Clinical trials and neonatal intensive care

EDITOR,—The Department of Health now acknowledges that randomised clinical trials are an essential part of routine practice and will lead to improved medical care for patients.1 The observation has also been made here that parental participation in a clinical trial has better outcomes than non-participants, regardless of the arm of the trial to which they are assigned.2 Randomised clinical trials therefore confer benefit upon both populations and patients. However, there is a moral obligation upon clinicians to advise their patients to enter randomised trials.

In neonatal intensive care, consent to enter a baby into a trial is sought from the parents. They have just had a baby and their baby is critically ill. They are asked to listen to complex medical arguments which spell out the uncertainties of treatment and they are asked to make a positive decision to consent that will determine the baby’s fate. In the context of neonatal care, in academic units, it is likely that, given the relatively small numbers of babies receiving intensive care, each infant may be suitable for entry into more than one trial, for each of which consent must be sought. Many parents in this situation find it easier to make no decision and so their baby is not entered.

There are a number of issues here that deserve further scrutiny. Parents clearly have the right to know about the uncertainties and the potential harms of their baby’s condition and so it must be unethical to reduce the chances of a baby’s entry into a randomised trial, given the advantages it is accepted that this will bring. Is there a way out of these dilemmas?

Education of the public in the concept and importance of randomised clinical trials has been advocated.3 Other options might also be considered. If a trial sets out to compare two treatment strategies, each of which is regarded as acceptable clinical practice and each of which individually might be implemented without parental consent, then it might be possible to legimate the trial without parental consent. An example might be a trial comparing antibiotic policies, each of which might be used as treatment without parental consent. Such an approach would clearly be inappropriate in, for example, a trial comparing conventional versus operative treatment, as operative treatment may only be given with parental consent. This approach would avoid having to force parents to grapple with issues that would not normally be presented to them and the equally morally questionable practice of forcing parents to...
make decisions about their baby that they would not normally be asked to make and at a time when they are emotionally stressed. It also restores the right of the baby to be entered into a trial, a right which is jeopardised by the common occurrence of parents opting out of positive decision making by refusing trial entry. This well recognised reluctance to make positive decisions has led to the further suggestion that for certain research studies it might be appropriate to ask parents to opt out rather than to opt in.4

A kinder, gentler approach to the care of babies and parents should extend to the area of clinical research. In the first instance the public need to be better educated about the intentions of research. Ethics committees need to appreciate that there are different approaches to seeking consent and should consider what method is most appropriate for a given study. Finally perhaps, we might reflect that to accept that there are occasions when a requirement to obtain parental consent is not in either the baby’s or the parent’s best interests, is also to place the burden of consent squarely on the shoulders of those who are most able to give truly informed consent, namely the clinician and the institution’s ethics committee.

NEENA MODI
Department of Paediatrics and Neonatal Medicine,
Royal Postgraduate Medical School,
Hammersmith Hospital,
Du Cane Road,
London W12 0NN


Early or late parenteral nutrition for the sick preterm infant?

EDITOR—The concern expressed by Brownlee et al regarding whether intravenous lipid should be administered to sick preterm infants early or later strikes me as not unlike a discussion of the wisdom of酒精ics drinking in the morning as opposed to the evening.1 Intralipid (Kabi Pharmacal, like alcohol, is reasonably innocuous when given to healthy subjects below a defined limit. On the other hand giving Intralipid to a hypoxic, acidic, septic preterm infant with respiratory distress syndrome fills me with the same apprehension as a gift of a bottle of whisky to someone in hepatic failure.

Sixteen years have now elapsed since pulmonary fat embolism as a complication of Intralipid infusion was first described in neonates in this very journal.2 This observation described many times since and the circumstances in which pulmonary embolism occurs has remained unchanged. Repeated pulmonary macroembolism from prolonged parenteral nutrition is the most likely cause for ‘chronic lung disease in preterm infants’ as documented by Cooke.3 The term bronchopulmonary dysplasia used in this connection by Brownlee and his colleagues is misleading. Bronchopulmonary dysplasia is a well defined pathological entity related to oxygen toxicity and barotrauma rather than Intralipid.

In both these papers discussion of the pathogenesis of the chronic lung disease is negated by the total absence of any description of the appearances of the diseased lung tissue. While I do not wish to discourage investigation of the least harmful time to give Intralipid to the most beneficial effect I would suggest two further areas of research that are likely to be fruitful.

Firstly, paediatricians need to know what form of chronic lung disease is produced by Intralipid or other components of their parenteral regimens. Historically, defining the morphology of a new disease has often proved valuable in its prevention. Biopsy and postmortem examination are the only means of doing this. Secondly, pressure should be brought to bear on the pharmaceutical industry to devise an emulsifying agent for vegetable oil which is stable in the clinical circumstances in which paediatricians wish to use it. It is the coalescence of emulsified fat globules that leads to blockage of pulmonary capillaries.

Unless steps of this kind are taken the increase in chronic lung disease in sick preterm infants is likely to continue over the next 16 years.

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AJ BARSON
St Mary’s Hospital for Women and Children,
Whitworth Park,
Manchester M13 0JH

1 Brownlee KG, Kelly EJ, Ng PC, Kendall-Smith SC. Dear PRF. Early or late parenteral nutrition used to define the sick preterm infant? Arch Dis Child 1993; 68: 281-3.

Dr Dear comments:

In his comments on our study into the timing of Intralipid administration to preterm infants Dr Barson makes four points. Firstly, in his analogy with alcoholism, he maintains that Intralipid should never be given to sick preterm infants. If the definition of ‘sickness’ is confined to those infants who are hypoxic, acidic, or septic then we would be sympathetic with Dr Barson’s point of view, but the vast majority of preterm babies receiving intensive care are in a reasonably well controlled physiological state and in desperate need of nutrition.

The second point relates to the terminology used to define the sick preterm infant. We agree that we should use the generic term ‘chronic lung disease’ unless we are in a position to define more fully the pathological and aetiological factors. The practical difficulties relate to the fact that radiography is of little help in defining the pathology, lung biopsy is difficult and dangerous, and postmortem examination is of very limited applicability.

In this third paragraph Dr Barson supports the need for studies into the risks and benefits of using Intralipid in preterm infants. That is what we were attempting to do and, to reiterate our results, we were unable to demonstrate an adverse effect on the incidence of severity of chronic lung disease, of whatever aetiology, in association with the early introduction of Intralipid into a parenteral nutrition regimen.

Fourthly, Dr Barson points to the need to encourage the manufacturers of parenteral nutrition solutions to produce products likely to have a greater safety profile when infused into preterm infants. We support that view and we are hopeful that we may be able to extend our studies into that area.
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N Modi

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