Canadian Paediatric Surveillance Program confirms low incidence of hemorrhagic disease of the newborn in Canada

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OBJECTIVES: To determine the incidence of hemorrhagic disease of the newborn (HDNB) in Canada and its relationship to the administration of vitamin K_1 (hereafter referred to as vitamin K) following birth.
METHODS: The Canadian Paediatric Surveillance Program sent monthly surveys to over 2100 Canadian paediatricians requesting identification of infants with defined criteria for HDNB. Reports were confirmed with subsequent case-specific data, including coagulation test results.
RESULTS: Of the 26 reports (10 in 1997, eight in 1998, four in 1999, four in 2000), two were from before the start of the study, three were duplicate reports, four cases erroneously identified hemolytic disease of the newborn, three had coagulation studies which were normal or not done, and seven had other disorders with bleeding. Of the six confirmed cases of infants with HDNB (one classic, five late), all had intracranial bleeding and five suffered neurological sequelae. The estimated incidence of HDNB in Canada (including infants who had oral vitamin K prophylaxis or did not receive vitamin K) is approximately 0.45/100,000.
CONCLUSION: This study confirmed the relatively low incidence of HDNB in Canada and validated the Canadian Paediatric Society's recommendation that all newborns should be given intramuscular vitamin K shortly following birth. To alleviate confusion with haemolytic disease of the newborn, Britain and Australia modified the title of their subsequent HDNB study to vitamin K deficiency bleeding.

Keywords: *Hemorrhagic disease of the newborn; Surveillance programs; Vitamin K deficiency*

Le Programme canadien de surveillance pédiatrique confirme la faible incidence de syndrome hémorragique du nouveau-né au Canada

OBJECTIFS : Déterminer l'incidence de syndrome hémorragique du nouveau né (SHNN) au Canada et son lien avec l'administration de vitamine K_1 (désignée « vitamine K » aux présentes) après la naissance.
MÉTHODOLOGIE : Le Programme canadien de surveillance pédiatrique a envoyé une enquête mensuelle auprès de plus de 2 100 pédiatres canadiens leur demandant d'indiquer les nourrissons présentant des critères définis de SHNN. Ces rapports étaient ensuite confirmés par des données propres au cas, y compris les résultats des examens de coagulation.
RÉSULTATS : Sur les 26 rapports (10 en 1997, huit en 1998, quatre en 1999, quatre en 2000), deux avaient été observés avant le début de l'étude, trois étaient des rapports dédoublés, quatre étaient une maladie hémolytique du nouveau-né mal dépistée, les études de coagulation de trois nourrissons étaient normales ou non effectuées et sept souffraient d'autres troubles accompagnés de saignements. Des six cas confirmés de nourrissons atteints de SHNN (un cas classique, cinq tardifs), tous avaient souffert d'hémorragie intracrânienne et cinq présentaient des séquelles neurologiques. L'incidence estimative de SHNN au Canada (y compris chez les nourrissons ayant reçu une prophylaxie de vitamine K par voie orale ou qui n'en avaient pas reçu) est d'environ 0,45 cas pour 100 000 nourrissons.
CONCLUSION : La présente étude a confirmé l'incidence relativement faible de SHNN au Canada et validé la recommandation de la Société canadienne de pédiatrie d'administrer de la vitamine K par voie intramusculaire à tous les nouveau-nés peu après leur naissance. Pour éviter la confusion avec la maladie hémolytique du nouveau-né, l'Angleterre et l'Australie ont modifié le titre de leur étude subséquente sur le SHNN pour les saignements par carence en vitamine K.

In 1986, the British Paediatric Surveillance Unit emerged as the first national paediatric surveillance system. By the time the Canadian Paediatric Surveillance Program (CPSP) was established in 1996, similar programs were functioning in Europe, Australia and Malaysia. The goal of surveillance programs is to obtain epidemiological and medical information on rare diseases and conditions for which similar data are not available, and surveillance is the most appropriate means of collecting the data.

