DTP immunisation of steroid treated preterm infants

Preterm infants respond well to the three doses of diphtheria, tetanus, and whole cell pertussis (DTP) vaccine, but dexamethasone treatment may impair immunogenicity. We investigated whether four, rather than three, DTP doses may be preferable for primary immunisation of steroid treated preterm infants. Twelve infants born at < 30 weeks gestation who had received dexamethasone for chronic lung disease were given doses of DTP vaccine combined with Hib (ActHIB DTP; Pasteur-Mérieux-Merck) at 2, 3, and 4 months of age. A fourth dose was administered six weeks after the third immunisation (table 1). With the use of standardised enzyme linked immunosorbent assay (ELISA) methods, paired sera obtained before and eight weeks after the fourth DTP dose were analysed at the Health Protection Agency (Porton Down, Wilts, UK) for antibody titres against diphtheria toxoid (DT), tetanus toxoid (TT), and three pertussis antigens (filimbrin agglutinogens 2+3 (FIM), pertussis toxin (PT), filamentous haemagglutinin (FHA)). A pre-fourth DTP serum sample was available for 12 infants, and 11 infants had paired sera. Median (range) gestational age was 25 weeks (24–29) and birth weight was 830 g (550–1235). Median (range) duration of dexamethasone treatment was 15 days (3–153), and cumulative dose was 3.9 mg/kg (1.5–25.6).

Antibody titres of 0.1 IU/ml against DT and TT are considered to correlate with individual protection. After three doses, all infants had already achieved titres > 0.1 IU/ml against DT and TT, and titres remained above this concentration after the fourth dose. No significant increase in antibody titres against diphtheria or tetanus antitoxins resulted from the fourth DTP immunisation (table 2). Despite a trend towards higher mean pertussis antibody titres after four DTP doses compared with after three doses, the increase was not significant in any of the three pertussis antibodies. Although there are no reference protective antibody concentrations for pertussis, mean antibody titres achieved against the three pertussis antigens after three DTP doses compared favourably with those in historical cohorts of UK term and preterm infants who received the accelerated DTP schedule.

All infants showed excellent immunogenicity to three DTP doses; a fourth dose did not improve antibody responses further. In a recent study using diphtheria/tetanus/acellular pertussis vaccine, responses of 15 preterm infants appeared unaffected by recent steroid treatment. These data suggest that dexamethasone treated preterm infants are able to mount satisfactory responses to a standard three dose DTP regimen administered at the same chronological age as term infants, and that supplementary doses are unnecessary in early infancy.

Acknowledgements

We warmly thank the parents and infants for participating in this study. We thank Carol Thornton and Moya Burrag at the Health Protection Agency for respectively performing the serological testing and assisting with data retrieval, and Dr Stephen Roberts for allowing study of one of his patients.

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Table 1 Timing of vaccinations and serum samples

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>1st DTP</th>
<th>2nd DTP</th>
<th>3rd DTP</th>
<th>1st blood sample</th>
<th>2nd blood sample</th>
<th>Days between 4th DTP and 2nd blood sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 (60–89)</td>
<td>97 (92–121)</td>
<td>142 (125–170)</td>
<td>205 (164–218)</td>
<td>255 (229–274)</td>
<td>54 (31–59)</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (interquartile range). DTP, diphtheria, tetanus, and pertussis vaccine.

Table 2 Geometric mean antibody titres (95% confidence intervals) for paired serology measurements after the 3rd and 4th DTP doses

<table>
<thead>
<tr>
<th>Antibody</th>
<th>3rd DTP</th>
<th>4th DTP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DT (IU/ml)</td>
<td>2.08 (1.39 to 3.10)</td>
<td>2.11 (1.13 to 3.92)</td>
<td>0.94</td>
</tr>
<tr>
<td>TT (IU/ml)</td>
<td>3.15 (1.67 to 5.93)</td>
<td>3.12 (1.61 to 6.01)</td>
<td>0.97</td>
</tr>
<tr>
<td>FHA</td>
<td>3.15 (1.67 to 5.93)</td>
<td>3.12 (1.61 to 6.01)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Mean titres were compared using Student’s t test for paired samples. Diphtheria and tetanus antibody concentrations are reported as IU/ml corrected against National Institute of Biological Standards and Control (NIBSC) reference sera 91/534 and 26/488 respectively; pertussis antibodies are reported as titre corrected against NIBSC reference serum 89/530.

