Numbers (percentages) of patients complying with and defaulting from treatment for tuberculosis in Botswana, 1984-90

Year	No (%) complying	No (%) defulting
1984	1876 (60·5)	1225 (39·5)
1985	1821 (67·3)	381 (14·1)
1986	2049 (78·0)	360 (13·7)
1987	3011 (94·9)	162 (5·1)
1988	2570 (93·8)	170 (6·2)
1989	2410 (95·2)	122 (4·8)
1990	2711 (92·3)	227 (7·7)

in 1984 to above 90% in 1987-90. Defaulter rates decreased from 40% in 1984 to less than 10% in 1987-90.

The programme did not insist on the sputum status of patients being reported at the end of chemotherapy as it was difficult to obtain sputum from many of the patients who completed the treatment course. Hence meaningful cure rates could not be obtained. This is one aspect in which the programme could be strengthened. Of the sputum positive cases notified in 1987-9, sputum results were available in 788 (44%), 664 (41%), and 546 (35%) of the cases; the cure rates for these years were 772 (98%), 644 (97%), and 546 (98%) respectively.

Discussion

Short course chemotherapy has been shown to be more cost effective than standard 12 month regimens,[5 6] but compliance of patients is essential.[7 8] One of the controversies in the management of patients with tuberculosis has been supervision of treatment.[9] In Botswana we have shown that daily supervised treatment of all patients with tuberculosis improved compliance. High compliance has been achieved by intensive repeated health education to patients and their relatives and constant supervision and follow up of health workers at all levels of the health care system. Health education has been integrated into primary health care activities at district and peripheral levels. Education of health workers and the community on tuberculosis has been incorporated into in service training programmes, which occur at least two to three times a year in each district. At the national level seminars and workshops are held every six months to update district tuberculosis coordinators on the latest advances and methods of preventing and controlling tuberculosis.

Case holding has been one of the main successes of the Botswana tuberculosis programme. This can be attributed to introduction of short course chemotherapy, good health infrastructure, integration of the programme into primary health care system, and vigorous health education. The costs of providing short course chemotherapy and daily supervised treatment to all patients needs to be evaluated. Further study of the epidemiology of tuberculosis is also needed in view of the well established interaction between tuberculosis and HIV worldwide.

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Childhood cancer, intramuscular vitamin K, and pethidine given during labour

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Abstract

***Objective*—To assess unexpected associations between childhood cancer and pethidine given in labour and the neonatal administration of vitamin K that had emerged in a study performed in the 1970 national birth cohort.**

***Design and setting*—195 children with cancer diagnosed in 1971-March 1991 and born in the two major Bristol maternity hospitals in 1965-87 were compared with 558 controls identified from the delivery books for the use of pethidine during labour and administration of vitamin K.**

***Main outcome measures*—Odds ratios for cancer in the presence of administration of pethidine or of intramuscular vitamin K. Both logistic regression and Mantel-Haenszel techniques were used for statistical analyses.**

***Results*—Children of mothers given pethidine in labour were not at increased risk of cancer (odds ratio 1·05, 95% confidence interval 0·7 to 1·5) after allowing for year and hospital of delivery, but there was a significant association (p=0·002) with intramuscular vitamin K (odds ratio 1·97, 95% confidence interval 1·3 to 3·0) when compared with oral vitamin K or no vitamin K. There was no significantly increased risk for children who had been given oral vitamin K when compared with no vitamin K (odds ratio 1·15, 95% confidence interval 0·5 to 2·7). These results could not be accounted for by other factors associated with administration of intramuscular vitamin K, such as type of delivery or admission to a special care baby unit.**

***Conclusions*—The only two studies so far to have examined the relation between childhood cancer and intramuscular vitamin K have shown similar results, and the relation is biologically plausible. The prophylactic benefits against haemorrhagic disease are unlikely to exceed the potential adverse effects from intramuscular vitamin K. Since oral vitamin K has major benefits but no obvious adverse effects this could be the prophylaxis of choice.**

Introduction

Most studies of the factors acting in fetal or early life that are relevant to childhood cancer have been, for obvious reasons, case-control and retrospective in design.[1-4] Retrospective studies have the advantage that large numbers of affected subjects may be covered, but they can also be subject to biases such as differential recall between cases and controls of events often long since past. It is therefore important to test the findings wherever possible by prospective studies.

