Key messages

- Intramuscular vitamin K given to babies is known to be effective in the prevention of vitamin K deficiency bleeding but it has been suggested that these preparations, or one of their constituents, may increase the risk of childhood cancer
- Most studies have not shown a significant association between childhood cancer and vitamin K but are unable to exclude the possibility that its use increases the risk of childhood cancer by up to 10%
- Intramuscular vitamin K has been given to "high risk" babies as part of all the various prophylaxis policies in the United Kingdom; this should continue
- As a small risk cannot at present be excluded it seems prudent to recommend a policy of giving intramuscular vitamin K only to those babies at particularly high risk and giving it orally to others
- It is essential that a record should be made of whether or not vitamin K is given and of the preparation, route of administration, and dose

results are not independent. Those for the present paper, however, are based on more cases, and the method of analysis is entirely different and, in particular, does not use the controls from the other studies. Although (with some minor and possibly questionable exceptions) the results of the present analyses are not significant and there is no suggestion of a doubling of the risk of malignant disease arising from the use of intramuscular vitamin K, the findings for childhood leukaemia are compatible with an increased risk of around 20-30%, as, by using the same argument as at the end of the section on statistical methods, it can be shown that an individual relative risk of 1.25 gives a risk ratio of 1.14, and such values occur in table 3. These largely negative results are in agreement with those from our own case-control study and with most of the other papers on this subject, the results and implications of which are discussed in the accompanying paper by Passmore et al.[3]

Various colleagues are thanked in the accompanying paper. We are very grateful to Dr Hey and the members of the Scottish Neonatal Network for providing carefully validated information on numbers of births and vitamin K prophylaxis policies in Scottish hospitals.

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Neonatal vitamin K administration and childhood cancer in the north of England: retrospective case-control study

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Abstract

Objective: To explore the possible association between intramuscular vitamin K given to neonates and the subsequent development of childhood cancer.
Design: Retrospective case-control study on the basis of hospital records.
Setting: The former Northern Health region of England.
Subjects: 685 children who were born and lived in the region and who developed cancer before their 15th birthday, and 3442 controls also born between 1960 and 1991 and matched only for date and hospital of birth. The notes of a further 701 index cases were untraceable.
Main exposure measure: Administration of intramuscular vitamin K versus no exposure to vitamin K.
Results: There was no association between the administration of vitamin K and the development of all childhood cancers (unadjusted odds ratio 0.89; 95% confidence interval 0.69 to 1.15) or for all acute lymphoblastic leukaemia (1.20; 0.75 to 1.92), but there was a raised odds ratio for acute lymphoblastic leukaemia developing 1-6 years after birth (1.79; 1.02 to 3.15). No such association was seen in a separate cohort-based study not dependent on case note retrieval in which the rates of acute lymphoblastic leukaemia in children born in hospital units where all babies received vitamin K were compared with those born in units where less than a third received prophylaxis.
Conclusions: It is not possible, on the basis of currently published evidence, to refute the suggestion that neonatal intramuscular vitamin K administration increases the risk of early childhood leukaemia. Any

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association may have been masked in earlier studies that did not use controls matched for time and locality by other unidentified factors affecting the spatiotemporal variations in incidence of leukaemia.

Introduction

Recent studies[1–5] have been interpreted[6] as providing no support for Professor Golding's suggestion that neonatal intramuscular administration of vitamin K is associated with a subsequently increased risk of childhood cancer, including lymphoblastic leukaemia.[7 8]

Several of the studies, however, were small[1] or involved historical comparisons.[2 3] Although the incidence of acute childhood leukaemia in particular is known to show clear geographical variation,[9] only one of the recent studies has used hospital matched controls.[5] The northern region children's malignant disease registry holds records of all children diagnosed since 1968 as having malignant disease while they are resident in the northern region and still under the age of 15.[10] We therefore carried out a retrospective, case-control study based on birth records by using cases ascertained from this register of children known to have been born in the northern region and control children matched for date and hospital of birth.

Methods

Children born in the region between 1960 and 1991 who developed cancer between 1968 and 1992 were identified from the register. Birth records were seldom available for babies born before 1960. Selection was limited to babies born in hospital and first diagnosed as having cancer when over 3 months old but less than 15 years old. Birth records were found for 731 of these children, but babies given oral vitamin K at birth (n = 30) or born after a multiple pregnancy (n = 16) were excluded from the case-control study. A further 701 birth records could not be traced, usually because the unit in question had retained only its most recent case records or because the unit had closed and the records could no longer be located. Of the 46 maternity units open in the region in 1960, 22 had closed by 1991, and seven others had been resited. The loss of these records raises important issues but is not likely to have biased the conclusions reached in the present study.

