Antibody response to accelerated Hib immunisation in preterm infants receiving dexamethasone for chronic lung disease

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Abstract

***Aim*—To study the effect of dexamethasone on the routine immunisation of preterm infants with chronic lung disease.**

***Methods*—Serum samples were obtained before and after immunisation from an unselected cohort of 59 preterm infants. *Haemophilus influenzae* antibodies were measured using an ELISA method and differences in the geometric mean values between the two groups of babies analysed.**

***Results*—Sixteen infants received no dexamethasone. Before and after immunisation antibody titres for those receiving no dexamethasone were 0.16 and 4.63 mcg IgG/ml. Corresponding values for those receiving dexamethasone were 0.10 and 0.51 mcg IgG/ml, respectively.**

***Conclusion*—Dexamethasone used in the treatment of chronic lung disease seems to significantly affect the antibody response of preterm infants to immunisation against *Haemophilus influenzae*.**

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Since the introduction of immunisation against *Haemophilus influenzae* (Hib), there has been a substantial fall in reported cases of invasive *H influenzae* disease.[1] The use of unconjugated *H influenzae* vaccines before the age of 18 months used to be unsatisfactory because of poor immunogenicity. The accelerated schedule using conjugated vaccine, which was introduced in 1992,[2] induced antibody titres in term infants of greater than 1.0 mcg/ml. Satisfactory immunisation titres have been obtained when the conjugate vaccine was given in conjunction with triple vaccine into the same site.[3]

There are few data on immunisation in preterm infants. Washburn[4] examined a small group of preterm infants with chronic lung disease immunised with conjugated vaccine at 2 and 4 months, and showed an antibody titre of greater than 1.0 mcg/ml in 55% of infants two months after the second dose. D'Angio studied a smaller group of infants of less than 1000 g in birthweight or 29 weeks of gestation, immunised at 2, 4, and 6 months, with a conjugated vaccine and demonstrated an antibody titre of greater than 1.0 mcg/ml against *H influenzae* in 82% of infants.[5] There are no data for preterm infants in the UK, particularly those who may be expected to have impaired immunological responsiveness because of the concurrent use of steroids.[6]

Table 1 Details of infants given dexamethasone compared with those not given this treatment

	No dexamethasone median (IQ range)	*Dexamethasone median (IQ range)*
No of infants	16	43
Males	8 (56.3%)	22 (51.2%)
Gestational age (days)	196 (186–208)	189 (175–196) p=0.004
Birthweight (g)	1110 (966–1301)	860 (712–1026) p=0.0017
Days ventilated	5 (2–8)	24 (16–36) p<0.0001
Days O_2	13 (3–111)	94 (66–236) p=0.0053

Methods

An unselected cohort of 59 infants weighing less than 1500 g at birth or 32 weeks of gestation was studied between October 1992 and February 1996, after approval from ethics committees at participating units and informed parental consent had been obtained. Infants were immunised with 0.5 ml conjugated Hib vaccine containing 10 mcg of purified *H influenzae* b polysaccharide (ACT-Hib Pasteur Mérieux) in the opposite leg to that used for diphtheria, tetanus, and pertussis (DTP; Trivax-AD Evans) at 2, 3, and 4 months of postnatal age. Blood (2 ml) was drawn at the time of the first, and two months after, the third immunisation and was spun, separated, and deep frozen at −70°C until paired serum specimens could be analysed at the Centre for Applied Microbiology and Research at Porton Down. An enzyme linked immunosorbent assay (ELISA) was performed using HBO-HA as the coating antigen with monoclonal pan IgG conjugate and FDA Hib reference serum as the primary antibody standard.

STATISTICS

Group baseline characteristics were compared using the Mann-Whitney U test. Geometric mean antibody titres (GMT) for infants in receipt of or not receiving dexamethasone were calculated and differences compared in an analysis of variance of the logged data while accounting for days between the two samples. Stepwise regression analysis was also performed to assess the significance of potential risk factors.

Results

Not surprisingly, the infants receiving dexamethasone were younger, smaller, required more ventilation and a longer period in oxygen than those who did not receive the drug (table 1). Immunisations were given at comparable times. The median timing of the second blood

Table 2 Timing of second blood sample

	No dexamethasone median (IQ range days)	*Dexamethasone median (IQ range days)*
Age in days at first sample and first Hib immunisation	63 (60–71)	64 (59–70) p=0.939
Age in days at 2nd immunisation	101 (90–129)	100 (92–114) p=0.885
Age in days at 3rd immunisation	166 (124–185)	141 (126–174) p=0.475
Time in days of 2nd sample after 3rd immunisation	77 (56–115)	129 (74–239) p=0.026
Postmenstrual age at time of 2nd sample	435 (414–468)	464 (402–577) p=0.341

Table 3 Hib antibody (mcg IgG/ml)

	No dexamethasone	*Dexamethasone*
Before immunisation	0.16 (0.07, 0.04)	0.10 (0.05, 0.17)
After immunisation	4.63 (2.10, 10.22)	0.51 (0.25, 1.04)

Values are geometric means with 95% confidence intervals; differences in GMT: p=0.047.

specimen in infants receiving dexamethasone was seven weeks later than that of infants who did not receive dexamethasone (table 2).

