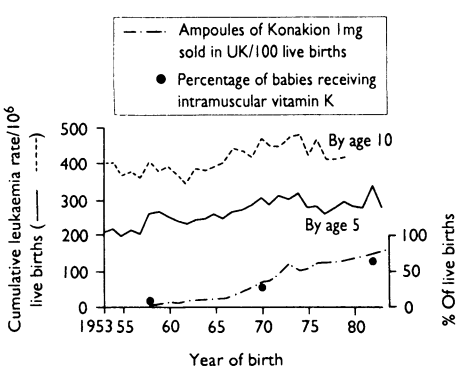
Intramuscular vitamin K and childhood cancer

EDITOR,—Jean Golding and colleagues report an association between neonatal administration of intramuscular vitamin K and the subsequent occurrence of childhood leukaemia.[1] They find a smaller degree of association with other childhood cancer. Oral administration does not show a similar effect. From this, trends in the incidence of childhood leukaemia might be expected to reflect trends in the proportion of babies receiving intramuscular vitamin K.

We estimated the cumulative incidence of childhood leukaemia in Great Britain using data from the National Registry of Childhood Tumours. Our data on the incidence of childhood cancer and the proportion of this due to leukaemia differ considerably from those used by Golding *et al.* Data on the use of intramuscular vitamin K came from three sources. Firstly, Golding and colleagues give estimates for 1958 and 1970 based on the British national birth surveys. Secondly, we estimated use in 1982 by using data from a national survey of special care baby units (J H Tripp, personal communication).[2] Thirdly, we used sales figures for Konakion 1 mg ampoules in Britain during 1958-83; these ampoules seem to have been almost the sole source of intramuscular vitamin K in the United Kingdom since their introduction in 1958 to replace Synkavit. We have assumed that the amount used in any one year is 75% of the sales for that year plus 25% of the sales for the previous year. In the figure the ratio of the estimated number of ampoules used to the total number of live births in the United Kingdom is expressed as a percentage. Some of the Konakion was given orally, and therefore the rates given will tend to overestimate the percentage of babies given intramuscular vitamin K. At least up to and including 1970, however, all of the ampoules used would probably have been given intramuscularly, and even by 1982 only about 10% would have been given orally (J H Tripp, personal communication). The rate for 1958 may be an underestimate as some Synkavit may have been given. The estimates based on sales of intramuscular vitamin K agree well with the independent estimates.

We cannot say with certainty whether trends in the use of intramuscular vitamin K are compatible with the trends in the rates of childhood leukaemia because other factors may influence the rates. For example, we calculate that decreases in antenatal exposure to *x* rays may have led to a 5% decrease in incidence,[3] while improved ascertainment of cases may have led to an increase of a similar magnitude.



Estimates of rates of childhood leukaemia and percentages of babies receiving intramuscular vitamin K, 1953-83

Advice to authors

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Golding and colleagues remark that the increase in incidence of leukaemia between 1962 and 1974 reported previously[4] is compatible with a relative risk of around 2·0 and the increase in the rate of administration of intramuscular vitamin K between 1958 and 1972. Our data on use of intramuscular vitamin K suggest that the trend for the incidence of leukaemia should have continued up to 1982, but there is so far no evidence of any increase among births since the early 1970s. The figure suggests that from the early 1960s to the early 1970s the percentage of babies given vitamin K increased by about 30%, with a similar increase taking place in the next decade. The increase in the incidence of leukaemia in the 1960s is compatible with most of the increase in use of vitamin K being due to intramuscular administration with a relative risk of 2·0, which is similar to the argument presented by Golding and colleagues.

If, on the other hand, we accept their relative risk estimate of 2·65 for leukaemia, we have to assume that about half the increase in use of vitamin K is accounted for by oral administration. This seems unlikely, which suggests that the risk, if it exists, is less. For the remainder of the period under consideration the increase in the level of use of intramuscular vitamin K seems to predict an increase in leukaemia, but no increase was observed. There are several possible explanations for this. Firstly, there may have been a balancing decrease in the completeness of ascertainment of cases; we do not believe that this occurred.[5] Nor is it likely that such a decrease occurred as a result of a trend towards describing cases as non-Hodgkin's lymphoma since registrations for this condition have decreased.[6] Secondly, there may have been a balancing decrease due to the removal of some other leukaemogen; we know of no evidence of this. Thirdly, the increase in use of vitamin K may be attributable entirely or almost entirely to increasing use of the oral route, with a low or zero risk. This last is at variance with Handel and Tripp's report[2] and, in particular, with the estimate given here, based on their survey, of 62% as the minimum percentage of babies who received intramuscular vitamin K in 1982.

We believe, therefore, that the absence of an increase in the incidence of leukaemia in the more recent period studied throws considerable doubt on the risks ascribed to intramuscular vitamin K. To settle this question, large cohort studies of groups of children given intramuscular vitamin K, oral vitamin K, and no vitamin K should be carried out as rapidly as possible.

We have one other comment: table II shows that most of the informative case-control comparisons came from hospital B in the period 1971 onwards. Table I shows that in this hospital in this period almost the only babies receiving intramuscular vitamin K were those who were born following an assisted delivery. This suggested that the excess of cases with intramuscular vitamin K found in this period may have contained a large proportion of babies delivered by these means. The alternative would seem to be that the spontaneous deliveries in which intramuscular vitamin K was administered had an exceptionally high cancer risk. Assisted delivery is not a known risk factor for childhood cancer. This raises the question of whether there could be some artefactual difference arising from the different methods by which the cases and controls were chosen and which might account for the apparent association.

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EDITOR,—Jean Golding and colleagues report a case-control study of the relation between neonatal administration of vitamin K and childhood cancer.[1] Comparing children born in two Bristol hospitals who were given intramuscular vitamin K with those given oral vitamin K or no vitamin K, they estimated an odds ratio for cancer of 2·0 (95% confidence interval 1·3-3·0) using a logistic regression model that also included the variables year of delivery and hospital.

Golding and colleagues made great efforts to check several potential confounders, of which one was type of delivery. When analysing the possible confounding effect of type of delivery, however, they do not take into account the fact that the correlation between type of delivery and vitamin K administration differed drastically between the two hospitals studied. Table I in the article showed that there was little difference in vitamin K administration between spontaneous and non-spontaneous deliveries among controls of hospital A, whereas in hospital B, 81% (56/69) of the non-spontaneously delivered controls and 4% (8/199) of the spontaneously delivered controls had been given intramuscular vitamin K. Furthermore, since in hospital B vitamin K administration showed very little variation given the time period (table I of the article), most of the information regarding the relation of vitamin K and cancer came from hospital B. This was clearly shown in the Mantel-Haenszel analysis reported in table II, in which only two out of 21 informative year strata were from hospital A.

Thus the result obtained comes to a large extent from a comparison in one Bristol maternity hospital between children given intramuscular vitamin K