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## Administration of vitamin K to newborn infants and childhood cancer

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## Abstract

**Objectives**—To investigate whether childhood cancer is associated with intramuscular administration of vitamin K to newborn infants.

**Design**—Routines for administration of vitamin K to infants born after normal deliveries during 1973-89 were obtained from maternity hospitals. Occurrence of cancer up to the end of 1991 was identified by comparing these records with the national cancer registry. Adherence to the routine method of administering vitamin K was checked with the medical records of a sample of 396 infants (196 who had developed childhood cancer and 200 controls).

**Setting**—All maternity hospitals in Sweden.

**Subjects**—1384 424 full term infants born after non-instrumental deliveries, 1085 654 of whom were born in units where vitamin K was routinely given by intramuscular injection and 272 080 of whom were born where it was given orally.

**Main outcome measures**—Odds ratios for cancer after intramuscular administration of vitamin K versus oral administration after stratification for year of birth.

**Results**—Adherence to routine method of administering vitamin K was 92% in the 235 cases where individual information could be found. The risk of cancer after intramuscular administration of vitamin K was not elevated compared with that after oral administration: odds ratios of 1.01 (95% confidence interval 0.88 to 1.17) for all childhood cancers and 0.90 (0.70 to 1.16) for childhood leukaemia.

**Conclusions**—The alleged association between intramuscular vitamin K prophylaxis to newborn infants and childhood cancer could not be verified in the present study of full term infants born after non-instrumental delivery.

## Introduction

In a case-control study performed on a birth cohort in Great Britain 33 infants with childhood cancer and 99 matched controls were studied for a number of prospectively ascertained possible risk factors.<sup>1</sup> Neonatal administration of vitamin K appeared as a risk factor. This unexpected finding was again studied with an independent sample of 195 infants in whom childhood cancer had been diagnosed during 1971-March 1991 and 558 controls who had been born in two major Bristol hospitals during 1965-87.<sup>2</sup> Two methods of neonatal treatment with vitamin K were studied: intramuscular injection and oral administration. Intramuscular injection was associated with an increased risk of cancer, with an odds ratio of 1.97 (95% confidence interval 1.3 to 3.0) compared with oral vitamin K or no vitamin K (there was no difference between these two groups). The association was strongest for childhood leukaemia with an odds ratio of 2.65 (1.34 to 5.24). An editorial

and a series of letters in the September issues of the *BMJ* discussed these findings and stressed the need for independent cohort studies of this problem.<sup>3,4</sup> We present such a study based on information from Swedish health registers supplemented with data from medical records.

## Subjects and methods

Two central health registries in Sweden were used: the Medical Birth Registry, which contains information on all infants born,<sup>5</sup> and the Swedish Cancer Registry, which contains information on all cancers diagnosed in Sweden.<sup>6</sup> By linking records with the unique personal identification number which everyone living in Sweden gets shortly after birth we identified perinatal characteristics for each case of cancer. The study population consisted of full term infants (a gestation of 37-42 weeks to the last menstrual period) who survived and who were born in 1973-89 after a delivery without use of forceps or vacuum extraction (non-instrumental). The infants were followed up to 1 January 1992, and any occurrences of cancer were identified. Cancers diagnosed within 30 days of birth were regarded as congenital and were excluded from the analysis. All types of cancer were included, but leukaemia (ICD (seventh revision) code 204 up to 1974 and ICD (eighth revision) codes 204-209 after 1974) was analysed separately.

In order to get information on infants' exposure to vitamin K, we asked all maternity hospitals (95) to complete a form giving, for each year (and month when relevant), the method of administration that had been used for infants born full term after a non-instrumental delivery. For such routine deliveries instructions on vitamin K prophylaxis were available in the delivery room. Completed forms were obtained from all the hospitals, but information was not always available for the whole study. In order to check the validity of this information, we randomly selected 102 infants with cancer and 100 control infants from those who, according to the routine exposure information, received intramuscular vitamin K and 94 infants with cancer and 100 control infants from those who should have received oral vitamin K. We retrieved copies of the original medical charts for these 396 infants. All delivery hospitals in Sweden use the same medical forms with a box to show if and how vitamin K was administered. From these charts, sometimes supplemented with information from other medical documents, the actual method of administration of vitamin K was identified as far as possible.

We determined odds ratios for the development of cancer and of leukaemia in infants who had received vitamin K intramuscularly versus infants who had received the vitamin orally by Mantel-Haenszel analysis after stratification for year of birth. The 95% confidence intervals were determined with a test based method.

