MATTERS ARISING

Clinical evaluation of extracellular amino acids in severe head trauma by intracerebral in vivo microdialysis

The article by Kanthan and Shuaib¹ is a timely reminder of the potential importance of clinical applications of intracerebral microdialysis. However, there are several methodological and interpretive shortcomings in their case report. Firstly, the microdialysis probe used (Carnegie CMA-10) is one which is designed solely for experimental use in animals. It has no human product licence. Conventional techniques for sterilisation of products to be used in humans can damage the components of the probe, alter its microdialysis characteristics, and may even result in the release of toxic substances. There are also examples of the dialysis membrane becoming detached from the probe shaft and being left in situ (R Bullock, personal communication, 1995). These problems, compounded by the lack of a dialysis probe licensed for intracerebral use in humans, are the basis for the lengthy delay in extrapolating this exciting technique from experimental to clinical studies.²

The interpretation offered for the results of Kanthan *et al* is conjectural. High concentrations of all neurotransmitters analysed were found during a three hour period of microdialysis preceding brain death. Are these consequent to neuronal death or a cause of it? The authors did not describe any in vitro testing of probe recovery rate for the measured compounds on removal of the probe from the patient. Without this vital information and in the absence of any reported correlation between the measured neurotransmitter concentrations with either neuroradiological (CT or MR) findings or neuropathology their results provide information of questionable value. Other important information was lacking from their report—namely, details of probe position in either white or grey matter, the relation of the probe tip to any contusion or other macroscopic intracranial pathology, and the presence of hypoxia, pyrexia or hypotension all of which are “secondary insults”, commonly found in patients with head injury, which aggravate brain damage. This type of information is crucial if we are to explain the large differences previously reported both between and within patients monitored by microdialysis.³ The contribution of excitotoxic neurotransmitters to secondary brain injury is still controversial.⁴ We agree with the authors that intracerebral microdialysis of patients with head injury may be a useful tool in understanding the pathogenesis of neuronal injury, but this monitoring method must be carefully assimilated into a multimodality patient monitoring system.⁵ Speculative and poorly designed case reports do not contribute to scientific advancement in this field.

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Kanthan and Shuaib reply:

We thank Mr Whittle for his comments.

As regards the microdialysis probe CMA-10; we are aware that this product has not been marketed for human use. However, for research purposes these are being used in accordance with strict protocol regimes as followed in Professor Ungerstedt's laboratory. In our laboratory, extensive bench work has been carried out regarding presterilisation and post-sterilisation effects on the efficacy of the probe, concentrations of neurotransmitters, and on decay. The exact placement of the probe in the cortex of the frontal lobe was also done both in fresh necropsy and cadaveric brains before clinical use. These and other issues regarding the methodology have been published in our methods paper (*J Neurosci Methods* 1995;60:151–6).

The issue regarding the exact interpretation of the high concentrations of neurotransmitters remains speculative. We agree with Mr Whittle that it is conjectural whether these are the result or the cause of neuronal death. We also agree that the exact role of excitotoxic neurotransmitters to “secondary brain injury” remains unclear. It is precisely with this in mind that other extraneous factors were not explored in our case. However for the record, our patient was not hypoxic, hypotensive, or febrile during the in vivo microdialysis. Nevertheless, earlier such insults may be contributing factors to the high concentrations noted. This remains a complex issue and we advocate intracerebral in vivo microdialysis as an additional monitoring tool in understanding and unravelling these and other related phenomena of the exact pathogenesis of head trauma.

Visually induced paroxysmal nausea and vomiting as presenting manifestations of multiple sclerosis

Khan *et al* reported an interesting patient with visually induced paroxysmal nausea and vomiting as a presenting manifestation of multiple sclerosis.¹ Their patient was able to suppress the nausea and vomiting by closing the eyes or avoiding visual motion stimuli. This case illustrates the potential for activation of vestibular and autonomic centres from visual pathways.