In utero HIV infection in pregnancies complicated by tuberculosis in Durban, South Africa

At the core of the HIV-1 and tuberculosis (TB) epidemics, a defined effect of these combined pathogens on maternal and child health has been observed at King Edward VIII Hospital in Durban South Africa. Here we report on the adverse effect of maternal HIV-1 infection with TB disease on fetal acquisition of HIV-1. In a prospective cohort study conducted at the hospital between April 1997 and July 1999, 42 HIV-1 infected pregnant women with active TB disease were investigated for intrauterine transmission of HIV-1. Intrauterine infection was diagnosed by a positive HIV-1 RNA polymerase chain reaction (PCR) (Amplicor; Molecular Diagnostic Systems, Branchburg, New Jersey, USA; limits of detection 50 copies/ml) detected on a neonatal sample obtained within the first 72 hours of birth, with a subsequent positive HIV-1 PCR or clinical progression of disease. Assays were performed in a single laboratory which was participating in a continuing quality certification programme for HIV-1 RNA quantitation sponsored by the National Institutes of Health.

Eight newborns were HIV-1 RNA PCR positive by 72 hours of birth resulting in a 19% in utero transmission rate of HIV-1 for singleton live births exposed to maternal HIV-1 infection and TB disease in Durban. The rate of intrauterine transfer of HIV-1 in this category of ill women was much higher than the overall 5–10% in utero transmission rates recorded in resource poor countries. Maternal CD4 (427 (278) v 318 (289) cells/mm³ (mean (SD)); p = 0.37), plasma viral
burden (median log 5.0 ± 4.7), extrapulmonary sites of TB disease, and sputum smear or culture positive rates for Mycobacterium tuberculosis were no different between in utero transmitting and non-transmitting mothers. A further nine babies were HIV-1 PCR positive on follow up (intrapartum or post-partum transmission), resulting in an overall HIV-1 mother to child transmission rate of 40.4% (17/42).

This observation augments current knowledge on the impact of perinatal infections on mother to child transmission of HIV-1. High maternal viral burden and CD4 suppression, which are characteristic of advancing AIDS, have been associated with higher overall vertical transmission of HIV-1 and greater risk of rapidly progressive infant HIV-1. Here we quantify this intrauterine risk in HIV-1 infected pregnant women ill with TB disease, and suggest that, in these situations, regimens of antiretroviral therapy which are likely to reduce fetal acquisition of HIV-1 will need to be considered. These should supplement public health programmes to detect and prevent TB disease in HIV-1 infected pregnancies in endemic regions.

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References

Quantification of peripheral oxygen consumption by near infrared spectroscopy

Oxygen consumption (VO2) is a measurement used to determine the metabolic rate, and is affected by environmental temperature, body temperature, physical activity, blood flow, and nutrition. Measurements of VO2 have been used to study energy balance in newborn infants and to determine the optimal thermal environment for nursing preterm babies. More recently it has been suggested that measurements of peripheral VO2 may provide an indication of the need for circulatory support during critical care.

Methods used to assess VO2 are either based on the Fick’s principle or a gas exchange technique. The standard units used to express VO2 are ml O2/kg/min. Neonatal cerebral VO2 values using near infrared spectroscopy (NIRS) and jugular venous oxygenation have been reported and have been expressed in ml/100 g/min. NIRS has been used to measure VO2 in limbs, and the results are generally expressed in μmol O2/100 g/min. This non-standard unit makes it impossible to make a direct comparison between global, cerebral, and peripheral VO2 values. We describe a method of expressing NIRS derived peripheral VO2 units in ml O2/kg/min.

Methods
The basic units for expressing peripheral VO2 by NIRS using the arterial occlusion method are mM HbO2/cm/min (mM HbO2/cm/min litre/ min). This can be converted into ml O2/kg/min by multiplying by 4 x 10(1.04 x 3.59 x L x L). On the basis that the molecular ratio of Hb to O2 is 1.4, and the density of skeletal tissue is 1.04 g/ml. The distance between the light emitting and receiving electrode is L cm, and the path length correction factor is taken as 3.59. This is required to correct for scattering of light within the tissue. This equation reduces to 10 L/7. L.

Conversion of μmol O2 into ml can be achieved using the molecular mass of oxygen (M02) which is 16 and the density (dO2) which is 1.249 g/L. Consequently 1 μmol O2 is converted into ml using:

\[(M02 x 10^{-3})/dO2 x 10^{-3} \times (16 x 10^{-3})^2/\]
\[1.249 = 1.1\]

Therefore conversion from mM HbO2/cm/min into ml O2/kg/min requires a multiplication factor of 1.1 x 10/7 L. In studies where L = 3 cm the conversion factor is simply 3.92.

Results
We used data from previous studies to examine the feasibility. Peripheral VO2 was measured by NIRS using arterial occlusion and the oxyhaemoglobin (HbO2) decremental slope. Global VO2 values were obtained by open circuit calorimetry. Table 1 gives the converted values of peripheral VO2 for comparison with global VO2 values.

