

Immunisation of infants at risk of perinatal transmission of hepatitis B: retrospective audit of vaccine uptake

Diane E Wallis, Elizabeth H Boxall

Walsall Health Authority, Lichfield House, Walsall WS1 1TE
Diane E Wallis, senior registrar in public health medicine
Public Health Laboratory, Birmingham Heartlands Hospital, Birmingham B9 5SS
Elizabeth H Boxall, consultant clinical scientist
Correspondence to: Dr Boxall eboxall@rvl.globalnet.co.uk

BMJ 1999;318:1112-3

Perinatal transmission of hepatitis B virus is the infection of infants at birth by mothers who are positive for hepatitis B surface antigen.¹ Around 85% of babies born to mothers who are also positive for hepatitis B e antigen become infected.²

Immunoprophylaxis initiated shortly after birth—that is, after exposure to the virus—can prevent perinatal transmission. Passive prophylaxis with hepatitis B immunoglobulin is 50-90% efficacious, active prophylaxis with hepatitis B vaccine is 75-90% efficacious, and combined active and passive prophylaxis is >90% efficacious.²

Antenatal screening for hepatitis B surface antigen is universal in the West Midlands. The vaccination schedule for all babies of mothers with hepatitis B virus is 0 (within 48 hours of birth), 1, 2, and 12 months. Babies of mothers positive for hepatitis B e antigen are given 200 IU of hepatitis B immunoglobulin at birth as additional protection. Blood samples are taken at 12 months to monitor the effectiveness of vaccination, to audit uptake, and to identify children who have become carriers.

We carried out a retrospective audit on the six maternity units serving Birmingham to establish vaccine uptake and identify problems associated with compliance.

Subjects, methods, and results

We assessed immunoprophylaxis uptake by searching hospital records of all babies born in a 2 year period to mothers who were carriers of hepatitis B virus. Doctors were asked for details of any subsequent hepatitis B and childhood vaccinations in the infants through a postal survey with three mailings, and 116/130 (89%) doctors responded.

The table shows immunoglobulin and vaccine uptake according to maternal hepatitis B e antigen status. Twenty (15%) of the mothers were positive for hepatitis B e antigen. Six infants did not receive

immunoglobulin: four were born to mothers positive for hepatitis B e antigen and two to mothers of unknown status for this antigen. Immunoglobulin was given late in two cases and in error in three.

Overall, 128 babies (99%) received a first dose of vaccine. Two babies admitted to a special care baby unit were not vaccinated. Three doses of vaccine were given to 66% (86) of babies, but by 12 months only 36 babies (28%) were vaccinated within the accepted time limit. A 0, 1, and 6 month schedule was followed in half of the cases.

Infants were more likely to undergo serological testing (total = 28; 22%) if the mother was positive for hepatitis B e antigen. Two infants were positive for hepatitis B surface antigen and hepatitis B e antigen; one, whose mother was positive for hepatitis B e antigen, was given immunoglobulin, the other's mother was positive for hepatitis B e antibody.

Doctors' data showed a lower uptake for hepatitis B vaccination (86/113; 76%) than for routine childhood vaccinations (101/113; 90%). Of those children whose mothers had the same doctor, 56/85 (66%) completed their vaccination schedule compared with 29/85 (34%) where the doctor had changed ($P=0.008$, χ^2); 76/130 (58%) mothers had the same doctor as that listed in the hospital notes. Family size, social class, language, and ethnic origin were not associated with non-completion of hepatitis B vaccination.

Comment

We found that the impression of low uptake of hepatitis B vaccination as judged by serological testing at 12 months (22%) was inaccurate; 66% of babies received three doses of vaccine. Fewer infants completed hepatitis B vaccination than routine immunisations, suggesting a fault in delivering the service rather than parental reluctance.