Controls were selected by taking the 4th, 8th, and 12th birth before and after the index birth by using the birth or admission registers for the hospital where the index child was born (after the exclusion of multiple births and children who died before discharge). Six controls were selected for most of the index cases, but this number was later reduced to three because of time constraints. When the notes for control children could not be located after a diligent search or when the child selected was found to be on the malignant disease register the next possible control was selected. The neonatal notes or maternal notes, or both, were then abstracted by one of four experienced research nurses. No attempt was made to prevent the abstracters from knowing which records belonged to index children because of the selection process adopted. In addition, the child's neonatal records were often filed with the paediatric records, making it hard to disguise the later development of a malignant condition. Permission to abstract information from the case notes was obtained from each of the 16 research ethics committees in the region.

Case notes and hospital policies

A single vitamin K preparation (Konakion, Roche Products) at a single 1 mg intramuscular dose was the standard treatment for all babies offered prophylaxis during the years covered by this study in all units from which data abstraction was attempted. In many hospitals it was not possible to be entirely certain whether vitamin K had been given because unit policy required an entry in the case notes only when treatment *was* given. If there was nothing in the notes an assumption was made that treatment had been in accordance with current unit policy: 22% of the children whose notes contained no mention of prophylaxis were coded as having had intramuscular vitamin K on this basis (almost 90% of whom were born in hospitals with a policy of universal prophylaxis). A more rigorous approach was possible in cases from units where an entry was always made in the case notes, both when treatment was given and when it was not, which made it unnecessary to "impute" treatment in the manner adopted during all earlier studies.[4 5 8] Almost all the informative (discordant) case sets from the analyses in table 2 came from these centres.

Information on hospital policy with regard to prophylaxis was obtained separately and independently by two people and then cross validated. A senior research nurse obtained information from midwifery and neonatal staff in each unit in the region, while a paediatrician collected comparable information from both current and recently retired medical staff. When inconsistencies were uncovered case notes were sampled to determine what policy had actually been followed. A similar approach was used to confirm the date of any change of policy in those hospitals in which policy had changed during the study period. In units with a policy of selective prophylaxis less than 30% of babies received intramuscular vitamin K at birth; in units offering prophylaxis to all, sampling of case notes showed that more than 95% of babies received vitamin K. Nine small units whose records could not be found seemed to have had no single uniform policy.

Odds ratios and their confidence intervals for intramuscular treatment versus no treatment were calculated by conditional logistic regression.[11] Adjusted odds ratios were also calculated separately for each of the following prespecified possible confounding factors: sex, gestation, birth weight, opiates during labour, assisted delivery, signs of asphyxia at birth, admission to special care, or neonatal blood transfusion.

Because the neonatal case notes of almost half the children known to the northern register could not be traced we undertook a separate analysis to see if the incidence of acute lymphoblastic leukaemia among children born in hospitals with a policy of universal prophylaxis was different from that experienced when a selective policy was in operation. For this review information on 494 children born in the region between 1960 and 1990 and known to the northern region children's register by the middle of 1996 was augmented by information on 14 further children

born in but diagnosed outside the region provided by Dr Draper of the Childhood Cancer Research Group in Oxford (births between 1965 and 1986 when a diagnosis was made before the age of 15 and before the end of 1986). That this step increased the number of known cases so little suggests that loss due to migration out of the study area during childhood was uncommon (<5%). Information on annual delivery rates for maternity units was provided before their abolition from national SH3 returns to the Department of Health. Similar annual information was collected informally by the Information Systems section of the former Northern Regional Health Authority, at the request of the Regional Maternity Survey's Coordinating Group, after 1986. The findings from this cohort (or "ecological") study were analysed with a Poisson log linear rates model.[12]

Results

Case-control study

There was no evidence of any association between neonatal treatment with intramuscular vitamin K and the incidence of all childhood cancer; and the odds ratio for the 207 children with acute lymphoblastic leukaemia (table 1) was not significantly raised either. Two secondary analyses, however, were conducted to look at cases typical of the peak of incidence seen in early childhood. Firstly, the 92 children who had T cell leukaemia (or for whom subtype characterisation was not available) were excluded from the sample. Secondly, an analysis was done on the 144 children who were between 1 and 6 years old when they were first diagnosed. Many children were, of course, in both these subgroups. No other subgroup analyses were performed.