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TABLE I—Number (percentage) of full term infants born after non-instrumental delivery each year in Sweden during 1973–89 by hospital routines for neonatal administration of vitamin K

Year	Unknown	Intramuscularly	Orally	Both	Maternally*	Total
1973	723 (0.8)	75 045 (84.5)	9 472 (10.7)	0	3 585 (4.0)	88 825
1974	680 (0.8)	76 515 (85.5)	8 661 (9.7)	0	3 606 (4.0)	89 462
1975	611 (0.7)	69 526 (82.4)	11 240 (13.3)	0	2 961 (3.5)	84 338
1976	455 (0.6)	69 311 (87.4)	6 460 (8.1)	1 170 (1.5)	1 945 (2.5)	79 341
1977	249 (0.3)	70 263 (91.0)	3 628 (4.7)	1 105 (1.4)	1 939 (2.5)	77 184
1978	52 (0.1)	68 934 (92.7)	3 545 (4.8)	0	1 793 (2.4)	74 324
1979	9 (0.0)	71 442 (93.0)	3 557 (4.6)	0	1 806 (2.4)	76 814
1980	11 (0.0)	74 987 (95.8)	3 270 (4.2)	0	0	78 268
1981	15 (0.0)	73 083 (95.6)	3 341 (4.4)	0	0	76 439
1982	29 (0.0)	69 889 (95.3)	3 395 (4.6)	0	0	73 313
1983	18 (0.0)	70 203 (95.5)	3 311 (4.5)	0	0	73 532
1984	64 (0.1)	71 487 (94.8)	3 857 (5.1)	0	0	75 408
1985	29 (0.0)	74 019 (92.8)	5 158 (6.5)	0	566 (0.7)	79 772
1986	12 (0.0)	67 633 (81.4)	15 443 (18.6)	0	0	83 088
1987	19 (0.0)	39 323 (45.6)	46 821 (54.3)	0	0	86 163
1988	15 (0.0)	24 217 (26.2)	64 920 (70.3)	3 211 (3.5)	0	92 363
1989	12 (0.0)	19 777 (20.6)	76 001 (79.3)	0	0	95 790
Total	3 003 (0.2)	1 085 654 (78.4)	272 080 (19.7)	5 486 (0.4)	18 201 (1.3)	1 384 424

\*Given to mother before delivery.

TABLE II—Comparison of hospital routines for neonatal administration of vitamin K and actual method of administration obtained from individual medical records of 196 infants with childhood cancer (cases) and 200 control infants. Values are numbers (percentages)

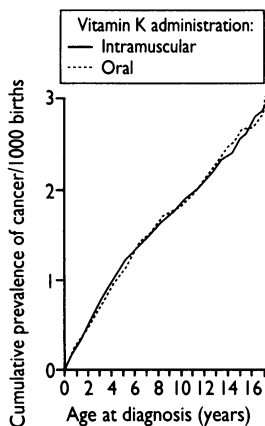
Individually identified method of administration	Hospitals' routine method of administration					
	Intramuscularly			Orally		
	Cases (n = 102)	Controls (n = 100)	Total (n = 202)	Cases (n = 94)	Controls (n = 100)	Total (n = 194)
Intramuscularly	44	39	83	4	5	9
Orally	0	1	1	61	72	133
Subcutaneously	2	1	3	0	1	1
Maternally*	2	1	3	2	0	2
Total	48	42	90	67	78	145
Not given in records	47	54	101	23	16	39
Records not traced	7	4	11	4	6	10
Total	54	58	112	27	22	49
Agreement with routine method	44/48 (92)	39/42 (93)	83/90 (92)	61/67 (91)	72/78 (92)	133/145 (92)
Method unknown	54/102 (53)	58/100 (58)	112/202 (55)	27/94 (29)	22/100 (22)	49/194 (25)

\*Given to mother before delivery.

## Results

Table I shows the numbers of infants born in each year of the study grouped according to hospitals' routine methods of administration of vitamin K. No information was available for a total of 3003 (0.2%) of the infants (most delivered during 1973–7); vitamin K was given intramuscularly for a total of 1 085 654 (78.4%) of the infants; vitamin K was given orally for 272 080 (19.7%) of the infants; both methods of treatment were used in parallel for 5486 (0.4%) of the infants; and vitamin K was given before delivery to mothers of 18 201 (1.3%) of the infants. The use of oral vitamin K increased substantially after 1986 while the use of intramuscular vitamin K declined. From 1991, however, most hospitals returned to the intramuscular route after a recommendation from the National Board of Health and Welfare, which was based on observations of increasing incidence of late haemorrhagic disease in newborn infants who had received vitamin K orally.

