

Unexplained fever in neonates may be associated with hepatitis B vaccine

Nehama Linder, Meirav Raz, Lea Sirota, Brian Reichman, Dan Lubin, Jacob Kuint, Avner Herman Cohen, Asher Barzilai

Abstract

Aim—To investigate whether hepatitis B vaccination has increased the number of cases of unexplained neonatal fever.

Method—The files of all infants born from 1 January 1991 to 31 December 1992, in whom a diagnosis of “injected antibiotic” or “disease of temperature regulation” was recorded, were reviewed. Those who had unexplained fever of 38°C or higher during the first three days of life were divided into two groups: infants who did not receive the hepatitis B vaccine (1991) and infants who did (1992).

Results—In 1992 the incidence of unexplained fever in hepatitis B vaccinated neonates was significantly higher than in the 1991 group of pre-vaccination neonates (35 out of 5819 (0.6%) vs 14 out of 5010 neonates (0.28%) respectively, $p=0.013$).

Conclusions—The increase in the number of cases of unexplained neonatal fever seems to be associated with the introduction of routine hepatitis B vaccination on the first day of life. The possibility that an excess number of neonates will undergo unnecessary procedures and treatment to diagnose unexplained fever justifies planning a controlled study to determine whether these preliminary findings point to a significant problem.

(Arch Dis Child Fetal Neonatal Ed 1999;81:F206-F207)

Keywords: hepatitis B vaccine; fever

Adverse events have been reported in 1.0 to 7.3% of infants who received hepatitis vaccine,^{1,2} the most common in neonates being fever (37.5–39°C) with an incidence of 1.0 to 3.7%.² Routine administration of hepatitis B vaccine to all neonates on the first day of life was introduced in Israel on 1 January 1992. This study aimed to determine whether an increased incidence of unexplained early neonatal fever occurred in the wake of vaccination.

Table 1 Comparison of infants with neonatal fever before (1991) and after (1992) introduction of routine hepatitis B immunisation

	1991 group	1992 group	p Value
Total infants	5010	5819	
Neonatal fever above 37.5°C	27	68	0.001
Neonatal fever above 38.0°C	27	50	0.05
Explained neonatal fever	13	15	NS
Unexplained neonatal fever	14	35	0.013

Methods

We reviewed the charts of all full term infants (37 weeks of gestation or more and birthweight ≥ 2.5 kg) born at the Chaim Sheba Medical Center, Israel, from 1 January 1991 to 31 December 1992, who had a discharge diagnosis of “temperature regulation disease” or who had received intravenous antibiotics as an inpatient. In our department temperature is measured using a digital rectal thermometer (IIVAC 281 model 811, San Diego, CA) in all instances of suspected fever.

“Unexplained” neonatal fever was defined as a temperature of $\geq 38^\circ\text{C}$ during the first three days of life in the absence of sepsis (positive blood and/or cerebrospinal fluid cultures), dehydration (loss of at least 10% of birth-weight), maternal fever ($\geq 38^\circ\text{C}$ at delivery), or respiratory distress (oxygen required for > 4 hours after birth). Chart entries concerning these specific diagnostic details for infants not vaccinated with hepatitis B, born during 1991, were compared with entries for infants born during 1992, who were vaccinated against hepatitis B. No other changes in nursery staff or routine policies had occurred during the two year period.

Results

Twenty seven out of 5010 full term infants born in 1991 and 68 out of 5819 born in 1992 had had a diagnosis of neonatal fever. Initial review of the 1992 group yielded 18 infants with fever $<38^\circ\text{C}$ who were excluded from the final analysis (table 1). Further review of case files revealed identifiable causes of fever (sepsis, dehydration, maternal fever, respiratory distress) in 13 infants in the 1991 and 15 infants in the 1992 groups, respectively. These infants were excluded from analysis (table 1).

Among the remaining infants with unexplained fever occurring within three days of birth, an increase of more than 100% was noted between 1991, when hepatitis B vaccine was not administered (0.28%), and 1992, when hepatitis was given routinely in the first day of life to all neonates (0.6%) ($p=0.013$) (table 1).

All charts of infants with unexplained fever were then reviewed for descriptive clinical characteristics (table 2). The only significant difference between the two groups was the longer duration of fever in the vaccinated group ($p<0.05$).

Discussion

Hepatitis B vaccine is the first vaccine to be universally recommended for neonates.³ The rate of febrile reaction to it reportedly ranges

Department of Neonatology
Schneider Children's Medical Center of Israel
14 Kaplan St
Petah Tikva 49202
Israel
N Linder
L Sirota

Department of Neonatology
Chaim Sheba Medical Center
Tel Hashomer and the Sackler School of Medicine
Tel Aviv University
M Raz
B Reichman
D Lubin
J Kuint

Department of Paediatric Infectious Diseases
A H Cohen
A Barzilai

Correspondence to:
Dr N Linder.

Accepted 17 May 1999

from 0 to 7.3 hours.^{1 2} A lower rate of adverse events was reported in infants and children than in adults.¹ In neonates the most common subsequent event was fever (37.5–39.0°C) and was the most common serious sign reported by the Vaccine Adverse Event Reporting System (VAERS).² Their median reported time from vaccination to onset of fever was 1 day and mean maximum temperature was 38.9°C.