Information collected prospectively on a nationally representative sample of pregnancies delivered in 1970 was examined to assess potential factors associated with subsequent cancer in childhood.[5] Information on 16 193 infants delivered in Great Britain in one week of

April 1970 was collected by the midwives at the birth of the child and during the first seven days of life.[6] Follow up of the children took place at the ages of 5 and 10 (when there was a 94% ascertainment rate); in addition all death certificates of children in the cohort were forwarded to the survey team.[7,8] By using multiple sources of ascertainment, 33 children who developed cancer were identified, giving an incidence of 2·04 per 1000 total births by the age of 10.

These 33 children and their mothers were compared with a control group of children and their mothers, with three controls for each index case, matched for maternal age, parity, and social class. Statistically significant unadjusted associations were found with maternal smoking and the use of pethidine during labour.[5] Unexpected significant associations were found with delivery of the child outside term and with the neonate receiving a drug in the first week of life. Receipt of a drug was found not to be explained by neonatal abnormalities in the child but to be related almost entirely to the prophylactic administration of vitamin K, given to prevent the development of haemorrhagic disease of the newborn. Logistic regression analyses using the whole data set identified neonatal drug administration and maternal smoking as independently significant factors; in contrast, although pethidine had an odds ratio of 1·7 after adjustment, its 95% confidence interval included 1.

Although there had been other reports of associations with maternal smoking in pregnancy[9] and with pethidine in labour,[1] the vitamin K results were unexpected, although we have since become aware that the hypothesis had already been raised in Canada (L G Israels, personal communication) and Germany (A H Sutor, personal communication). We thought that both the pethidine and vitamin K findings needed assessing in a larger study using data recorded at the time of birth. That significant associations had been shown with a small number of cases suggested that the power to be expected from a larger study would be considerable.

Initially we planned to analyse the data according to whether or not vitamin K had been given, but this plan was severely criticised (R von Kries, personal communication) because it did not take the route of administration into account, since the immediate effects of oral and intramuscular doses have been shown to be different, even though the dose is identical. In the early study vitamin K was almost certainly delivered intramuscularly. We therefore distinguished between intramuscular injections and oral administration of vitamin K in assessing the effect of vitamin K.

Patients and methods

Avon is a county 100 miles west of London. It includes the city of Bristol, an industrial port (Avonmouth), seaside towns, and farming communities. It has a stable population with little migration out of the area (<2% a year) and is demographically representative of Britain as a whole.[10]

There are about 10 000 deliveries a year in the three Bristol based health districts of Avon. In the past several general practitioner units operated, and home deliveries were fairly common, but latterly 94% of births have occurred in two Bristol hospitals.

CASES AND CONTROLS

Information on cancers occurring in children born at these two hospitals was obtained from two sources: the oncology register of the regional paediatric oncology unit at Bristol Children's Hospital and the national registry of children's tumours maintained by the childhood cancer research group in Oxford. The study considered all children who were diagnosed as having cancer in the period 1971 to March 1991 and who had been born from 1965 to 1987. In all, 217 children with cancer fulfilling these criteria were identified from those whose NHS numbers indicated that they had been born in Bristol or had been treated in the South West region. These included 74 with leukaemias, 24 with lymphomas and other reticuloendothelial neoplasms, 35 with central nervous system tumours, 13 with sympathetic nervous system tumours, eight with retinoblastomas, 18 with renal tumours, two with hepatic tumours, six with bone tumours, 16 with soft tissue tumours, six with germ cell tumours, three with carcinomas and other malignant epithelial neoplasms, and 12 with "miscellaneous" tumours, using the classification of the childhood cancer research group.

At each hospital every 300th birth in each year was selected as a control. At one hospital the delivery books for 1967-9 had been destroyed by a flood, so controls could not be selected for those years at that site.

DATA ABSTRACTION

One clerk was responsible for identifying the unit numbers of 111 cases of cancer in the Bristol register and the controls. Other clerks then abstracted 319 pieces of information on the history of pregnancy, labour, delivery, and the neonatal period blind to both the identity of the cases and the hypotheses being tested. Information was abstracted using a standardised proforma which had already been tested on births within the area. Further cases of cancer were subsequently identified from various sources, but it was not possible then to abstract data blind to case-control status.