Hemorrhagic disease of the newborn (HDNB), first identified over one hundred years ago by Townsend (1), presents as unexpected bleeding in neonates, often with gastrointestinal hemorrhage, ecchymosis and, in many cases, intracranial hemorrhage as a result of vitamin K deficiency. In 1961, the American Academy of Pediatrics recommended that 0.5 mg to 1 mg of vitamin K be administered intramuscularly to all newborns shortly after birth to prevent this problem (2). This recommendation occurred before the

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TABLE 1
Haemorrhagic disease of the newborn (HDNB) classification

- Early (0 h to 24 h): associated with an impairment of vitamin K function by maternal medications (eg, anticonvulsants, antituberculous).
- Classic (two to seven days): all newborns are vitamin K deficient at birth due to minimal placental transfer of vitamin K. Classic HDNB is rarely seen with the correct use of vitamin K.
- Late (three to eight weeks): manifested secondary to inadequate vitamin K intake (breastfeeding) cholestasis or malabsorption (neonatal hepatitis, biliary atresia or cystic fibrosis).

TABLE 2
Reports

Year (Number of cases)	1997 (10)	1998 (8)	1999 (4)	2000 (4)
Hemorrhagic disease of the newborn	1	4		1
Before the start of the study	2			
Duplicate reports	1	1		1
Discards				
Hemolytic disease of the newborn	1	2	1	
Coagulation studies normal/not done	2		1	
Other disorders with bleeding	3	1	1	2
Did not meet the case definition			1	

issue of a potential relationship between intramuscular vitamin K and childhood cancer was raised and subsequently shown to be invalid (3). In 1988, the Canadian Paediatric Society (CPS) indicated that the oral administration of 2 mg of vitamin K within 6 h of birth was an acceptable alternative (4). Several other countries similarly recommended the alternative oral route.

Subsequently, late HDNB occurring between three to eight weeks of age almost exclusively among breastfed infants began to emerge as a serious concern in Germany (5), Britain (6), Sweden (7,8) and Australia (9,10). At four to six weeks of age, biochemical signs of vitamin K deficiency were evident in 19% of infants given 2 mg of vitamin K orally at birth compared with 5.5% of infants given a 1 mg dose intramuscularly (11). In 1997, the CPS revised recommendations to indicate that a single intramuscular dose of 0.5 mg (birthweight 1500 g or less) or 1 mg (birthweight greater than 1500 g) should be given to all newborns within the first 6 h of life (12). While articles recommending continued use of oral vitamin K following birth continued to be published, the ideal dose, timing and formulation for oral prophylaxis were unclear and varied throughout (13-17).

Early, classic and late HDNB are described in the CPS statement (12) and summarized in Table 1.

The low incidence (1% to 2%) of classic HDNB in newborns not given vitamin K can be reduced almost to zero with vitamin K administration at birth (18). The risk of late HDNB with intramuscular vitamin K following birth is reported to be approximately 0.25 per 100,000 (19). To obtain information on the incidence of HDNB in the Canadian population and the relationship to vitamin K administration, a decision was made to include this condition in the CPSP in 1997.

TABLE 3
Other bleeding disorders initially reported as haemorrhagic disease of the newborn

Factor VIII deficiency
Disseminated intravascular coagulopathy
Sepsis and pulmonary hemorrhage
Exchange transfusion complication
Familial hemangiomatous disease
Adrenal hemorrhagic mass
Liver disease

METHODS

The CPSP requested monthly reports on HDNB from over 2100 Canadian paediatricians and paediatric subspecialists. For each case report, a follow-up detailed questionnaire was sent to collect case-specific data confirming the astuteness of the diagnosis. During the four years of the study, the average annual response rate was 83% (82% in 1997, 86% in 1998, 83% in 1999, 82% in 2000) and the detailed questionnaire completion rate was 93%.