Discussion
Conversion of standard NIRS units into those normally recognised for VO2 has been achieved. This allows comparison between global, cerebral, and peripheral VO2 values and comparison between studies. The value of using a range of methods to measure tissue oxygenation is enhanced if the results can be compared through the use of standard units. For example, important relations between global and peripheral VO2 have been described.

In making the conversion, two key physical variables are used which have so far only been measured in adults. The skeletal tissue density value of 1.04 g/ml has been used for adult muscle studies. The differential path length factor (DPF) value of 3.59 (0.32) has been reported for adult forearm for inter-optrode distances over the range 1–6 cm. It has also been shown that the DPF is “almost constant” beyond 2.5 cm. In the studies illustrated in table 1, the inter-optrode distance is 3 cm for all infants, hence variation in the calculated peripheral VO2 resulting from changes in DPF is minimal.

Clearly if tissue density and DPF values become available for newborn forearm, then the calculations can be refined. In the meantime, this conversion still provides a valuable method for comparing the relation between cerebral and peripheral VO2. No previous NIRS research using peripheral VO2 methods has been reported using the proposed units. The units commonly used are confusing and difficult to understand. It is recommended that in future peripheral VO2 measurements are reported in ml O2/kg/min.

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References
good as any other treatment. In this same time frame, however, antibiotic resistance has spread, altering the microbial environment of maternity and neonatal units. Rates of neonatal staphylococcal sepsicaemia will always be changing—may be increasing. Admission times of mothers and infants in district general hospitals have shortened too, facilitating a rapid bacterial exchange between our hospitals and communities. Antimicrobial resistance among healthy individuals is a field of growing concern. This combination of events may become a risk factor in the spread of antibiotic resistance in the United Kingdom and a major source of neonatal infection. A parallel pattern has been observed in Japan with neonatal toxic shock syndrome caused by the spread of a methicillin-resistant Staphylococcus aureus (MRSA) clone.5

It might be reasonably argued that there should be a reintroduction of formal umbilical sterilisation, aimed at reducing the bacterial load in our maternity units. Reducing the burden of colonising organisms by the use of topical or systemic antibiotics has been shown to reduce subsequent invasive infection in renal dialysis.6,7 This approach has been limited by the emergence of antimicrobial resistance. An alternative to antiseptic and antiseptic soap is methicillin used in the past may be a more appropriate long-term strategy. Would the production of an appropriate guideline, ensuring umbilical disinfection as well as maternal and staff hand washing in maternity units reduce risks to infants and limit bacterial traffic and potential antibiotic resistance? The debate on the cost effectiveness of this approach should be reopened and the lessons of history reconsidered.

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Effect of laser photocoagulation for retinopathy of prematurity on C reactive protein
Retinopathy of prematurity (ROP) is the major cause of blindness in premature babies, and in the developed world it is a disease of the most immature and unwell infants. Treatment is needed more often in extremely premature babies, taking place in 14% of those born before 26 weeks completed gestation.1 Treatment of severe ROP was originally by cryotherapy, but is now more commonly undertaken with laser, either as transpupillary or trans-scleral diode photocoagulation. C reactive protein (CRP) is an acute phase protein first discovered in the 1930s. It is a product of the innate immune system. Increased production is thought to be beneficial because of its ability to bind phosphocholine and thus recognise foreign pathogens.1 Tissue damage including burns, trauma, and surgery is known to increase CRP.

Babies undergoing treatment for ROP often have regular CRP measurements to help identify the onset of sepsis. There is currently no evidence as to whether cryotherapy or laser photocoagulation cause a rise in CRP irrespective of sepsis.

To ascertain whether CRP is affected by treatment of ROP, a retrospective case note review of infants treated with laser photocoagulation was undertaken. The notes of 16 infants (11 female and five male) requiring treatment for ROP (mean age 24 weeks and 6 days) were reviewed. Fifteen of the babies received laser photocoagulation by transpupillary diode laser, and one received trans-scleral diode treatment. CRP concentration before surgery and the first measurement after surgery were obtained. CRP was measured using an automated discretionary discrete analyser (Olympus 600; Olympus Optical Equipment). Units are mg/L.

The time interval between the operation and CRP measurement was 12 hours to 12 days; the median time was three days. CRP concentration before surgery ranged from < 5 to 53 (median < 5). After surgery, the range was < 5–51 (median < 5). The data were non-parametric. A Wilcoxon signed rank test was used to determine whether the null hypothesis (laser does not alter CRP concentration) was correct. This study did not find a significant difference in CRP concentration after surgery. (Sample size means this study has a 90% power to show significance (p < 0.05) if there were a difference in CRP concentration of 20.)

Our negative findings give some reassurance that if, after treatment for retinopathy, there is concern about infection, a raised CRP concentration is unlikely to be a result of the procedure and more likely to reflect sepsis. However, a prospective study of CRP concentrations after treatment for retinopathy will be necessary to confirm our findings.

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