Initially 287 controls were selected at one hospital and 278 at the other. One of them was a known case, so the previous delivery was taken as the control. For seven of the 565 controls the notes were missing. Six of the control deliveries were of twins, and the twin used as the control was randomly selected.

The annual numbers of controls identified were: 19, 20, 5, 5, 8, 15, 17, 17, 17, 17, 19, 22, 27, 29, 31, 32, 31, 31, 37, 38, 40, 40, 41. The small numbers of controls in 1967-9 were due to the flood damage at one hospital already described. Consequently the children who later developed cancer born in these years at that hospital were also omitted from further analyses (n=2, 1, 12 respectively). Of the remaining 202 cases, information was obtained on 195.

One of the problems encountered in abstracting data from the notes was the fact that the route of vitamin K administration was often not recorded, although vitamin K was noted as having been given. The protocol at the two hospitals varied greatly over time and according to type of delivery and whether or not the infant was admitted to special care. Several strategies were therefore used to identify the probable route of administration. The clerks returned to the data and the instructions within the two maternity hospitals. From the information available they were able to assign a code change to most of those within the two categories "given not known how" and "not known if given." This was achieved blind to case-control status. For example, in hospital A there was no record of any vitamin K being used before 1975. Between 1975 and 1984 intramuscular vitamin K was used but not oral; and oral vitamin K was introduced only towards the end of 1985. Thus for a baby boy born in hospital A in 1980 and known to have had vitamin K, the route must have been intramuscular. A full list of changes made on this basis is available from the authors.

VITAMIN PREPARATION

Throughout the period studied the preparation of vitamin K used was 1 mg phytomenadione

(Konakion; Hoffman-La Roche, Basle, Switzerland). The preparation contains 1 mg phytomenadione (vitamin K_1), 10 mg polyoxyl 35 castor oil (Cremophor EL), 10 mg propylene glycol, and 5 mg phenol. The study compares those given this preparation intramuscularly with those given it orally or not at all. The few instances of intravenous administration were combined with the intramuscular group.

STATISTICAL ANALYSES

There was no matching of cases and controls, and we assumed that the controls were representative of the total population of births at risk in the two hospitals. Since the ratio of cases to controls differed over the years and between hospitals all analyses took these two factors into account, using the biomedical programs data package (BMDP) for both logistic regression and Mantel-Haenszel techniques for stratified data presented in 2×2 tables. Confidence intervals for the latter used the method described by Robins *et al.*[11]

Results and comment

PETHIDINE

Whether or not pethidine was used was recorded for 99% of the cases and controls. In all, 47% of mothers had received pethidine, but there was a strong relation over time, the proportions receiving pethidine falling from 73% in 1965-70 to 63% in 1971-6, to 44% in 1977-82, and to 27% in 1983-7. Mothers delivering in hospital A were significantly less likely to have received the drug (153/358 (43%)) than mothers in hospital B (195/387 (50%); $p<0.05$).

There was no significant relation with admission to special care or with non-spontaneous delivery. There was an increased unadjusted relation between pethidine and childhood cancer (odds ratio 1·25, 95% confidence interval 0·89 to 1·73), although this was not significant. Adjustment for year of birth and hospital using Mantel-Haenszel analyses resulted in an estimated odds ratio of 1·02 (95% confidence interval 0·73 to 1·53). Logistic regression analyses showed a similar result (odds ratio=1·01, 95% confidence interval 0·70 to 1·45).

TABLE I—*Vitamin K status of control children studied according to whether they were delivered spontaneously; admitted to special care baby unit; and given intramuscular, oral, or no vitamin K (after looking at hospital policy)**

Type of delivery	Admitted to special care baby unit	Hospital A		Hospital B	
		Period	IM:oral:none	Period	IM:oral:none
Forceps, caesarean section, ventouse	Yes	-1975	0:0:2	-1970	0:0:2
		1975-84	6:0:0	1971-79	7:0:0
		1985-	1:0:0	1980-	4:0:0
	No	-1975	0:0:5	-1970-	0:0:5
		1975-84	37:0:1	1971-79	18:2:2
		1985-	1:18:0	1980-	27:2:0
Spontaneous	Yes	-1975	0:0:4	-1970	1:0:2
		1975-84	10:0:0	1971-79	3:0:0
		1985-	2:1:0	1980-	0:7:0
	No	-1975	0:0:46	-1970	1:0:26
		1975-84	84:0:6	1971-9	2:43:19
		1985-	1:14:0	1980-	1:91:3

IM=Intramuscular.
*Excluding 37 controls for whom data on one variable or more was missing.

