THE EFFECT OF LARGE DOSES OF 'SYNKAVIT' IN THE NEWBORN

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Experimental work during the years 1929 to 1934 established the fact that a haemorrhagic disease observed in chicks was due to deficiency of a fat-soluble dietary factor: in 1935 Dam proposed the name vitamin K (Koagulations vitamin) for this factor. Dam, Schönheyder and Tage-Hansen in 1936 demonstrated a hypoprothrombinaemia which prolonged the clotting time in vitamin-K-deficient chicks, although vitamin K itself had no thrombin-like activity. In 1935 it was shown that mammals might develop vitamin K deficiency with its associated hypoprothrombinaemia and haemorrhagic tendency. Warner, Brinkhous and Smith described the syndrome in human adults in 1938, relating it to destructive jaundice: meanwhile, haemorrhagic disease of the newborn with hypoprothrombinaemia had been observed in 1937 by Brinkhous, Smith and Warner.

Treatment with vitamin K has now become an established form in haemorrhagic disease of the newborn and its effect on the prothrombin time is widely recognized. Waddell and Guerry found that the period of most marked prothrombin deficiency occurred from 48 to 72 hours after birth, and drew attention to the apparent seasonal variation in prothrombin deficiency, which is most marked in winter and maximal in March judged by the incidence of deaths due to haemorrhagic disease (Waddell and Guerry, 1939a and b; Waddell, Guerry and Birdsong, 1940; Waddell, Guerry, Bray and Kelley, 1939; Waddell and Lawson, 1940).

It has become the general practice in maternity units to administer a routine prophylactic dose of vitamin K to all infants at birth.

Physiology of Vitamin K

As far as is known, vitamin K has only one function in the body. It is essential for the synthesis of prothrombin by the liver. Vitamin K participates in the enzyme system in the liver, producing

prothrombin, but is not itself part of that glycoprotein.

Natural fat-soluble vitamin K requires bile salts for its absorption from the gastro-intestinal tract but the synthetic water-soluble analogues do not. Vitamin K is produced by bacteria in the small bowel which synthesize sufficient to cover normal daily requirements. The human requirements of vitamin K are not known, but Hardwicke (1944) has estimated that 0.5 to 5 μ g. daily are sufficient to prevent hypoprothrombinaemia in the newborn. Dam has shown that human milk contains little or no vitamin K. A small but definite amount of vitamin K can be stored in the liver (Lord, Andrus and Moore, 1940) and any excess is excreted in the stool.

Toxic Effects of Vitamin K

Until recently no toxic effects had been observed clinically from the administration of vitamin K and its analogues. Experimentally, massive doses of the vitamin were given to mice by Molitor and Robinson in 1940 and by Ansbacher, Corwin and Thomas in 1942, and both groups noted injury to the circulating blood cells, while Smith, Ivy and Foster in 1943 remarked on the production of an aplastic anaemia in experimental animals after massive doses of vitamin K. Respiratory depression and 'acute vascular congestion' are also mentioned as toxic effects. Very recently, the effect of vitamin K on the red cells has been emphasized by Allison (1955) who noted increased haemolysis in newborn premature infants given large doses. Moore and Sharman (1955) produced haemoglobinaemia in vitamin E-deficient rats with massive doses of vitamin K. About the same time, Laurance (1955) observed a remarkable increase in the incidence of kernikterus in premature babies following an increase in the routine dosage of vitamin K. In a retrospective survey, Crosse, Meyer and Gerrard (1955) found that there had been a steadily increasing incidence of kernikterus of prematurity which could be related to an increasing dosage of vitamin K.

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All these findings tend to verify the suspicions raised by Gasser in 1953 who mentioned vitamin K as a possible cause of severe haemolytic anaemia in 14 premature babies.

Present Investigation

This was undertaken in order to compare the serum bilirubin levels of groups of babies (full-term and pre-

FIG. 1.—Bilirubin levels in 106 full-term and 93 premature babies with and without 'synkavit'.

mature) who were given no vitamin K with comparable groups who were given vitamin K ('synkavit') intramuscularly.

The routine vitamin K dosage in the unit concerned was as follows:

(a) Full-term babies (over 5 1/2 lb. or 2,500 g.) were given 10 mg. 'synkavit' intramuscularly at birth and no further dose.

(b) Premature babies (5 1/2 lb. or 2,500 g. or less) were given daily doses of 10 mg. 'synkavit' intramuscularly until feeding was begun, and the average total dose received by the premature babies in the 'synkavit' group was 30 mg. The 'synkavit' group comprised 93 babies of all weight groups and the 'no-

synkavit' group comprised 106 babies of all weight groups.