Treatment with intramuscular vitamin K was associated with a raised incidence of acute lymphoblastic leukaemia in 1 to 6 year old children (table 1); and the unadjusted odds ratio remained high even when the analysis was limited to children from units where the neonatal case notes clearly recorded both when the baby did and when the baby did not have vitamin K, making it unnecessary to make any "imputation" about treatment from a knowledge of local policy (table 2), although, with only 28 discordant data sets, the difference was of only borderline significance.

Adjustment for gestation, birth weight, sex, opiate exposure during delivery, signs of asphyxia at birth, or neonatal blood transfusion did not change any of the odds ratios by more than 10%; adjustment for assisted delivery or admission to special care caused a larger rise in the odds ratio. The ratio for 1 to 6 year old children, after adjustment for opiate exposure in labour or assisted delivery, was significantly increased (table 1), even when the analysis was limited to cases for which intramuscular vitamin K was unambiguously recorded in the case notes (table 2).

Cohort analysis

If intramuscular vitamin K exposure at birth was a major factor influencing the likelihood of early childhood leukaemia, then the incidence among children born in units where all babies were offered prophylaxis at birth would be expected to be higher than in units where less than 30% received prophylaxis.

Table 1 Incidence of cancer in children given parenteral vitamin K compared with children not given vitamin K in neonatal period. Evidence as to whether vitamin K was given was taken either from case notes or ascertained from knowledge of local unit policy

Category	No of cases	Odds ratio (95% CI)	No of discordant sets
All cancer	664*	0.89 (0.69 to 1.15)	310
All cancer except acute lymphoblastic leukaemia	457	0.79 (0.59 to 1.08)	223
All acute lymphoblastic leukaemia:	207	1.20 (0.75 to 1.92)	87
Non-T cell acute lymphoblastic leukaemia	115	1.63 (0.91 to 2.91)	54
Acute lymphoblastic leukaemia diagnosed at 12-71 months†	144	1.79 (1.02 to 3.15)	58

*21 cases excluded because policy at local unit could not be ascertained.
†Odds ratio 1.83 (1.04 to 3.21) and 2.57 (1.29 to 5.13) after adjustment for opiate exposure and assisted delivery, respectively.

Table 2 Incidence of cancer in children given parenteral vitamin K compared with children not given vitamin K in neonatal period. Evidence as to whether vitamin K was or was not given taken exclusively from case notes

Category	No of cases	Odds ratio (95% CI)	No of discordant sets
All cancer	438	0.96 (0.67 to 1.37)	148
All cancer except acute lymphoblastic leukaemia	306	0.83 (0.54 to 1.26)	107
All acute lymphoblastic leukaemia:	132	1.38 (0.71 to 1.70)	41
Non-T cell acute lymphoblastic leukaemia	81	1.80 (0.82 to 3.91)	30
Acute lymphoblastic leukaemia diagnosed at 12-71 months*	94	2.26 (0.98 to 5.22)	28

*Odds ratio 2.42 (1.03 to 5.66) and 3.56 (1.31 to 9.65) after adjustment for opiate exposure and assisted delivery, respectively.

Table 3 Relative risk of leukaemia in hospitals with policy of universal versus policy of selective prophylaxis

Policy	No of births	No of cases	Expected No	Relative risk* (95% CI)
All cases of acute lymphoblastic leukaemia†				
All hospitals:				
Universal policy	516 144	188	192	0.95 (0.78 to 1.17)
Selective policy	469 234	179	175	
Hospitals where policy changed during study:				
Universal policy	105 081	34	39	0.8 (0.53 to 1.20)
Selective policy	175 762	71	66	
All acute lymphoblastic leukaemia diagnosed at 12-71 months				
All hospitals:				
Universal policy	516 144	134	131	1.05 (0.82 to 1.35)
Selective policy	469 234	116	119	
Hospitals where policy changed during study:				
Universal policy	105 081	23	24	0.94 (0.57 to 1.56)
Selective policy	175 762	41	40	

*Adjustment for year of birth or year and hospital of birth did not make any of relative risks significant.
†This total excludes 77 children born at home, and 64 children delivered in small units whose policies remain unknown.

There was no evidence of any such trend (table 3). The proportion of babies born in hospital and estimated to have been offered prophylaxis rose from 42% in 1960 to 92% in 1990.

