PostScript

LETTERS

DTP immunisation of steroid treated preterm infants

Preterm infants respond well to the three doses of diphtheria, tetanus, and whole cell pertussis (DTP) vaccine,[1] but dexamethasone treatment may impair immunogenicity.[2 3] 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-Mèrieux-MSD) 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 (fimbrial 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).

Table 1 Timing of vaccinations and serum samples

	Age (days)
1st DTP	65 (60–89)
2nd DTP	97 (92–121)
3rd DTP	143 (127–170)
1st blood sample and 4th DTP	205 (164–218)
2nd (post-4th DTP) blood sample	255 (229–274)
Days between 4th DTP and 2nd blood sample	54 (31–59)

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

Antibody titres of 0.1 IU/ml against DT and TT are considered to correlate with individual protection.[4] 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[1 5] and preterm[1] 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.[6] 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.

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

	After 3rd DTP dose	After 4th DTP dose	p Value
Diphtheria			
DT (IU/ml)	2.08 (1.39 to 3.10)	2.11 (1.13 to 3.92)	0.94
Tetanus			
TT (IU/ml)	3.15 (1.67 to 5.93)	3.12 (1.61 to 6.01)	0.97
Pertussis			
FIM	15922 (6869 to 36908)	21477 (11289 to 40859)	0.44
PT	1567 (613 to 4005)	2188 (820 to 5837)	0.14
FHA	3011 (1806 to 5022)	4314 (2443 to 7619)	0.25

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 titres corrected against NIBSC reference serum 89/530.
DTP, diphtheria, tetanus, and pertussis vaccine; DT, diphtheria toxoid; TT, tetanus toxoid; FIM, fimbrial agglutinogens 2+3; PT, pertussis toxin; FHA, filamentous haemagglutinin.

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References

1 **Ramsay ME**, Miller E, Ashworth LA, *et al*. Adverse events and antibody response to accelerated immunisation in term and preterm infants. *Arch Dis Child* 1995;**72**:230–2.
2 **Robinson MJ**, Campbell F, Powell P, *et al*. Antibody response to accelerated Hib immunisation in preterm infants receiving dexamethasone for chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F69–71.
3 **Robinson MJ**, Heal C, Gardener E, *et al*. Antibody response to diphtheria-tetanus-pertussis immunization in preterm infants who receive dexamethasone for chronic lung disease. *Pediatrics* 2004;**113**:733–7.
4 **World Health Organization**. The control of diphtheria in Europe. Report on a WHO meeting. Copenhagen: WHO, 1990.
5 **Booy R**, Aitken SJ, Taylor S, *et al*. Immunogenicity of combined diphtheria, tetanus, and pertussis vaccine given at 2, 3, and 4 months versus 3, 5, and 9 months of age. *Lancet* 1992;**339**:507–10.
6 **Slack MH**, Schapira D, Thwaites RJ, *et al*. Acellular pertussis vaccine given by accelerated schedule: response of preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F57–60.

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.[1 2] 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; Roche 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%[3] in utero transmission rates recorded in resource poor countries. Maternal CD4 (427 (278) *v* 318 (289) cells/mm^3 (mean (SD)); p = 0.37), plasma viral

burden (median log 5.0 *v* 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 postpartum 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.[4] 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

1 **Khan M**, Pillay T, Moodley JM, *et al*. Maternal mortality associated with tuberculosis-HIV-1 co-infection in Durban, South Africa. *AIDS* 2001;**15**:1857–63.
2 **Pillay T**, Sturm AW, Khan M, *et al*. Vertical transmission of Mycobacterium tuberculosis in KwaZulu Natal: impact of HIV-1 co-infection. *Int J Tuberc Lung Dis* 2004;**8**:59–69.
3 **De Cock K**, Fowler M, Mercier E, *et al*. Prevention of mother-to-child HIV transmission in resource poor countries. *JAMA* 2000;**283**:1175–82.
4 **Abrams EJ**, Wiener J, Carter R, *et al*. Maternal health factors and early pediatric antiretroviral therapy influence the rate of perinatal HIV-1 disease progression in children. *AIDS* 2003;**17**:867–77.