Pre-immunisation GMTs were similar in both groups. The change in antibody titres was appreciably less in those infants who received dexamethasone. The differences in GMTs were significant (table 3). The rise in antibody titre for babies who received dexamethasone was approximately one fifth of that in those who were not given dexamethasone (p=0.047, ratio change 0.21, 95% CI 0.05–0.98). Numbers of infants with antibody titres greater than 1.0 mcg/ml were substantially reduced in those infants receiving dexamethasone (table 4).

Birthweight, gestational age, days in oxygen, days ventilated, days between samples 1 and 2 and dose of dexamethasone were regarded as potential risk factors in the regression analysis but none was found to be a significant predictor of the change in antibody titres. The stepwise method suggested that the dose of dexamethasone was the most significant predictor of the change in antibody titre of all factors considered (p=0.014), but only accounted for 10.4% of the total variation.

Initial antibody titres of less than 0.15 mcg/ml were associated with greater rises in Hib titres—8.4 times greater (95% CI 2.3–30.1) This was seen in infants in the non-dexamethasone group (p=0.001) and in the dexamethasone group (p=0.013).

Discussion

Geometric mean titres in infants who did not receive dexamethasone were similar to those seen in term infants where Hib was given as a separate or combined vaccine.[1 3 5] Dexamethasone substantially reduces GMT to *H influenzae* and this observation is in keeping with the effect of dexamethasone on antibodies to diphtheria, tetanus, and pertussis (unpublished observations). The higher antibody rise among infants with a lower initial titre may reflect the influence of a passive inhibitory maternal antibody effect, although it could be a spurious result. This finding agrees with the observations of some authors in relation to Hib,[7] diphtheria,[8 9] pertussis,[8 10] tetanus[7] and polio,[8] but not those of others in relation to Hib.[2] This effect is reduced, although not abolished, by dexamethasone.

The reason for the delay in obtaining the second specimen in the dexamethasone group is not known. The dates of the immunisations in both groups of infants were concordant so that this delay is unlikely to have been due to demographic factors. Immunisation in term infants following the accelerated schedule for DTP offers significant protection during pre-school years.[11] It is unlikely, although possible, that the lower Hib antibody concentration seen in the dexamethasone treated group after immunisation could simply reflect a rapid decrease from an earlier level initially comparable with that obtained in the untreated group.

The protective antibody concentration is currently unclear. Protective levels related to antibody titres to polysaccharide antigen are put at 0.15 mcg/ml in unvaccinated and 1.0 mcg/ml in vaccinated individuals.[12-14] These levels may be inappropriate in individuals immunised with conjugated antigens in whom there is immunological memory and for whom a later antigenic exposure may stimulate the production of an adequate antibody titre, whatever the baseline level. There are no data on protective titres available for the current conjugated antigens. This study shows that 28% or 56% of infants in the dexamethasone treated group were unprotected against *H influenzae* at 0.15 mcg/ml and 1.0 mcg/ml, respectively, as a protective antibody level. The numbers studied are small but if the findings were generally applicable there may be between 500 and 1100 unprotected infants each year in the United Kingdom. These infants would be protected by the high level of herd immunity. Natural immunity is assumed to build up following exposure to wild *H influenzae* and possibly through cross reactivity with specific *E coli* surface antigens.[14] As *H influenzae* carriage rates would be expected to fall as protection in the childhood population rose, these infants may not develop natural immunity and may thus be particularly susceptible to subsequent *H influenzae* type b infection. Until such time as the protective Hib antibody titre is clarified, at risk infants will require further immunisation. A study is currently in progress to ascertain when such an additional immunisation should be given.

Table 4 Hib protection rates (%)

	≥0.15 mcg/ml		*≥1.0 mcg/ml*	
	No dexamethasone	*Dexamethasone*	*No dexamethasone*	*Dexamethasone*
Before immunisation	56	40	13	9
After immunisation	94	72	88	44
		p=0.09*		p=0.003*

* Fisher's Exact test for post immunisation results.

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