Table II shows the concordance between the hospitals' routine methods of administration of vitamin K and the actual method of administration used in 396 individual deliveries. The individual information could not be found for a substantial proportion of the infants: 55% of those who would have been expected to receive vitamin K intramuscularly and 25% of those who would have been expected to receive it orally. This difference between the two methods of administration of vitamin K is because the infants' individual medical charts usually gave the dose of vitamin K given but not how it was administered—thus a dose of 1 mg could mean it was given intramuscularly or orally, but a dose of 2 drops had to mean oral administration.



Cumulative prevalence of cancer every six months among those infants born in hospitals where routine neonatal administration of vitamin K was oral and among those where routine administration was intramuscular

When the method of administration of vitamin K was recorded it agreed with the stated routine method of administration in 92% of cases (table II). The proportion of misclassification is therefore apparently 8%, but this is probably an overestimate because incomplete information was probably given more often when the method of administration was the same as the routine method. The proportion of misclassification could therefore have been as low as 3.7% (7/191) for routine intramuscular administration and 6.5% (12/184) for routine oral administration. These two proportions did not differ significantly (Fisher's exact test,  $p = 0.24$ ), and the combined results gave a proportion of misclassification of 5.1% (19/375).

Table III shows the number of infants with childhood cancer (including leukaemia) by their year of birth and the routine method of administration of vitamin K, and table IV gives the same information for childhood leukaemia alone. Based on this information the odds ratios for cancers occurring after intramuscular administration of vitamin K versus oral administration were 1.01 (95% confidence interval 0.88 to 1.17) for all childhood cancers and 0.90 (0.70 to 1.16) for childhood leukaemia after stratification for year of birth.

The results were grouped into births occurring during 1973–81 (to include cancers diagnosed at ages up to 18) and births occurring during 1982–9 (to include only cancers diagnosed at ages up to 10). The odds ratios for the first group were 0.96 (0.80 to 1.14) for all cancers and 0.83 (0.61 to 1.14) for leukaemia. The odds ratios for the second group were 1.11 (0.88 to 1.40) for all cancers and 1.20 (0.69 to 2.08) for leukaemia.

The figure shows that the cumulative prevalence of

TABLE III—Number of infants born each year during 1973–89 who developed childhood cancer (including leukaemia) before 1 January 1992 by hospital routines for neonatal administration of vitamin K

Year	Unknown	Intramuscularly	Orally	Both	Maternally*	Total
1973	2	222	22	0	10	256
1974	2	201	29	0	15	247
1975	2	175	26	0	11	214
1976	1	164	15	6	0	186
1977	1	148	9	0	6	164
1978	0	131	7	0	5	143
1979	0	129	4	0	2	135
1980	0	141	12	0	0	153
1981	0	123	7	0	0	130
1982	0	120	3	0	0	123
1983	0	99	7	0	0	106
1984	0	92	6	0	0	98
1985	0	106	2	0	2	110
1986	0	91	18	0	0	109
1987	0	35	26	0	0	61
1988	0	16	46	2	0	64
1989	0	10	45	0	0	55
Total	8	2 003	284	8	51	2 354

\*Given to mother before delivery.

TABLE IV—Number of infants born each year during 1973–89 who developed childhood leukaemia before 1 January 1992 by hospital routines for neonatal administration of vitamin K

Year	Unknown	Intramuscularly	Orally	Both	Maternally*	Total
1973	0	50	6	0	3	59
1974	0	55	9	0	4	68
1975	0	52	8	0	4	64
1976	1	52	7	0	0	60
1977	0	44	4	0	1	49
1978	0	41	2	0	3	46
1979	0	43	1	0	2	46
1980	0	37	5	0	0	42
1981	0	41	1	0	0	42
1982	0	45	2	0	0	47
1983	0	38	2	0	0	40
1984	0	25	3	0	0	28
1985	0	41	0	0	1	42
1986	0	38	7	0	0	45
1987	0	14	10	0	0	24
1988	0	1	14	1	0	16
1989	0	0	10	0	0	10
Total	1	617	91	1	18	728

\*Given to mother before delivery.

