Correspondence

Effect of exogenous surfactant on total respiratory system compliance

Sir,

I should like to comment on the paper by Milner et al on the effect of the Cambridge artificial surfactant on lung compliance of intubated preterm babies at birth.1

In 1980 Fujiwara2 claimed that an ‘artificial surfactant’ dramatically improved the oxygenation of babies with respiratory distress syndrome. Since then there has been considerable interest in exogenous surfactant treatment. Four years later, however, there are few published reports with results of clinical trials that can be interpreted with confidence. In most studies there are too few babies and no controls, or unsatisfactory controls.3-6 Even the careful study of Halliday7 did not include enough babies to show conclusive results.

The publication of Milner’s paper1 adds another example of tantalisingly inconclusive data to the published reports. It is such a small study that it is not possible to make an satisfactory conclusion. The reasons for this study being unsatisfactory are:

(1) There is no consideration of the numbers of babies needed in their trial to show a significant difference between the compliance measurements of the surfactant treated babies and the controls. For this trial the way to calculate the number of babies needed is firstly to determine what change in compliance could be considered a significant improvement or ‘the smallest medically relevant difference’. Milner mentions that there was no ‘significant improvement’ without defining what he considered to be significant. Obviously this value depends on the accuracy and reproducibility of the compliance measurements. Compliance varied three to fourfold among the controls before (0·21 to 0·61 ml/cm H2O) and after saline (0·15 to 0·69 ml/cm H2O). With this enormous variation the smallest acceptable difference would need to be quite large, that is, a 50% change. The mean lung compliance of the controls before saline was 0·36, therefore a 50% change would be 0·18. Using the relevant Table in ‘Statistics in Practice’8 it can be calculated (using this value of 0·18 and the sample’s standard deviation of 0·22) that a trial size of 70 babies would be needed to detect a 50% change in compliance at the one per cent level with an 80% power. Realistically, it might be surprising if surfactant treatment at this stage altered compliance by as much as 50%. To detect a smaller difference, however, a trial with many more babies would be needed. Milner’s study with only 16 babies has a power of less than 20%, that is only a 20% chance of detecting a significant difference at a one per cent level and not much more at the level of five per cent.

(2) The paper concentrates on the acute effect of surfactant treatment on static lung compliance without discussing why it was an appropriate measurement. Milner’s own published data9 show that newborn babies do not always accept lung inflation passively and often respond with a rejection reflex or an augmented inspiration. Both profoundly alter the tidal volume and therefore the calculation of compliance. Also the expiratory tidal volume might be reduced because the inhaled air is trapped in the lung as the peripheral airways collapse during expiration. Factors like this suggest that the measurement of compliance in this situation may produce results that are difficult to interpret. Perhaps functional residual capacity or thoracic gas volume would be more reliable measurements if they could be made accurately.

(3) Surfactant treated babies received a dose immediately after birth. The ‘before treatment’ measurement of compliance was therefore made before the second dose. This fact was not considered to be relevant by the authors even though the treated babies had a ‘before treatment’ compliance on average 50% higher than the control group (mean (SD) 0·54 (0·19) v 0·36 (0·22) ml/cm H2O). This, like the rest of the compliance data, was not statistically significant because the numbers are too small for such a large variation in the compliance measurement.

(4) The babies were not randomised to this particular study. They were extracted from a larger randomised trial.

Four years after Fujiwara’s original paper the role of exogenous natural or artificial surfactant remains undecided; I believe that it is counterproductive to publish small series of anecdotal data and then draw unsubstantiated conclusions from them.

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Professor Milner and co-workers comment:

Firstly, Dr Morley criticises the number of babies in our study.1 Our aim as stated in the paper was to see whether artificial surfactant given during resuscitation produced changes similar to those seen when added to animal models. For this, we considered that small numbers were adequate, similar indeed to those published by Dr Morley himself.10 We also stated that this type of study could not determine when artificial surfactant altered outcome and entirely agree that for this, vastly larger numbers would be required.

