclear. So far the exact mechanism and type of lesion in CIP has not been elucidated. Thus when confronted with CIP, one should bear in mind that classical polynuropathy, characterized by dying-back type axonal degeneration, is most likely not involved. Evidence for other mechanisms comes from electrophysiological studies and the observation that recovery is often very fast, that is much faster than expected in chronic axonal degeneration.3

Among the many authors reporting on CIP, only Bolton advocates phrenic nerve conduction studies and electromyography of the diaphragm.1 Until now, his group has published one series in which such studies were included.4 In this series, four of 16 patients with bilateral phrenic neuropathy had mild CIP according to electrodiagnostic examination of the limbs. One of these patients also had abnormal central respiratory drive. The degree of phrenic nerve involvement and diaphragmatic denervation was not quantified. Although we cannot exclude the possibility that some of our patients had significant phrenic neuropathy despite only minor abnormalities of the limbs, we feel that this is quite unusual in a generalized disorder such as CIP. We agree, however, that diaphragmatic EMG and phrenic nerve conduction studies should be performed in patients with persistent failure to wean, if repeated limb electrodiagnosis shows only minor abnormalities.

We discussed the issue of myopathy in our article. Most authors diagnose patients as having CIP without performing muscle biopsy. In general, such florid denervation activity, as observed in patients with CIP, is unusual in myopathy. After the advent of the report of Rich and colleagues,5 we included testing of electrical excitability of muscles in our protocol. So far none of our patients has been found to have electrically inexcitable muscles (unpublished result). Latronico and colleagues had a high number of patients with myopathic features on histopathological examination who were diagnosed as having only CIP on the basis of electrodiagnosis.6 However, all but two patients biopsied late in the disease course had histopathological findings consistent with the electrophysiological results. Thus in the later stages of sepsis, electrodiagnosis alone may give reliable results, while in the early disease state, muscle biopsy may be necessary for a correct diagnosis.