Uptake of hepatitis B immunoglobulin and vaccine, and results of serological testing at follow up. Values are numbers (percentages) of infants

Mother's hepatitis B e antigen status	Given immunoglobulin		Given 1st dose		Given 2nd dose		Given 3rd dose		Given 4th dose		Tested serologically	Serology results
	Total	Within 2 days	Total	Within time limit	Total	Within time limit	Total	Within time limit	Total	Within time limit		
Positive (n=20)	16 (80)	14 (70)	20 (100)	18 (90)	16 (80)	11 (55)	12 (60)	7 (35)	8 (40)	8 (40)	6 (30)	1 positive for HBsAg and HBeAg, 3 immune, 1 negative for HBcAg, 1 result not in notes
Negative (n=107)	3 (3)	1 (1)	105 (98)	93 (87)	84 (79)	50 (47)	72 (67)	29 (27)	26 (24)	23 (22)	20 (19)	1 positive for HBsAg and HBeAg, 13 immune, 1 not immune, 5 results not in notes
Unknown at delivery (n=3)	1 (33)	1 (33)	3 (100)	2 (67)	2 (67)	1 (33)	2 (67)	1 (33)	2 (67)	2 (67)	2 (67)	1 immune, 1 not received by laboratory
Total (n=130)	20 (19)	16 (12)	128 (98)	113 (88)	102 (78)	62 (61)	86 (66)	37 (43)	36 (28)	33 (92)	28 (22)	2 positive for HBsAg and HBeAg

As retrospective data collection is unsatisfactory, there is a need for childhood vaccination with hepatitis B to be registered on databases to generate appointments and audit uptake. This should be in place now that universal antenatal screening for hepatitis B surface antigen has been recommended.³

Contributors: DEW designed the audit, collected and analysed the data, and participated in writing the paper with EHB. EHB provided DEW with the list of subjects to be investigated, discussed core ideas, and participated in writing the paper; she

maintains the database of mothers who are hepatitis B positive and advises on appropriate immunisations. EHB will act as guarantor for the paper.

Competing interests: None declared.

- 1 Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med* 1975;292:771-4.
- 2 Boxall EH. In: A Zuckerman, ed. *Prevention of hepatitis B in the newborn, children and adolescent*. London: Royal College of Physicians, 1996.
- 3 Department of Health. Screening of pregnant women for hepatitis B and immunisation of babies at risk, 1998. (HSC 1998/127.)

(Accepted 10 December 1998)

Drug points

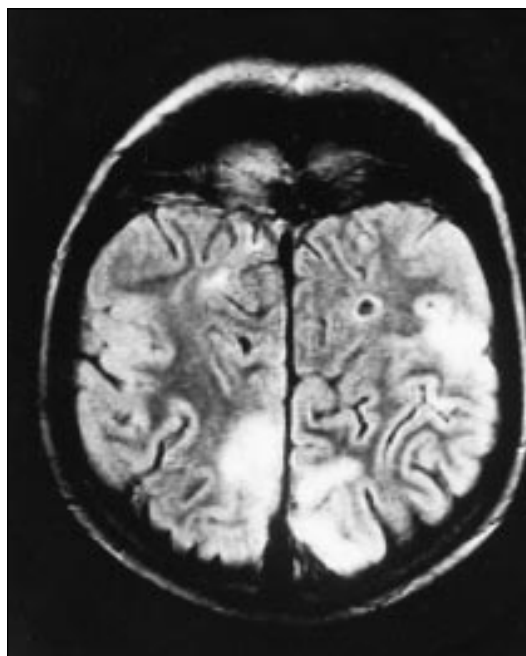
Cyclosporin neurotoxicity after chemotherapy

Deborah A Tweddle, Kevin P Windebank, Quentin Campbell Hewson, S Murray Yule, Department of Paediatric Oncology, Institute of Child Health, Royal Victoria Infirmary NHS Trust and University of Newcastle, Newcastle upon Tyne NE1 4LP

Cyclosporin neurotoxicity may result from interaction with chemotherapy used for transplant conditioning^{1,2} and to reverse multidrug resistance.³ We describe a case of neurotoxicity after chemotherapy for post-transplantation lymphoproliferative disease.