TABLE II—*Proportion of cases and controls receiving intramuscular vitamin K using all year-hospital informative strata*

Year-hospital	Cancer cases % (No)	Controls % (No)
1975A	67 (2/3)	14 (1/7)
1976A	100 (6/6)	90 (9/10)
1985A	0 (0/4)	5 (1/22)
1987A	0 (0/1)	14 (3/22)
1966B	25 (1/4)	6 (1/16)
1970B	0 (0/3)	10 (1/10)
1971B	20 (1/5)	30 (3/10)
1972B	0 (0/3)	33 (3/9)
1973B	100 (2/2)	40 (4/10)
1974B	56 (5/9)	29 (2/7)
1975B	67 (4/6)	29 (2/7)
1976B	83 (5/6)	50 (4/8)
1977B	50 (3/6)	27 (4/15)
1978B	50 (4/8)	25 (4/16)
1979B	33 (2/6)	33 (5/15)
1980B	50 (3/6)	35 (6/17)
1981B	0 (0/2)	31 (5/16)
1982B	57 (4/7)	6 (1/16)
1984B	25 (1/4)	31 (5/16)
1985B	50 (1/2)	22 (4/18)
1986B	25 (2/8)	21 (4/19)

Mantel-Haenszel odds ratio=2·16 (95% confidence interval, 1·27 to 3·67). $\chi^2=7·19$, $p=0·007$.

VITAMIN K

The administration of vitamin K varied greatly with year of birth. In the early years (before 1971) most children (96%) received no vitamin K; in 1971-6, 51% did so, but in 1977-87, 98·5% received it. The numbers where it is not known whether vitamin K was administered or not were relatively small (14/558 controls, 15/195 cancer). These were omitted from further analyses involving vitamin K.

Logistic regression analyses were run. In the presence of hospital and year of delivery (in 12 groups) the vitamin K variable (none, oral, intramuscular) was significantly associated ($\chi^2=11·2$, df=2, $p=0·004$). The adjusted odds ratios (and 95% confidence intervals) were: none 1·00, reference group; n=174; oral 1·15 (0·50 to 2·65); n=248; and intramuscular 2·17 (1·06 to 4·42); n=302. Although the odds ratio for oral vitamin K was slightly higher than the baseline, the difference between the two was very small ($\chi^2=0·11$, df=1, $p=0·74$). Since there was only a minimal difference in risk between oral vitamin K and no vitamin K, the two groups were combined in all further analyses.

As already stated, policies on the route of administration varied between the two hospitals. Table I shows for controls the clear differences over time. In Table II the strata where there are informative data are shown—that is, year-hospital combinations where all cases and controls received the same treatment are omitted. This gave an overall significant association between cancer and intramuscular vitamin K, with an odds ratio of 2·16 (95% confidence interval 1·27 to 3·67).

CONFOUNDERS

A key question concerns other differences between cases and controls that might have accounted for the apparent effect of intramuscular vitamin K. Data were collected on 319 other items in all controls and the 111 cases of cancer from the Bristol register. Of these only three were statistically significant at the 1% level—exactly the number that would be expected by chance. These items were: presence of rubella antibody, resuscitation using intermittent positive pressure, and paediatric estimate of gestation. The latter effect was not found for estimates using mother's last menstrual period and largely depended on an increased risk in the group where no paediatric estimate had been carried out. There were no differences in maternal age, marital status, social class, parity, or gravidity.