A case definition and protocol providing background information on HDNB were mailed to all CPSP participants. HDNB was defined as abnormal bleeding occurring in the first two months of life associated with an abnormal prothrombin time of greater than 18 s or an international normalized ratio of greater than 1.4 without other abnormalities of coagulation or explained by another primary diagnosis of liver, bowel or systemic disease. Only laboratory-specific information, sufficient to ensure that reports met these criteria, was requested on the detailed questionnaire.

After three years of surveillance (1997 to 1999), the study was extended for an extra year to obtain more complete information. The principal investigator analyzed case-specific clinical data provided on follow-up questionnaires and, when necessary, contacted the reporting physician for additional information.

RESULTS

The CPSP received a total of 26 reports (10 in 1997, eight in 1998, four in 1999, four in 2000). Information concerning these reports may be seen in Table 2. Six infants were confirmed to have HDNB (one classic and five late). Another two HDNB cases occurred before the start of the study and represented infants who did not receive vitamin K following birth. One was a home birth while the other infant was born outside of Canada. Three were duplicate reports. Surprisingly, four cases of hemolytic disease of the newborn were erroneously reported. There were three initial reports of HDNB with coagulation studies that were either normal or not done. In addition, seven had other etiologies with bleeding such as factor VIII deficiency, disseminated intravascular coagulopathy, sepsis, familial hemangiomatous disease and bleeding following an exchange transfusion (Table 3).

TABLE 4
Characteristics of infants with hemorrhagic disease of the newborn (HDNB)

Year	1997	1998	1998	1998	1998	2000
HDNB type	Late	Late	Classic	Late	Late*	Late
Breastfeeding	>90%	>90%	No	>90%	>90%	79%
Prior vitamin K	None	Intramuscular	Intramuscular	Intramuscular	Oral	None
Initial site of bleeding	Intracranial	Intracranial, nose	Intracranial	Intracranial, skin, nose	Intracranial	Intracranial
Neurological sequelae	Yes	Yes	No	Yes	Yes	Yes
Comments	Home birth					Home birth to hospital

**Infant also had biliary atresia and by a priori definition should be excluded*

Characteristics of the HDNB cases are seen in Table 4. Of the six confirmed HDNB cases identified during the study period, five infants were primarily breastfed. In spite of the recommendation for vitamin K prophylaxis, two infants born at home did not receive vitamin K after birth even though one subsequently went to hospital. HDNB did occur after both intramuscular (three infants) and oral (one infant) vitamin K administration in some infants. All infants presented between 10 to 50 days of age with intracranial bleeding and, unfortunately, five suffered neurological sequelae.

DISCUSSION

Given that the CPSP response rate was not 100% and that it is possible, but unlikely, that paediatricians were not involved with the care of an infant with HDNB, some cases may have been missed. The average annual response rates of 83% for the initial monthly reporting form and 93% for the detailed questionnaire are remarkable for this voluntary program. A previous audit done by the Canadian Paediatric Decision Support Network in conjunction with the Canadian Association of Paediatric Health Centres confirmed that the CPSP is a highly reliable epidemiological tool for identifying patients with rare diseases or conditions (20). It is likely, too, that most of the paediatricians who did not return their survey each month had nothing to report.

One of the biggest surprises of the study was the number of reports of hemolytic disease of the newborn. Granted the acronym HDNB may be somewhat confusing, but "haemorrhagic disease of the newborn" was written out in full along with the acronym (HDNB) on each monthly initial reporting form. Interestingly, subsequent studies in the United Kingdom and Australia were entitled "Vitamin K deficiency bleeding (VKDB)" and "VKDB (including haemorrhagic disease of the newborn)" respectively to alleviate this confusion (21,22). Careful attention to potential ways that words or acronyms could be misconstrued should be considered in future surveys of this kind.