This patient seems to be an extreme case

of what in neuro-otology clinics would be called “visual vertigo”.² These patients report unsteadiness, dizziness, or “sickish” sensations in environments with confusing visual cues or excessive visual motion (for example, supermarkets, moving crowds, disco lights). A history of vestibular disease, abnormalities in the neuro-otological examination, and added oculomotor findings—for example, old squints—are common. Khan *et al* also stress the importance of considering multiple sclerosis in cases like theirs, particularly because the possibility of a psychogenic disorder may be raised if there are no other indicators of neurological disease.¹ The same consideration applies to “dizzy” patients. Symptoms triggered or exacerbated in supermarkets or by people or traffic moving around, not surprisingly can be taken as phobic. Although the name “postural phobic vertigo” has been coined to describe those patients with dizzy or postural symptoms with no vestibular history or findings and a psychogenic background,³ both the report of Khan *et al* and our own report² emphasise the need for careful investigation in patients with visually induced vertigo, nausea, or postural imbalance.

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Persistent vegetative state

The editorial of Kennard and Illingworth¹ notes, correctly, that the persistent vegetative state syndrome raises immense ethical and social dilemmas. It might be added, further, that the syndrome incites highly litigious questions. And the spotlight of scrutiny should properly remain focused on the contentious ethical, social, and legal dilemmas arising from this interdisciplinary matter.

The extraordinary litigiousness of American society has often been commented on, and the matter of the dilemma of the persistent vegetative state does not depart from this tradition. A body of case law, germane to end of life decision making, has actually grown over the course of the past 20 years or so in the United States, with primal roots extending to the landmark case in 1976 involving Karen Quinlan.² More recently, in 1990, the United States Supreme Court decided its first “right to die” case, in a matter involving Nancy Cruzan.³ In this primordial case, decided by the highest court in the United States, it was held that the state of Missouri may require the continued treatment of a patient in a persistent vegetative state, in the absence of “clear and convincing” proof that the patient authorised explicitly the termination of treatment.

At least in American jurisprudence, the presumption, traditionally, has been that the patient in a persistent vegetative state would wish to be kept alive; and, in turn, the burden has fallen on those desiring to terminate the treatment of the patient in a persistent

vegetative state, rather than on the shoulders of those wishing to continue such treatment.⁴ As pertinent case law continues to evolve in America, however, this presumption, and accompanying burden, may be in danger of disintegrating. In this vein, one commentator has, indeed, espoused the view that it should be presumed that patients in a persistent vegetative state would not want to be kept alive indefinitely; and families objecting to the discontinuation of treatment would have the burden of showing why treatment should be continued after a specified time sufficiently long to establish irreversibility with high certainty.⁴

At this time juncture, however, the divisive legal, bioethical, and social issues emanating from cases involving a persistent vegetative state remain far from resolved; and continue to be considered on a piecemeal, or case by case, basis. In several very recent cases involving "medical futility", including one involving Baby K⁵ and another involving Baby Ryan,⁶ American courts have upheld the right of family members to insist on continued treatment over the objections of hospitals and doctors embracing a futility argument. Incidentally, healthcare providers in America who object to providing medical services which they claim are futile run a grave risk of being publicly charged with hypocrisy, or at least gross inconsistency. This is because medical services in the United States traditionally have been regarded as being simply another economic commodity, and have been dispensed based on ability to pay, rather than medical need. To embrace a differing mentality affecting, for example, patients in a persistent vegetative state, would constitute an obvious, and striking, departure from the accustomed path.

British courts have also been wrestling with contentious issues involving patients in a persistent vegetative state.² In a case involving a young man named Anthony Bland, in a persistent vegetative state as the result of a disaster at a football ground, the House of Lords sought to clarify the state of the law affecting the care of a patient in such a state. Their Lordships approved the withdrawing of artificial feeding; and the patient succumbed shortly afterwards. This case represents the first time an English court has riveted attention on the question of circumstances which may lawfully empower a physician to discontinue life sustaining equipment, including hydration and nutrition. Uncertainty lingers, however, regarding the withdrawal of care from patients who are incompetent, but not in a persistent vegetative state.