There was an excess of index mothers who had undergone *x* ray examination of the abdomen or pelvis during pregnancy (odds ratio 1·29) but this was not significant (95% confidence interval 0·80 to 2·10). In addition, more mothers of cases smoked during pregnancy (odds ratio 1·21), but the information was often missing and the differences were not significant (95% confidence interval 0·79 to 1·84). There were no differences in distribution of birth weight; the proportions of babies weighing under 2500 g were 5·9% among those with cancer and 5·2% among the controls and the proportions weighing 3500 g or more were 37·3% among those with cancer and 35·5% among the controls. Similar proportions of index babies and controls were admitted to special care (10·4% and 9·7%) and presented by the vertex (93·3% and 93·7%).

To ensure, nevertheless, that the apparent effect of intramuscular vitamin K was not due to any factor that might have been an intervening confounder we offered variables that might have been confounders to the model containing year of delivery (in 12 groups) and vitamin K to assess whether there was a consequent change in odds ratio. All variables which had either been reported as associated in published reports or which showed unadjusted associations with childhood cancer or which were known to be indicators for administering intramuscular vitamin K were assessed. In no instance did the odds ratio lose its statistical significance on adjustment (see table III for a subsample of items studied). Thus there was little to suggest that the effect of intramuscular vitamin K was an artefact consequent on other variables.

The logistic regression model for cancer was therefore obtained allowing just for year of delivery and hospital. Table IV shows once again a significant association with intramuscular vitamin K.

TABLE III—*Intramuscular vitamin K odds ratio* (95% confidence interval) before and after adjustment for each variable. Numbers in analysis vary according to availability of item in notes*

Variable	Unadjusted	Adjusted	No
Smoking in pregnancy	1·96 (1·24 to 3·10)	1·99 (1·26 to 3·15)	552
X ray examination of abdomen or pelvis in pregnancy	1·80 (1·16 to 2·80)	1·76 (1·13 to 2·73)	682
Rubella antibody	2·45 (1·38 to 4·34)	2·38 (1·34 to 4·23)	486
Type of delivery	1·90 (1·24 to 2·89)	1·97 (1·23 to 3·15)	721
Pethidine in labour	1·77 (1·16 to 2·72)	1·78 (1·16 to 2·72)	717
Intermittent positive pressure ventilation	1·68 (1·07 to 2·64)	1·62 (1·03 to 2·55)	681
Admission to special care baby unit	2·00 (1·29 to 3·12)	2·07 (1·32 to 3·26)	696

*All odds ratios were adjusted for year of delivery.

TABLE IV—*Logistic regression model for all births; outcome=cancer in childhood; n=724*

Variable	Adjusted odds ratio	95% Confidence interval	χ^2	df	p
Year of delivery:					
1965-6	1·00	Reference	36·4	11	<0·0001
1967-8	1·54	0·39 to 6·05			
1969-70	1·21	0·43 to 3·46			
1971-2	1·22	0·49 to 3·06			
1973-4	1·88	0·79 to 4·51			
1975-6	1·50	0·61 to 3·67			
1977-8	1·01	0·43 to 2·35			
1979-80	0·82	0·35 to 1·93			
1981-2	0·88	0·37 to 2·06			
1983-4	0·44	0·18 to 1·09			
1985-6	0·55	0·23 to 1·31			
1987	0·07	0·01 to 0·61			
Hospital:					
A	1·00	Reference	0·80	1	Not significant
B	1·19	0·82 to 1·73			
Vitamin K:					
None or oral	1·00	Reference	9·46	1	0·002
Intramuscular	1·97	1·28 to 3·04			

TYPE OF CANCER

Cases of leukaemia were next selected (from the whole study sample). Year of delivery and hospital were put into the model and intramuscular vitamin K offered. It was accepted with an improvement in χ^2 of 8·11 (df=1, p=0·004). The third level of vitamin K, separating oral and none, was then offered and rejected with a χ^2 improvement of 0·42 (df=1, p=0·52). The final odds ratio for leukaemia (controlling for hospital and year of delivery in 11 groups) associated with intramuscular vitamin K was 2·65 (95% confidence interval 1·34 to 5·24).

A similar analysis was carried out with all other cancers. In the presence of the year of delivery and hospital intramuscular vitamin K was accepted with an improvement in χ^2 of 4·5 (df=1, p=0·034) and an adjusted odds ratio of 1·72 (95% confidence interval 1·04 to 2·84).