Discussion

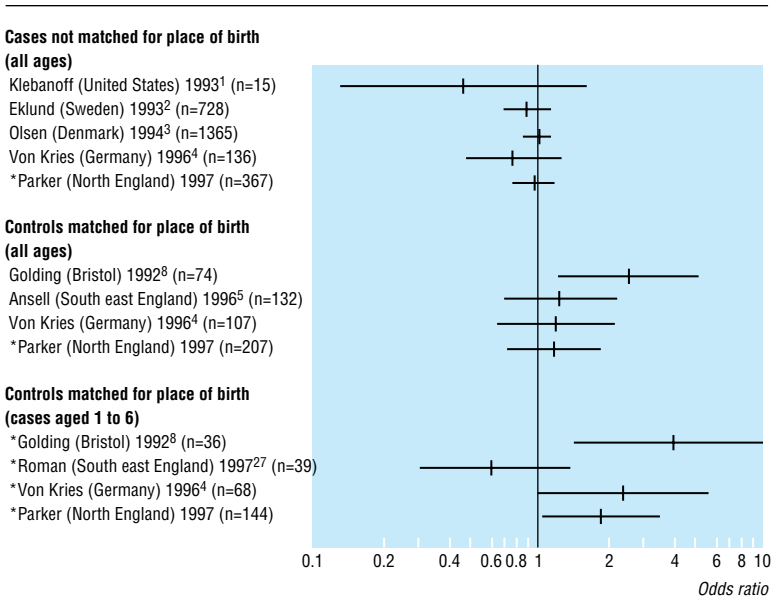
Leukaemia seemed to account for only a part of the increased risk of childhood cancer seen in Golding's study,[8] but subsequent studies have found no evidence to suggest that intramuscular vitamin K is a general carcinogen.[2–4] The present study (see table 1) also suggests that such prophylaxis does not produce even a small increase in the odds ratio for childhood malignancy other than leukaemia. Most subsequent studies have focused on the risk of leukaemia, or of acute lymphoblastic leukaemia, which accounts for

Key messages

- Two studies that used controls matched for date and place of birth have now failed to confirm a 1992 study reporting an increased risk of non-leukaemic childhood cancer in babies given 1 mg of intramuscular vitamin K at birth
- Three other such studies have failed to confirm the increase in the risk of leukaemia also found in the 1992 study but were not large enough to exclude a near doubling of the odds ratio
- Three of the four case matched studies now available have found a significant increase in the incidence of acute lymphoblastic leukaemia, first manifesting itself 1-6 years after birth
- A cohort study has not found any such increase in children born in units where all babies were offered vitamin K at birth compared with units where less than 30% received prophylaxis
- Regular low dose oral supplementation can be effective, making it unnecessary to give a form of treatment over which doubt still lingers

over 85% of childhood leukaemia. There has been a tendency to presume that because these studies found no unequivocal evidence of a raised odds ratio the risk was not raised.[6] Those studies that selected controls without matching for hospital or place of birth have consistently found no increased risk of leukaemia, but those that have included such a match have been unable to exclude the possibility that the true odds ratio associated with intramuscular vitamin K prophylaxis is as high as 1.9 (figure).

The incidence of acute lymphoblastic leukaemia in childhood (and, in particular, non-T cell leukaemia) tends to peak 1 to 6 years after birth in Western society, and it is widely thought that the excess seen in this age group may have a different aetiology.[13] There also seems to have been a 50% increase in the incidence of acute lymphoblastic leukaemia in young children in the United Kingdom during the past 35 years.[14] We therefore undertook a separate subanalysis of these cases, even though this had not been prespecified when the study was first planned. Our results suggested that there could be a significant increase in this form of leukaemia in early childhood among babies given intramuscular prophylaxis at birth. The quality of the neonatal records that were available in some local units made it possible to do part of this analysis without relying on any presumption of treatment on the basis of supposed unit policy (something that has not been possible in any other study published to date). No other ad hoc analyses were done. A significant association was also seen in the recent German study (odds ratio 2.28; 0.94 to 5.54; $P < 0.05$ on a one tailed test) in which local rather than state matched controls were used.[4] Golding also found a significant association in her Bristol study.[8] The odds ratio for 1-6 year old children in that study was 4.10 (1.53 to 10.96) (Golding, personal communication). It is difficult to explain why studies that do, and do not, match for place of birth should produce such different results. It may be that factors operating at birth are swamped by other unidentified factors affecting the known spatiotemporal variations in the incidence of childhood leukaemia[9] unless both date and place of birth are controlled for.