Blood samples were taken by syringe from the femoral vein on the second, fourth and sixth days of life. The blood was allowed to clot and retract for two to four hours at room temperature before being centrifuged and the serum taken off by pipette. The modification described by Malloy and Evelyn (1937) for the Van den Bergh reaction was used in the estimation of both direct- and indirect-reacting bilirubin. The former was not considered toxic and has been disregarded in this paper, the indirect reacting bilirubin only being given: in any case, the highest reading of direct-reacting pigment obtained was 3.4 mg., in a full-term baby.

Of the 199 babies included in the investigation, 106 were full term: 60 of those babies received no vitamin K and 46 each received a dose of 10 mg. 'synkavit' at birth. The remaining 93 were premature: 46 of those received no vitamin K and the remaining 47 received doses of 'synkavit' varying from 10 to 50 mg. (average 30 mg.). Fig. 1 shows the mean serum bilirubin levels in the 106 full-term and 93 premature babies.

There was a wide overlap of bilirubin readings of individual members of each group and the calculated standard deviation was large, but it is interesting to note that the mean levels of these babies who received no 'synkavit' (both full-term and premature) were so much lower than those who received a dose which had not been considered toxic.

The general increase in the mean bilirubin levels

FIG. 2.—Mean bilirubin levels per 500 g. weight groups.

on the second, fourth and sixth days after the administration of 'synkavit' is still seen when different birth weight groups are studied separately, with the exception of a group weighing 2,000 to 2,500 g.: in this group there was little difference between the serum bilirubin levels of the babies given 'synkavit' and babies given none (Figs. 2 and 3). This is difficult to explain but Bound (1955) had a similar experience.

Discussion

Kernikterus of prematurity in the absence of iso-immunization is known to be related to the level of bilirubin in the infant's serum (Claireaux, Cole and Lathe, 1953; Crosse *et al.*, 1955; Meyer, 1956). There is little doubt that intramuscular 'synkavit' in large doses causes some elevation of the serum bilirubin levels of the newborn baby, whether full-term or premature. In the case of the premature baby, with poor liver function, the added effect of the 'synkavit' may just raise the serum bilirubin to

a sufficiently high level to produce kernikterus. Table 1 (Crosse *et al.*, 1955) shows the incidence of kernikterus of prematurity compared with the dosage

FIG. 3.—Mean bilirubin levels per 500 g. weight groups with and without 'synkavit.'

of 'synkavit' employed in the unit concerned in this investigation.

During this 10-year period, the average number of babies admitted has risen gradually from 200 per year to 300 per year: after the inception of the National Health Service in 1948 the percentage of small babies went up, but since 1950 there has been no change in the type of baby admitted and no major

FIG. 4.—Mean bilirubin levels per 500 g. weight groups.

TABLE 1
INCIDENCE OF KERNIKTERUS OF PREMATURITY
COMPARED WITH DOSAGE OF 'SYNKAVIT'

Year	Total Dosage of 'Synkavit' (mg.)	Percentage Developing Kernikterus
1945	1-2	0.9
1946		2.1
1947		0.8
1948		0.5
1949		1.6
1950	10	1.2
1951		1.1
1952	30	0.4
1953		4.1
1954		3.6
	More than 30	

change in the care of the babies other than the increased dosage of 'synkavit' to account for the severe rise in the incidence of kernikterus in 1953 and 1954.

The mode of action may be an increased haemolysis of red cells which would increase the circulatory bilirubin. It is, therefore, of interest to find that there was no significant difference in the percentage of babies requiring blood transfusion amongst the group receiving 'synkavit', when compared with those who received none (babies whose haemoglobin dropped to 60% or less were transfused), but this is a very rough method of assessing the degree of anaemia. It is possible that the action of large doses of 'synkavit' might be hepatotoxic rather than haemolytic or it might have both haemolytic and toxic actions.

The mean bilirubin curve of the babies in the 2,000-2,500 g. weight group shows a marked contrast to those of other weight groups. Without 'synkavit', the 2,000-2,500 g. curve is the highest, and this does not fit into the general picture in which the mean bilirubin levels decrease as the birth weight increases (Fig. 4). We have already shown that the mean bilirubin levels in this weight group are practically unaltered by the administration of 'synkavit' (Fig. 2). The fact that the estimations were done in the same laboratory under standard conditions seems to discount any experimental error but the sample is small and the scatter of individual results wide. It may be that at this stage of development (34-37 weeks) there is an alteration in the susceptibility of the red cell leading to increased haemolysis, or some change in the rate of conversion

of bilirubin in the liver: these hypotheses do not, however, explain the absence of change when 'synkavit' is given compared with the change in the other weight groups.

Summary and Conclusions

The effect of large doses of 'synkavit' on the level of serum bilirubin in the first week of life is presented, and the possible mode of action is discussed. It is suggested that large intramuscular doses of 'synkavit' increase the risk of the development of kernikterus in premature babies by raising the already high level of serum bilirubin.

There is still a place for vitamin K in the prophylaxis and treatment of haemorrhagic disease but a dose of 1 to 2 mg. is sufficient.

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