A 9 year old boy presented with monoclonal post-transplantation lymphoproliferative disease six years after cardiac transplantation for congenital heart disease. He was taking azathioprine and cyclosporin (Neoral) 90 mg twice daily (6 mg/kg/day) with whole blood trough concentrations between 29 µg/l and 288 µg/l (Behring enzymatic assay) in the six months before diagnosis. Azathioprine treatment was discontinued, cyclosporin was reduced to 70 mg twice daily, and three courses of low dose chemotherapy were given: vincristine 1.5 mg/m², cyclophosphamide 300 mg/m², and 7 days of prednisolone 60 mg/m². Five triple intrathecal injections of methotrexate and hydrocortisone 15 mg and cytarabine 30 mg were also given. This was followed by high dose treatment: methotrexate 1 g/m², cyclophosphamide 2 g/m², vincristine, prednisolone, and one triple intrathecal injection as before.

Six days after starting high dose chemotherapy he presented with headache, fever (38°C), seizures, and visual agnosia. Abnormal serum concentrations included urea 11.9 mmol/l (2.5-6.4 mmol/l), magnesium 0.56 mmol/l (0.6-1.0 mmol/l), alanine aminotransferase 156 IU/l (<31 IU/l), and bilirubin 23 µmol/l (3-19 µmol/l). His cyclosporin concentration was 250 µg/l and his methotrexate concentration was 0.1 µmol/l (<0.1 µmol/l). An electroencephalogram showed diffuse slow wave activity, but a cranial contrast enhanced computed tomogram and results of lumbar puncture were both normal. Cyclosporin was discontinued and intravenous magnesium, broad spectrum antibiotics, aciclovir, phenobarbital, and diazepam were given. His condition improved, but concern over the possibility of rejection led to reintroduction of cyclosporin at the previous dose. Three days later he became confused, with auditory and visual hallucinations, hypertension, a parkinsonian-type tremor, and rigidity. His cyclosporin concentration was 219 µg/l and serum magnesium was 0.7 mmol/l. Magnetic resonance imaging of his brain showed abnormal, symmetrical non-enhancing signals throughout the parietal and occipital lobes (figure). Cyclosporin neurotoxicity was diagnosed.¹⁻³ The drug was withdrawn and his neurological abnormalities resolved. Three further courses of chemotherapy were given with no clinical evidence of rejection.



Magnetic resonance scan of head showing abnormal signal throughout cortex and white matter of the parietal and occipital lobes

To our knowledge, neurotoxicity has not been reported for cyclosporin when given with chemotherapy for post-transplantation lymphoproliferative disease. The temporal association between chemotherapy and the onset of symptoms implies that neurotoxicity was related to an interaction between cyclosporin and high doses of cyclophosphamide,¹ perhaps through inhibition of cytochrome P-450 enzymes⁴, and possibly to prednisolone,² vincristine,³ and methotrexate.³ We advise clinicians to be cautious if continuing cyclosporin during chemotherapy as normal concentrations do not preclude toxicity.

- 1 Ghany AM, Tutschka PJ, McGhee RB, Avalos BR, Cunningham I, Kapoor N, et al. Cyclosporine-associated seizures in bone marrow transplant recipients given busulphan and cyclophosphamide preparative therapy. *Transplantation* 1991;52:310-5.
- 2 Reece DE, Frei-Lahr DA, Shepherd JD, Dorovini-Zis K, Gascoyne RD, Graeb DA, et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. *Bone Marrow Transplant* 1991;8:393-401.
- 3 Bertrano Y, Capdeville R, Balduck N, Phillippe N. Cyclosporin A used to reverse drug resistance increases vincristine neurotoxicity. *Am J Hematol* 1992;40:158-9.
- 4 Leblanc GA, Waxman DJ. Mechanisms of cyclophosphamide action on hepatic P-450 expression. *Cancer Res* 1990;50:5720-6.
- 5 O'Sullivan DP. Convulsions associated with cyclosporin A. *BMJ* 1985;290:858.