

MANNITOL (Comment)

Were the clinical trials referred to in this monograph fabricated ?

The version of this *Formulary* issued in 2003, and again in 2006, referred to two trials that Dr Julio Cruz and his Brazilian colleagues published in 2001 and 2002. A third trial along similar was published in 2004. All three suggested that the rapid administration of a high IV dose of mannitol could reduce the risk of death or serious disability in adults with signs suggestive of brain swelling as a result acute head injury. All three trials, involving 178, 141 and 44 patients respectively suggested that such treatment more than halved the number of patients who were dead, and the number who were disabled six months later. They were the first formal controlled trials of such a strategy to be conducted, although there had been many observational studies showing that mannitol, by acting as an osmotic diuretic, can lower intracranial pressure. Indeed mannitol has been used intermittently, but quite widely, by neonatologists to control acute hypoxic cerebral oedema ever since the observational findings of Levene and Evans appeared in *Archives of Disease in Childhood* in 1985.

The result of the third trial by Dr Cruz was so dramatic that the editor of the journal that published the report of the trial sensed that it might not be reliable. Feeling that there was no way of challenging the trial's integrity directly he commissioned an editorial which said, somewhat cautiously, that while the results were of substantial interest they "also raise questions about how reliable and valid are clinical studies that show very dramatic improvements in outcome when they are performed at only one institution." The editorial called for further multicentre studies, but no such corroboration has yet been forthcoming, and serious doubts have now been raised as to whether the three trials reported by Dr Cruz ever took place (as a recent article written by Dr Ian Roberts on behalf of the Cochrane Injuries Group has now revealed).

These revelations come at a time when clinicians are just beginning to assemble reliable (controlled trial) information on what strategies are, and are not, helpful in the prompt management of severe neonatal cerebral insults – the commonest of which is perinatal asphyxia. The UK based TOBY whole-body cooling trial closed to recruitment, having reached its recruitment target of 325 babies ahead of time in November 2006, and many now await news of the two-year outcome so that the findings of this trial can be placed alongside those of the other trials that have already reported. There are encouraging signs that cooling can be beneficial, but much remains to be learnt. Many babies are going to recover spontaneously without help, and others are too damaged at birth for any treatment to be effective. The therapeutic 'time window' within which cooling is effective also remains to be defined more clearly. Cooling may be of some measurable benefit but the benefits are not as dramatic as many hoped. As so often in clinical medicine, advances are modest and incremental.

TOBY and the other cooling trials must not be seen as finished business therefore, but as the start of the slow process of discovering whether other neuroprotective strategies can be shown to augment the benefit achieved by early body cooling. Mannitol may be one such drug, but others are almost certainly higher on the list of strategies worthy of study. What all will have to accept, in the light of what Dr Roberts has now found, is that despite more than 30 years of use, we still do not have the *faintest* idea whether mannitol is a useful drug to use when there is evidence of acute cerebral oedema. The only controlled trial of its neonatal use failed to show benefit (Adhikari, 1990). While such oedema is clearly worthy of treatment in its own right if it is interfering with cerebral perfusion, the oedema is probably only a late secondary consequence of tissue necrosis when there has been anoxic cerebral damage.

One thing is clear. Those who have taken part in the recent early cooling trials must not sit back and think that we now know how to manage peripartum asphyxia – in truth a proper structured and disciplined study of how to protect the brain from damage is only just beginning, and all need to support the further trials that are clearly called for.

References

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