We reviewed the charts of infants with the diagnosis of temperature regulation disease, and of those who received intravenous antibiotics, to identify all infants with neonatal fever. The percentage of infants with unexplained fever during the first three days of life was significantly higher in 1992 (0.6%) when hepatitis B vaccine was given routinely on the first day of life to all neonates compared with 1991 (0.28%) when it was not given. The 0.32% difference is compatible with the 0 to 7.3% reported rate of febrile reaction to the vaccine.^{1 2 4-9} Notably, had we included infants with a temperature above 37.5°C, the significance would have been greater ($p < 0.001$). Furthermore, infants born to mothers with maternal fever were excluded from our analysis even though some should probably have been classified as having unexplained neonatal fever.

The more than twofold increase in the percentage of infants with unexplained fever was not associated with the increased rate of enteroviral illnesses in 1992. The monthly distribution of cases of unexplained neonatal fever was stable, except for November 1992, when eight cases were noted. No other changes in our nursery staff or routine policies were introduced during 1992.

In the report by VAERS 24 neonates had severe neonatal events after hepatitis B vaccination; fever was the most common serious neonatal event and was reported in 13 (54%) neonates. The 13 neonates with fever reported by VAERS were admitted for a median of three days and 10 underwent evaluation for sepsis.² In our study, all 35 neonates underwent a full sepsis evaluation, intravenous antibiotic treatment, and prolonged hospital stay.

Although Israel has a low incidence of hepatitis B carriers among the general Jewish Israeli population 0.5–0.6%,^{10 11} the Ministry of Health decided to provide active immunisation for every neonate on the first day of life, mainly

because of the large scale immigration from countries in which the virus is hyperendemic. It was expected that since the rate of transmission of anti-hepatitis B antibodies from Israeli mothers to offspring is only 23%, there would be a good antibody response to an early first immunisation.^{10 11}

In conclusion, we found that an increased incidence of unexplained neonatal fever, which resulted in evaluation for sepsis, administration of intravenous antibiotics, and prolonged hospital stay, may be associated with vaccination against hepatitis B on the first day of life. Although our data are significant, our numbers are small, therefore a larger controlled trial is justified to determine if the benefit conferred by universal vaccination of neonates against hepatitis B is outweighed by the risks and costs of unnecessary diagnostic procedures and treatments.

- 1 Andre FE. Summary of safety and efficacy data on a yeast-derived hepatitis B vaccine. *Am J Med* 1989;**87**(Suppl 3A):14S–20S.
- 2 Manette TN, David M, Davis BS, Ellenberg S. Recombinant hepatitis B vaccination of neonates and infants: Emerging safety data from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 1996;**15**:771–6.
- 3 Centers for Disease Control. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee (ACIP). *Morbidity and Mortality Weekly Report* 1991;**40**(Suppl RR-13):11–13.
- 4 Stevens CE, Taylor PE, Tong MJ, Toy PT, Vyas GN, Nair PV. Yeast recombinant hepatitis B vaccine: Efficacy with hepatitis B immune globulin in prevention of hepatitis B virus transmission. *JAMA* 1987;**257**:2612–16.
- 5 Polakoff S, Vandervelde EM. Immunization of neonatal at high risk of hepatitis B in England and Wales: National surveillance. *BMJ* 1988;**297**:249–53.
- 6 Gallo IA, Petrosillo N, Celletti S. Results of neonatal vaccination against hepatitis B in Frosinone. *Ann Ig* 1989;**1**:709–15.
- 7 del Canho R, Grosheide PM, Voogd M. Immunogenicity of 20 micrograms of recombinant DNA hepatitis B vaccine in healthy neonates: A comparison of three different vaccination schemes. *J Med Virol* 1993;**41**:30–4.
- 8 Lee CY, Huang LM, Chang MH, Hsu CY, Wu SJ, Sung JL, Safary A. The protective efficacy of recombinant hepatitis B vaccine in newborn infants of HBsAg positive hepatitis B surface antigen carrier mother. *Pediatr Infect Dis J* 1991;**10**:299–303.
- 9 West DJ, Calandra GB, Ellis RW. Vaccination of infants and children against hepatitis B. *Pediatr Clin North Am* 1990;**37**:585–601.
- 10 Bogomolski-Yahalom V, Granot E, Linder N, Adler R, Korman S, Manny N. Prevalence of HBsAg carriers in native and immigrant pregnant female population in Israel and passive/active vaccination against HBV of newborns at risk. *J Med Virol* 1991;**34**:217–32.
- 11 Isacson M, Halevy J, Eidelman Al, Rudensky B, Tadmor OP, Slater P. Prevalence of HBsAg carriers in pregnant women in Jerusalem: Risk for horizontal transmission to family members. *Israel J Med Sci* 1994;**30**:368–70.



Unexplained fever in neonates may be associated with hepatitis B vaccine

Nehama Linder, Meirav Raz, Lea Sirota, et al.

Arch Dis Child Fetal Neonatal Ed 1999 81: F206-F207
doi: 10.1136/fn.81.3.F206

Updated information and services can be found at:
<http://fn.bmj.com/content/81/3/F206.full.html>

References

These include:

This article cites 11 articles, 2 of which can be accessed free at:
<http://fn.bmj.com/content/81/3/F206.full.html#ref-list-1>

Article cited in:
<http://fn.bmj.com/content/81/3/F206.full.html#related-urls>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Hepatitis and other GI infections](#) (13 articles)
[Liver disease](#) (23 articles)
[Drugs: infectious diseases](#) (136 articles)
[Immunology \(including allergy\)](#) (259 articles)
[Vaccination / immunisation](#) (24 articles)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>