Odds ratios (95% confidence intervals) for leukaemia (plotted on log scale) in children under 15 years old given intramuscular vitamin K at birth compared with those given no treatment. Analyses marked with asterisk relate to cases of acute lymphoblastic leukaemia only. No study has yet been able to exclude possibility that true odds ratio for all ages after matching for place of birth could be as high as 1.9

The present evidence certainly does not establish that a 1 mg intramuscular dose of vitamin K (or one of its excipients) is carcinogenic. Further exploration of these issues, however, is going to become increasingly difficult because almost all the babies born in Europe and the United States in the past 10 years have had some form of prophylaxis at birth. Nevertheless, if it could be shown that oral administration is as effective as intramuscular prophylaxis in abolishing the risk of late vitamin K deficiency bleeding (late "haemorrhagic disease of the newborn"), many clinicians would now choose oral prophylaxis. The one formulation licensed for use in Europe before 1995 was only moderately well absorbed when given by mouth.[15] Even three separate 1 mg oral doses of this preparation did not eliminate the risk of late haemorrhage in breast fed babies in several recent studies.[16 17] It does look, however, as though a regular weekly 1 mg dose abolishes that risk,[18 19] and this is probably more than enough[17] as long as the doses that are given are well spaced out.[20] What constitutes a safe and effective prophylactic dose of the new well absorbed but more expensive micellar preparation[21] remains to be established. Even 4 mg of this product by mouth may not provide complete protection if it is all given in the first week of life,[17 22] possibly because retention does not then match that achieved by intramuscular injection.[23]

Oral prophylaxis may be the safest way of giving protection to those babies at risk of late haemorrhage, and repeated low dose administration may be the most effective as well as the most natural way of providing that protection (although some mothers may prefer maternal supplementation[24 25]). The advantages and disadvantages of intramuscular administration remain much more finely balanced than a recent *BMJ* editorial would seem to imply.[6] The current dilemma for breast feeding mothers could be cut at a stroke by adding vitamin K to the non-commercial multivitamin preparation that has been made available free, or at low cost, in the United Kingdom from all child health clinics by the Department Health since 1940.[26]

We are grateful to Diane Coulson, Heather Forshaw, Christine Kinsella, and Pamela McCrorie for the diligent way they did the case note abstraction; to Julian Smith for constructing and managing the database and for programming the portable computers used to collect this information; and to Susan Fritz for collecting information on policy with regard to vitamin K prophylaxis across the region and for locating the whereabouts of many of the obstetric and neonatal case notes. We are grateful to the staff of all the hospital medical records departments for facilitating access to records and to clinical colleagues, active and retired, for information on vitamin K policy. We thank Drs Olsen and Roman and Professors Golding and von Kries for providing data, and those responsible for the current national case-control study of childhood cancer for access to their data abstraction form, from which the form used in this study was developed. Copies of the full study report, as submitted to the Department of Health in May 1996, are available from the corresponding author in request.

Contributors: AWC initiated the study and coordinated the design of the project, discussed the analysis strategy and the interpretation of the results, and participated in writing the manuscript. ENH was involved in the discussion, developing the design of the project, and analysing and interpreting the results and took the lead role in writing the manuscript. MC performed the statistical analysis and participated in discussions on interpreting results. Julian Smith designed the database and downloaded data. LP designed the study and data abstraction procedure, supervised data collection, checked the data download before statistical analysis, discussed the interpretation of results, and participated in writing the manuscript. Diane Coulson, Heather Forshaw, Christine Kinsella, and Pamela McCrorie performed all the case note abstraction. LP, ENH, and AWC are guarantors for the study.

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Racial discrimination in the allocation of distinction awards? Analysis of list of award holders by type of award, specialty and region

Aneez Esmail, Sam Everington, Helen Doyle

There has been much concern about the possibility of discrimination in the allocation of distinction awards to consultants. The aim of this study was to assess whether there is any disparity between white and non-white consultants in the receipt of distinction awards.

Methods and results

We used the list of all consultants in England and Wales who are currently in receipt of a distinction award published by the Advisory Committee on Distinction Awards[1] to determine the ethnicity of award holders using the surname of the award holder as a proxy for ethnicity. We classified consultants with Asian, Chinese, and African names as non-white and consultants with Anglo-Saxon, East European, and South European names as white. All consultants are eligible for distinction awards, so for denominator data we obtained the number of consultants by region and specialty from the 1996 census of the NHS workforce carried out by the Department of Health.[2] This census categorises consultants as white, black, Asian, other ethnic, and not known. We classified black, Asian, and other ethnic as

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