Quantification of peripheral oxygen consumption by near infrared spectroscopy

Oxygen consumption ($\dot{V}O_2$) 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 $\dot{V}O_2$ have been used to study energy balance in newborn infants and to determine the optimal thermal environment for nursing preterm babies.[1] More recently it has been suggested that measurements of peripheral $\dot{V}O_2$ may provide an indication of the need for circulatory support during critical care.

Methods used to assess $\dot{V}O_2$ are either based on the Fick's principle or a gas exchange technique. The standard units used to express $\dot{V}O_2$ are ml O_2/kg/min. Neonatal cerebral $\dot{V}O_2$ values using near infrared spectroscopy (NIRS) and jugular venous occlusion have been reported[2] and have been expressed in ml/100 g/min. NIRS has been used to measure $\dot{V}O_2$ in limbs,[3–6] and the results are generally expressed in µmol O_2/100 g/min. This non-standard unit makes it impossible to make a direct comparison between global, cerebral, and peripheral $\dot{V}O_2$ values. We describe a method of expressing NIRS derived peripheral $\dot{V}O_2$ units in ml O_2/kg/min.

Methods

The basic units for expressing peripheral $\dot{V}O_2$ by NIRS using the arterial occlusion method are mM HbO_2.cm/min (mmol HbO_2.cm/litre/min). This can be converted into µmol O_2/kg/min[5 6] using $4 \times 10/(1.04 \times 3.59 \times L)$, on the basis that the molecular ratio of Hb to O_2 is 1:4, and the density of skeletal tissue is 1.04 g/ml.[4] The distance between the light transmitting and receiving probe is L cm, and the path length correction factor is taken as 3.59.[7] This is required to correct for scattering of light within the tissues. This equation reduces to 10.7/L.

Conversion of µmol O_2 into ml can be achieved using the molecular mass of oxygen (MO_2) which is 16 and the density (dO_2) which is 1.429 g/l. Consequently 1 µmol O_2 is converted into ml using:

$$(MO_2 \times 10^{-6})/(dO_2 \times 10^{-3}) \text{ or } (16 \times 10^{-6})/(1.429 \times 10^{-3}) = 1.1$$

Therefore conversion from mM HbO_2.cm/min into ml O_2/kg/min requires a multiplication factor of 1.1×10.7/L. In studies[5 6] where L is 3 cm the conversion factor is simply 3.92.

Results

We used data from previous studies[5 6] to examine the feasibility. Peripheral $\dot{V}O_2$ was measured by NIRS using arterial occlusion and the oxyhaemoglobin (HbO_2) decremental slope. Global $\dot{V}O_2$ values were obtained by open circuit calorimetry. Table 1 gives the converted values of peripheral $\dot{V}O_2$ for comparison with global $\dot{V}O_2$ values.

Table 1 Peripheral and global oxygen consumption ($\dot{V}O_2$) expressed in similar units

Study details	Peripheral $\dot{V}O_2$		Global $\dot{V}O_2$
	mM HbO_2.cm/min	ml O_2/kg/min	ml O_2/kg/min
1. Mild cooling of the hand (n = 10)			
Before	1.38	5.4	9.95
After	1.11	4.35	9.86
2. Moderate cooling of the hand (n = 12)			
Before	1.01	3.96	8.8
After	0.66	2.58	10.35
3. Bath (n = 19)			
Before	1.47	5.76	7.86
After	1.81	7.09	10.27

All values are means.

Discussion

Conversion of standard NIRS units into those normally recognised for $\dot{V}O_2$ has been achieved. This allows comparison between global, cerebral, and peripheral $\dot{V}O_2$ 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 $\dot{V}O_2$ have been described.[5 6]

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.[4] The differential path length factor (DPF) value of 3.59 (0.32) has been reported for adult forearm[7] 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[5 6] illustrated in table 1, the inter-optrode distance is 3 cm for all infants, hence variation in the calculated peripheral $\dot{V}O_2$ 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 $\dot{V}O_2$. No previous NIRS research using peripheral $\dot{V}O_2$ 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 $\dot{V}O_2$ measurements are reported in ml O_2/kg/min.

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References

1 **Hey EN**. The relation between environment temperature and oxygen consumption in the newborn baby. *J Physiol* 1969;**200**:589–603.
2 **Yoxall CW**, Weindling AM. Measurement of cerebral oxygen consumption in the human neonate using near infrared spectroscopy: cerebral oxygen consumption increases with advancing gestational age. *Pediatr Res* 1998;**44**:283–90.