LETTERS TO THE EDITOR

Randomised trial of early tapping in neonatal post haemorrhagic ventricular dilatation: results at 30 months

EDITOR,—In reporting the results of follow up from questionnaires to the clinicians involved in the care of children randomised after the official end of this multicentre trial, Johnson et al have highlighted an important issue.1

Major functional loss can be identified at the age of 30 months by questionnaire, particularly when there is an unbiased comparison group. The question raised in the text was whether early tapping carried an advantage over conservative treatment in the prevention of major functional loss detectable at the age of 2 years. What may be missed, however, are impairments which, at that age, are not perceived as major deviations from the norm.

Abnormalities and asymmetries of tone may escape notice in a routine examination and become obvious only at a later stage. It is therefore not surprising that there are large differences between the proportions of children reported as being ‘normal’ and those having neumotor impairment without functional loss, in children randomised before 31 January 1987 compared with those randomised after this date.

There may also be difficulties in categorising children as multiply or singly impaired without more formal testing. Silence or poor expression of outcome at this age is often attributed to shyness—particularly in the unfamiliar context of a short clinic visit.

However, for secondary questions concerning the relationship of early tapping to other sound findings and neurodevelopment at 30 months, the nature of the impairment matters. As always, the method to be used depends on what question is being asked. In this respect, the study of Johnson et al refines the questionnaire will succeed in identifying all the impairments which are unaccompanied by functional loss at 2 years, unless the respondents are prepared to undertake a more detailed and structured assessment. By 4 years, it may well be possible to devise questionnaires which focus on these problems. I would strongly support their initiatives to evaluate alternative strategies for measuring health status in children.

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Pro- or antioxidant activity of vitamin C in preterm infants

EDITOR,—It is with great interest that we read the paper by Silvers et al1 describing plasma ascorbic acid concentrations and plasma antioxidant activity in premature infants at birth, and potential implications for reactive oxygen species induced injury. The antioxidant activity of plasma was tested by measuring the rate of lipid peroxidation in rat brain homogenate, expressed as D_{max} (plasma volume in μL required for maximum inhibition of auto-oxidation). In this in vitro study, as mentioned by the authors,1 lipid peroxidation is vitamin C-dependent.2 It is therefore not surprising that plasma with low concentrations of caeruloplasmin (which has ferroxidase activity) and high concentrations of ascorbic acid (which can reduce free iron and initiate the formation of hydroxyl radicals through Fenton chemistry) has a low D_{max}.

Although ascorbic acid can act as a pro-antioxidant in the presence of free transition metal ions, it is a pro-oxidant under other oxidative stress conditions.3 Ascorbic acid scavenges directly a variety of reactive oxygen species, including superoxide and hydroxyl radicals, suppresses the inactivation of antioxidants by products generated by the myeloperoxidase-halide system, neutralises oxidants released from stimulated neutrophils in a dose dependent manner, and can regenerate membrane bound vitamin E.3 It should be noted that vitamin C also has important metabolic roles—for example, in the biosynthesis of collagen, carnitine, and catecholamines.

The question, therefore, is whether in vitro observations such as the ones made by Silvers and colleagues1 are relevant to the in vivo situation. The detection of non-transferrin bound iron in plasma of preterm and term infants4 seems to support the authors’ concerns regarding a potential pro-oxidant effect of ascorbic acid in vivo. However, the various antioxidant and metabolic properties of ascorbic acid also have to be considered, and the integrated effect of high plasma ascorbic acid concentrations on the health status of premature infants is unknown. Therefore, we caution readers not to conclude that ascorbic acid is harmful to premature infants and that ascorbic acid intake needs to be restricted in these infants. Only carefully designed and performed case/control studies of vitamin C depletion or supplementation will be able to answer these important questions.

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Dr Powers et al comment:

There is no doubt that ascorbic acid has several important biochemical functions in the body, including, under most physiological conditions, that of antioxidant. Under the particular conditions associated with prematurity, however, which include a low plasma concentration of plasma transferrin and caeruloplasmin, and possibly the presence of non-transferring bound iron, ascorbic acid present at high concentration would be expected to act as a pro-oxidant. Our published data suggest that this is indeed the case and that high plasma vitamin C concentration at birth is associated with poor outcome. As further support for this argument we have recently demonstrated that at ratios of vitamin C:caeruloplasmin which we observe in premature babies at birth, vitamin C strongly inhibits the ferroxidase activity of caeruloplasmin.1

We have not suggested that vitamin C per se is harmful to premature babies, but it is difficult to ignore the fact that high concentrations in infant formula are higher than those measured in human milk, and that many of the formulas for premature babies are even more generous. The case control approach shows that premature babies need high intake of vitamin C to catabolise tyrosine completely, but our stable isotope studies of tyrosine metabolism in preterm infants suggest this is not the case. Our main argument is that premature babies need high intakes of vitamin C to catabolise tyrosine completely, but our stable isotope studies of tyrosine metabolism in preterm infants suggests this is not the case. We contend that there is no good evidence that high vitamin C intakes are beneficial, there are indications that they may be harmful. We would therefore advocate a thorough re-evaluation of present recommendations for vitamin C intake in preterm infants rather than a reassurance that current intakes are appropriate.
Pro- or antioxidant activity of vitamin C in preterm infants?

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