AGE AT DIAGNOSIS

Of the 195 cancers, 19 were diagnosed in the first year of life. Some of these cancers might have been present before the baby was born and therefore could not have been initiated by an injection of vitamin K. When these 19 were omitted, however, allowing for year of delivery, intramuscular vitamin K was still statistically significant (χ^2=8·57, df=1, p=0·003) with an odds ratio of 1·97 (95% confidence interval 1·25 to 3·10).

COHORT EFFECTS

As already noted, there were some problems in comparing cases and controls in that cases born before 1971 would be included only if diagnosed after 1970, and births in the 1980s would be included only if diagnosed at a relatively early age. We therefore carried out an analysis of only those babies born between 1971 and 1980, all of whom would have been followed for at least 10 years. We selected those who had had cancer diagnosed before their 10th birthday (89 cancers, 214 controls). Although neither year of birth (χ^2=3·8, df=4) nor hospital (χ^2=1·6, df=1) were significantly associated, these were kept in the model. There was a significant association with intramuscular vitamin K (χ^2=5·11, df=1, p=0·024), with an adjusted odds ratio of 1·91 (95% confidence interval 1·08 to 3·39).

Discussion

CONSISTENCY OF RESULTS

This study provides an example of the unexpected generation of a hypothesis as the result of a data trawl followed by the testing of that hypothesis on a different data set (none of the index cases in this study were included in the 1970 cohort). These appear to be the only two studies that have ever looked at intramuscular vitamin K in relation to cancer. The fact that both, although methodologically different, have shown similar results strengthens each of those results.

CONTRASTS IN METHODS

There are merits and disadvantages in each type of study. In the hypothesis generating survey[5] information was collected at birth using a defined protocol which midwives completed at, or soon after, delivery. The question "was vitamin K given?" was answered for 99% of live births. Although the route of administration was not specifically asked about, almost all vitamin K at that time was given intramuscularly. Children of the cohort were followed up in a variety of ways, and the ascertainment of cancer by the age of 10 was probably complete. The disadvantage was that even though the cohort comprised 16 193 children, only 33 cancers were available for analysis.

The second study was carried out specifically to test the hypotheses that maternal pethidine and neonatal vitamin K administration were associated with subsequent childhood cancer. It started with children who were born in Bristol in 1965-87 and ascertained cases of cancer from two cancer registers. The first cases were children diagnosed with cancer at Bristol Children's Hospital who lived in the counties of Avon, Gloucestershire, and Somerset. The records of the two major Bristol maternity hospitals were then scanned to see whether the children had been born there and, if so, whether their obstetric and neonatal records could be found. There were inevitable problems with such an approach. Children whose surnames at the time of diagnosis of cancer differed from those of the mother at the time of delivery, for example, were unlikely to be linked. This problem was later overcome when the Oxford childhood cancer registry was finally able to link its records to appropriate birth certificates, and thus a further set of birth records became identifiable. There remains the question of how complete the case ascertainment may be. A guide is given by the numbers of cases born in the period 1971-6 who developed cancer by the age of 10; 56 were identified from a total population of about 33 000, giving an incidence of 1·87 per 1000. This may be compared with the 2·04 per 1000 found in the cohort study using more sources of ascertainment.

A question with this method of ascertaining a cohort arises over the choice of controls. The random set of controls used in this study took as the only criterion that the child should survive the neonatal period. We do not know how many of these controls were still alive and living in England and Wales throughout their childhood, although migration out of the area is known to be low (2% per year), and it is unlikely that more than 5% would have left the country or died before the age when they could have developed cancer.

Other problems lay in the fact that not all obstetric or neonatal notes could be found and that cases were more

at risk of this than controls (22 cancer, 21 controls). Notes tend to go missing, particularly in a teaching hospital, if births are "interesting" or abnormal. Thus, babies with complicated deliveries and asphyxiation are more likely to have been lost from this study—and these babies are more likely to have been given intramuscular vitamin K. Thus, the effect of the missing data is more likely to have reduced the true proportion of index cases receiving the intramuscular preparation in comparison with the controls.