Although an article on an approach to the bleeding newborn was published in *Paediatrics & Child Health* at the end of 1998 (23), and the definition for HDNB was provided in the CPSP protocol sent to all participants at the start of the study, physicians may have relied on a variety of different published educational resources to determine investigations for diagnosing causes of bleeding in the newborn. During the study period, there were reports of infants who did not have coagulation tests and of infants with other bleeding etiologies. This indicates both that cases could have been missed and that more education is still needed to reinforce a systematic approach to the investigations of bleeding in newborns.

Although there is evidence of vitamin K deficiency in the cord blood from newborns exposed to anticonvulsants (and antituberculous drugs) during pregnancy (24), there were no reports of such occurrence during the four years experience in Canada. Somewhat surprisingly, one classic and two late HDNB were reported in spite of intramuscular vitamin K administration following birth. No prophylaxis is totally efficacious and it is to be expected that some cases would be found in this majority group. Although five of the six newborns in the study were breastfed, no additional risk factors were found other than the one infant who was subsequently found to have biliary atresia (Table 2). The fact that two babies born at home (0.26% of Canadian births occur at home) (25) did not receive any vitamin K may indicate the need to better educate the public and those who assist with home births on the importance of this prevention measure. Physicians who see newborns with abnormal bleeding should check for vitamin K deficiency even if the baby has been documented to have previously received vitamin K prophylaxis.

All six infants with HDNB had intracranial bleeding and sadly, five suffered from neurological sequelae. In spite of the CPS recommendations, some babies born in Canada still do not receive vitamin K. Although two such occurrences were home births, one infant (36 weeks gestation) was subsequently admitted to a hospital as a newborn. While it may be that appropriate advice was given to parents who refused to permit vitamin K administration, clearly the importance of vitamin K prophylaxis must be emphasized to health care providers who participate in home births, and to the public in general. Treating physicians need to seek confirmation of previous administration of vitamin K and act accordingly.

During the four years of the study, approximately 1,360,000 babies were born in Canada, including 3528 home births (25,26).The calculated incidence of all types of HDNB in Canada during this period would be 0.45/100,000, whereas the calculated incidence of late HDNB would be 0.37/100,000. This is slightly higher than the rate of 0.25/100,000 reported by von Kries (19) and may be due to the fact that two infants did not receive any

vitamin K following birth and another received a single oral dose of the parenteral form of vitamin K. As data are not available on the relative frequency of oral versus parenteral vitamin K during the study period, the relative incidence of HDNB among Canadian babies who received vitamin K orally rather than intramuscularly cannot be determined. A comparison of the incidences of late HDNB from 1995 to 2000 in Canada, Australia, New Zealand, Switzerland, Germany and Britain showed Canada to have the lowest rate (0.37/100,000) (27). Included in this rate is a late report confirmed after this publication. In this international comparison of 82 cases of late HDNB (including five in Canada), no vitamin K was given in 27, intramuscular vitamin K was given in six, oral vitamin K (mixed micellar form) was given in 46 and vitamin K administration data was unknown in three cases. Countries that use oral vitamin K either in single or multiple doses, or do not give vitamin K, have higher incidences of late HDNB. Many of these countries use the more absorbable mixed micellar formulation of vitamin K (not available in Canada) in a two- or three-dose regimen, although compliance with such regimens may be problematic (28). The relatively low incidence of HDNB during this study period in comparison with other countries suggests that the recommendations of the CPS are generally followed in Canada.

CONCLUSION

The CPSP's confirmation of the relatively low incidence of HDNB in Canada is congruent with the position of the CPS that all newborns should be given intramuscular vitamin K shortly following birth. The failure of some babies to receive any vitamin K, and perhaps the occurrence of vitamin K deficiency bleeding in a baby who received oral prophylaxis, suggest that implementation of the CPS HDNB guidelines is not universally accepted. However, the relative infrequency of HDNB reports in the latter two years of the study (one infant) suggests that the incidence of late HDNB has been reduced almost to the absolute minimum, preventing short-term morbidity and serious long-term neurological sequelae for Canadian children.

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