In his second point, he claims that our measurements might be inaccurate due to respiratory efforts by the babies. We were, of course, very careful to exclude inflations where the baby made any respiratory efforts whatsoever. Also we know of no conclusive evidence that air is trapped in the lungs during expiration immediately after delivery and would be grateful to receive a reference on this.

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Thirdly, as stated in our paper, it is possible that some of the first dose remains in the upper airway before resuscitation. We think this unlikely as the babies had not breathed and were ‘sucked out’ during the resuscitation period. The differences in the initial compliance were more likely due to the fact that the control group had more very immature babies.

Fourthly, the babies were randomised as stated in the paper, certainly to a greater extent than in Dr Morley’s previous publication.9

Finally, we consider that the studies were not anecdotal and that investigating the physiological response to forms of treatment are valid, even if they do not measure whether a particular form of treatment alters the long term outcome.

References

Diet and behaviour

Sir.

The recent annotation ‘Diet and behaviour’ by Eric Taylor1 is timely in view of the current public interest in this country in hyperactivity. But I would take issue with him on several points. ‘There is no smoke without fire’ is an old saying and the very consistent reports from many sources, here, in Australia, and the United States on the stimulant effect of some common foods and food colours cannot be so lightly dismissed. Although open trials ‘no longer contribute to the debate’, few have been carried out in this country; but having been involved in one myself I believe they point the way. Hyperactivity is probably multifactorial but, although so difficult to define in precise terms, is readily recognised by the usual criteria of inappropriate attention span, impulse control, restlessness, and rule governed behaviour developing in late infancy and not associated with gross neurological, sensory, or motor impairment or severe emotional disturbance. It is prevalent in two to three per cent of the child population, predominantly in boys.2,3 Our open trial showed initial improvement in 30 of 35 (86%) children after exclusion diet and challenge testing. As most of this was due to the removal of food colouring, the eventual diet was neither harmful nor irksome, but a good dietician is needed to work out the details.

I fully accept the placebo effect but do not think this explains all the benefits of the diet. Some children continued to react to the additives over an 18 month period while many others did not (the ‘diet’ responders), but the mechanism is not clear. Psychometric testing, using elements of the Stanford Binet test under 4 years of age and the Wechsler intelligence scale for school aged children, serially at six month intervals over a year (three assessments) showed significant improvement in two of four preschool and six of eight school aged children on diet alone—two of the latter increased their overall IQ by 15 and 20 points respectively over a six month period and this was maintained. A comparison may be made with two recent papers in Clinical Allergy on the effect of house dust mite hyposensitisation, where the beneficial effect was clearly seen clinically but no in vitro immunological change could be found to support the effect scientifically.4,5

Again I take issue on the subject of allergy. Several writers agree (as I do myself) that hyperactive children and their families show more signs of allergy to a wide range of foods than normal children; but that does not make hyperactivity an allergic condition.6 Even the late Ben Feingold denied that this was an allergic response,7 and Dr Collins-Williams in Toronto was unable to find a significant number of hyperactive children with positive skin prick tests to foods (Collins-Williams C. Fourth Charles Blackley Symposium, Nottingham 1981). In our trial none of the 35 children had a positive radio-allergosorbent test for dairy foods, wheat, or nuts but five were positive for grass pollen and three for domestic animals and house dust mite.

Thirdly, I think Dr Taylor falls into the trap that often leads psychiatrists to disappoint paediatricians, in that he looks at the problem situationally and not aetiologically. If, as has been claimed, 10% of the population will react atypically to almost any drug, then some hyperactive behaviour may be caused by one of these atypical reactions to food chemicals. It is worth investigating. Dietary treatment does need careful supervision but it is not too difficult and is well worthwhile for the ‘responders’. Psychologically troubled children do need psychological help but the behaviour one sees in the children may be the result of misunderstanding and be induced by inappropriate adult behaviour resulting from failure to recognise the primary cause. If we accept that in many cases the condition persists into adult life (although the problem may change in form or intensity)8-9 then the primary cause of hyperactivity is developmental (genetic)? as suggested by Barkley2 and the American Psychiatric Association. But environmental factors may make it worse and be-