An immediate problem with returning to obstetric notes lies in their variable quality. The fact that potentially confounding variables, such as smoking in pregnancy, were not significantly associated in the analysis might have been due to the large number of instances in which the information was not given (20% in the case of smoking). Nevertheless, in the early study, where smoking was accurately recorded, there was no diminution in the odds ratio associated with vitamin K after allowing for smoking.[5]

A further source of potential bias lay in the fact that the route of vitamin K administration was not always clearly described. In this paper the probable route was used, having been derived blind to case-control status. This may have produced a bias in either direction. When, however, the analysis was confined to records where the route was clearly stated the results remained essentially the same (odds ratio 1·98, 95% confidence interval 1·17 to 3·34) using a weighted combination of the Mantel-Haenszel test.

CONFOUNDING

It remains possible that the relation between cancer and intramuscular vitamin K may be a proxy for other features of the pregnancy or baby. There is, however, little evidence of this; there have been many studies of childhood cancer but none have shown associations with positive indications for intramuscular vitamin K prophylaxis such as low birth weight, admission to a special care baby unit, or difficult delivery.

The fact that the association with vitamin K found in the 1970 birth cohort (when it was almost certainly given entirely intramuscularly) had a similar odds ratio (2·6; 95% confidence interval 1·3 to 5·2) as that for the present study (2·0; 95% confidence interval 1·3 to 3·0) reinforces the possibility that the association may be causal.

CAN THE RELATION WITH VITAMIN K BE CAUSAL?

If intramuscular vitamin K causes cancer should not the incidence have changed over time? This is difficult to quantify without accurate data on the proportion of infants treated. There was certainly discussion in the early 1940s about the efficacy of vitamin K in preventing haemorrhagic disease,[12] but whether it was being used before that is not clear. The national data from the 1958 and 1970 national birth surveys show 5% and 28% of babies respectively receiving intramuscular vitamin K. This implies that there might have been an additional 1·9% of babies receiving vitamin K each year between 1958 and 1970. If we assume a constant 700 000 births each year an extra 13 300 would have been given intramuscular vitamin K each year. If the incidence of cancer in the first 10 years is of the order of 1·4 per 1000 in the absence of vitamin K then the consequent extra cancers should be about 19 per year. This is equivalent to an increase in the rate of cancer to each birth year cohort of 2·7 per 100 000 births. As leukaemia comprises about 30% of all cancers, the implication is that there would have been an increase in the rate of leukaemia of about 0·9 per 100 000 for each year of birth.

Are the trends in intramuscular vitamin K prophylaxis reflected in the incidence of cancer? An analysis of registrations in England and Wales, with correction for differential ascertainment, indicated an increasing incidence of leukaemia in children born from 1962 to 1974. From published data it is possible to calculate an increase in the risk of developing leukaemia by the age of 10 of 0·97 cases per 100 000 births per year of birth. The authors interpret this as indicating "an aetiological factor which is encountered very early in life."[13] These results are compatible with our predictions of an increase caused by the increasing use of intramuscular vitamin K of the order of 2% per year. Subsequent unpublished data (G Draper, personal communication) indicate a plateauing in the incidence of leukaemia to children born in the mid-1970s. Unfortunately national data on the use of intramuscular vitamin K do not exist for the mid-1970s and therefore we cannot assess whether the plateau in the incidence of leukaemia is reflected in a plateau in the use of intramuscular vitamin K.

As Elwood has described, epidemiologists have identified several criteria which taken together would make it "more provident to act on the basis that the association is causal rather than to await further evidence."[14] The most important criteria, he notes, are biological plausibility as well as strength and consistency between studies. Many epidemiologists would describe an odds ratio of 2 as strong. The fact that two out of two studies have produced similar results provides consistency, though more studies would be even better.

Biological plausibility may be evidenced from several sources. The infant's plasma vitamin K concentration some 12-24 hours after injection may be up to 5000-fold higher than found in normal breast fed infants.[15,16] Such high concentrations have been shown to increase sister chromatid exchanges in human placental lymphocytes in vitro and sheep fetal lymphocytes in vivo.[17] Although one study of six babies who had had intramuscular vitamin K showed no difference in sister chromatid exchanges compared with six controls, the small numbers make interpretation difficult,[15] and one index child who had high serum vitamin K concentrations was omitted, and no attempt was made to look at changes in the children before and after the injection. Vitamin K_1 accelerates the tumour producing activity of benzo(a)pyrene,[18] and there is increasing evidence that vitamin K_1 can play an adjuvant role in benzo(a)pyrene mutagenicity and carcinogenicity.[19] The phytomenadione preparation used contains phenol as well as vitamin K_1: together these might provide the reactions needed for carcinogenesis. This might not, however, be the only mechanism: rather than vitamin K being harmful, the deficiency state might be protective. Experiments with rodents have indicated a significant reduction in tumour growth in animals made artificially deficient in vitamin K.[20]