### Public health implications

- Vitamin K prophylaxis to the newborn is beneficial in preventing early and late haemorrhagic disease
- Recent epidemiological studies indicated that intramuscular vitamin K prophylaxis doubled the risk for childhood cancer
- In this study all Swedish infants born full term after non-instrumental delivery during 1973-89 were followed up for cancer until 1992
- No increase in risk of childhood cancer or childhood leukaemia was found with intramuscular vitamin K prophylaxis

cancer among the infants who had received vitamin K intramuscularly did not differ from that of the infants who had received vitamin K orally.

As the study was restricted to non-instrumental deliveries, we determined the odds ratio for cancers developing in children who had undergone instrumental deliveries versus the total population. The odds ratios were 0.89 (0.75 to 1.06) for all cancers and 0.81 (0.59 to 1.12) for leukaemia after stratification for year of birth.

### Discussion

We chose the study design in order to be able to study a large number of infants born in many hospitals over several years. The alternative, to make a classic case-control study and retrieve information about vitamin K prophylaxis from the medical records, would have been very tedious for a study comprising more than 2300 cases. Furthermore we thought that a considerable proportion of the medical records would have no information on the method of administration of vitamin K—and this we verified (see table II).

We restricted our study to full term infants with a non-instrumental birth because intramuscular administration of vitamin K is often preferred for preterm and complicated deliveries. Instrumental delivery was not found to be a risk factor for child leukaemia either in this or in a previous study.<sup>7</sup> Risk of childhood cancer in Sweden has not been shown to be affected by maternal age or parity<sup>8</sup> or maternal smoking.<sup>9</sup> None of these factors is likely to affect the method of administration of vitamin K, and they would therefore not have appeared as confounders in our study. As smoking during pregnancy is a strong indicator of social class in Sweden,<sup>10</sup> it is also unlikely that social class has an impact on the risk of childhood cancer. Social class would not affect the method of vitamin K prophylaxis except for a very few instances when a mother strongly wishes her baby to receive

vitamin K orally instead of intramuscularly. This might have occurred once in the sample described in table II. Golding *et al* searched for possible confounders of significance for their analysis but found none.<sup>3</sup> Thus we adjusted our analysis only for the year of birth.

The present study does not support the conclusion of Golding *et al* that intramuscular vitamin K carries a substantial risk for the development of childhood cancer,<sup>1,2</sup> at least not in our study population of full term infants born by non-instrumental delivery. The doses of vitamin K given in our study (usually 1 mg) were similar to those in the study by Golding *et al*, and the same vitamin preparation was used (phytomenadione (vitamin K<sub>1</sub>), Konaktion). We cannot explain the discrepancy in results. It may be due to differences in the two populations studied or to differences in the study designs.

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### Correction

#### Rural population mixing and childhood leukaemia: effects of the North Sea oil industry in Scotland, including the area near Dounreay nuclear site.

An authors' error occurred in this paper by Kinlen *et al* (20 March, pp 743-8). The second and third sentences in the second paragraph of the results section should have read: "This peak at age 2 contrasts with that at age 3 (in all three periods) in the rural low and medium areas, as was found in the rural high oil group in the earlier period, 1974-8. In 1984-8, when incidences at ages 0-4 had declined, the usual high oil group continued to show a peak at age 2, as in urban areas in all three periods."

### ONE HUNDRED YEARS AGO

#### A CONGRESS OF QUACKS.

A motley assembly, claiming to be a "National Congress for the Free Practice of Medicine," met in Paris on November 20th. All sorts and conditions of irregular practitioners—*masseurs*, magnetisers, faith-healers, bone-setters *et hoc genus omne*—were invited to take part in the proceedings, the only essential condition of membership apparently being the fact of being engaged in the practice of the healing art without a legal qualification. In such a gathering the possessor of a regular diploma would have been as much out of place as the *testiculi sibi conscius mus* in the temple of the Bona Dea. Unfortunately, no report of

the proceedings has reached us, but it is not difficult to imagine the nature and general drift of the discussions. A special feature of the "Congress" was that patients who had been cured by members of the unqualified fraternity were invited to come forward and recount their experiences, for all the world like the brands snatched from the burning at a revival meeting. When the Greek philosopher Bion had his attention called to the votive offerings of persons who believed themselves to have been saved from shipwreck by the power of the gods, he answered, "But where is the list of those who were drowned?" The moral of which remark lies, as Jack Bunsby would say, in the application of it. (*BMJ* 1893;iii:1233.)