The weighty ethical, social and legal questions inextricably intertwined with the dilemma of the persistent vegetative state will not be resolved in the absence of embellished understanding of the attendant issues. The challenge now is to push ahead with robust debate of such issues, in both public and professional forums.

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Pretarsal injection of botulinum toxin for blepharospasm and apraxia of eyelid opening

Aramideh *et al*¹ recently reported the results of botulinum toxin type A (BTA) treatment in patients with isolated blepharospasm or a combination of blepharospasm and "involuntary levator palpebrae inhibition". They concluded that the addition of two injections into the pretarsal portion, lateral and medial, of the upper eyelid to two injections into the junction of the preseptal and orbital portion of the upper eyelid, and one injection into the lower eyelid improved the beneficial response from 81% to 95% and prolonged the mean duration of benefit from 8.5 weeks to 12.6 weeks.

Our long term experience with pretarsal injections seems to support their findings.² We have used this approach in over 300 patients treated for blepharospasm in our movement disorders clinic since 1983 and have also obtained a successful response rate of 95%. More recently, we have conducted a "single blind", controlled study comparing the effects of injecting BTX (BOTOXTM, Allergan) in the medial and lateral segments of the preseptal versus pretarsal portion of the orbicularis oculi in 14 patients with blepharospasm.³ The pretarsal portion of the right eyelid and the preseptal portion of the left eyelid were injected with the same dose of BTA found to be effective in relieving blepharospasm during previous treatments. The mean dose per eyelid was 10.7 (range 5-15) mouse units. There was no difference in response between the two sides (latency: 6.4 days, peak effect: 3.9, mean duration of maximum benefit: 13.5 weeks, mean duration of total benefit: 16.2 weeks). Although eight patients reported ptosis in the left eye (preseptal), none had complications in the right eye (pretarsal) during the follow up period (3-5 months). The ptosis lasted a mean of 31.9 (range 14-64) days.

These findings strongly support the conclusion that BTA injections into pretarsal eyelids are associated with higher efficacy and lower frequency of complications than injections into the preseptal or orbital eyelids. Four patients of Aramideh *et al*¹ who initially failed to respond to preseptal-orbital injections, but later improved with pretarsal injection, were found by EMG to have "involuntary levator inhibition" in addition to blepharospasm. We have also found that pretarsal injections of BTA are very effective not only in patients with blepharospasm, but also in patients with apraxia of eyelid opening (eyelid freezing), particularly when the involuntary eye closure is associated with or "triggered" by blepharospasm.

In our opinion, pretarsal injections of BTA into the upper eyelid are sufficient to obtain optimum results in patients with blepharospasm and eyelid freezing. There is usually no reason or need to additionally inject the preseptal or orbital portion of the orbicularis oculi. Our results are similar to those of Aramideh *et al*,¹ even though we have not employed an EMG guided approach. It is unlikely that the use of EMG would further enhance the already highly successful response rate.

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NOTICES

Announcement from the British Neuropsychiatry Association: 1996 summer meeting

The 1996 Summer meeting will be held on 14-16 July at Robinson College, Cambridge. It will include topics on neurodevelopment, language, and the presentation of short scientific papers and single case videos by members. The Association's AGM will be held on 16 July.

For further details of these meetings please contact: Sue Garratt, Administrative Assistant, BNPA, 17 Clocktower Mews, London N1 7BB. Telephone/Fax: 0171 226 5949.

For details of membership of the BNPA, which is open to medical practitioners in psychiatry, neurology, and related clinical neurosciences, please contact: Dr Jonathan Bird, Secretary BNPA, Burden Neurological Hospital, Stoke Lane, Stapleton, Bristol, BS16 1QT. Telephone: 01179 701212 ext 2925/2929 or Sue Garratt at the address given above.