CAUSAL CONSEQUENCES

If there is a causal relation between vitamin K administration and childhood cancer it is important to weigh the health benefits of intramuscular vitamin K against the costs. Vitamin K is used to prevent haemorrhagic disease of the newborn, the most important facet of which is preventing late haemorrhagic disease, which often includes cerebral haemorrhage and can be fatal.[12]

A recent British study identified cases in the British Isles during 1987-90.[21] The authors showed that the risk varied from 4·4 per 100 000 in those given no vitamin K prophylaxis to 1·4 per 100 000 in those given oral vitamin K and 0·11 per 100 000 in those given intramuscular vitamin K. A similar study in Germany produced similar results (7·2, 1·4, 0·25 respectively).[12]

These figures provide the means to calculate the

possible benefits in a population with 700 000 births annually.

- If no one received any vitamin K 30-60 cases of late haemorrhagic disease might occur.
- If all received one dose of oral vitamin K 10 cases of late haemorrhagic disease might occur.
- If all received intramuscular vitamin K at most one case of late haemorrhagic disease might occur.

Conversely, calculation of the numbers of cancers that might be initiated is as follows. Assume that the incidence of cancer among those who did not receive vitamin K is 1·4 per 1000 by the age of 10 (data from the 1970 cohort study) and that the odds ratio for cancer if given intramuscular vitamin K is 2·0; then if intramuscular vitamin K is causally related:

- If no one received any vitamin K 980 cancers would occur.
- If all received oral vitamin K 980 cancers would occur.
- If all received intramuscular vitamin K 1960 cancers would occur.

The figures vary according to the assumptions made. If the estimate of the incidence of cancer in the absence of intramuscular vitamin K is higher then more cancers would be associated with intramuscular vitamin K. The balance appears approximately as follows:

- If no one received any vitamin K then there would be about 30-60 cases of late haemorrhagic disease and no extra cancers.
- If all received oral vitamin K there would be about 10 cases of late haemorrhagic disease and no extra cancers.
- If all received intramuscular vitamin K there would be one case of late haemorrhagic disease and 980 extra cancers.

Conclusion

It has always seemed physiologically perverse that evolution should have permitted the development of what is termed vitamin K deficiency in normal term infants who are breast fed, resulting in a small but definable risk of haemorrhagic disease of the newborn. The most likely explanation for this situation is that there is some evolutionary advantage that outweighs this risk. The finding of an increased incidence of childhood cancer in children given intramuscular vitamin K in the neonatal period suggests that a relative deficiency in vitamin K during this critical phase of rapid growth and development may protect vulnerable tissues from mutagenesis. The protection afforded by oral vitamin K against haemorrhagic disease does not appear to carry the same risk of inducing malignancy, so it may be prudent to use oral rather than intramuscular vitamin K.

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Fluoxetine treatment of severe premenstrual syndrome

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Premenstrual symptoms are common and may be disabling in 3-10% of women of reproductive age.[1] A link between the premenstrual syndrome and depression is suggested by symptom overlap and by the observation that pre-existing depression is often aggravated during the premenstruum.[2] The activity of brain serotonin systems, thought to have a role in the regulation of mood, seems blunted premenstrually.[3] It is thus surprising that so few attempts have been made to test the efficacy of serotonin enhancing antidepressants in the premenstrual syndrome.[4] We report a double blind, placebo controlled crossover trial of fluoxetine in severe premenstrual syndrome.

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Subjects, methods, and results

Subjects were selected from a community sample of 200 volunteers. Careful screening excluded those outside the age range 18-48, those taking regular psychotropics or diuretics or using hormonal contraception, and any with appreciable menstrual irregularity or psychiatric or substance use disorder. Samples of