

DRUG INFORMATION

Jonathan Banks
Bob Buckham
Sharon Gardiner



CLINICAL PHARMACOLOGY

Murray Barclay
Evan Begg
Chris Hutchinson
Petra Lowe
Jane Vella-Brincat
Mei Zhang

PROPHYLACTIC VITAMIN K WITH ANTICONVULSANT USE IN PREGNANCY

Question:

Is there a requirement for prophylactic vitamin K administration in pregnant women receiving sodium valproate during pregnancy?

Answer:

Haemorrhagic disease of the newborn

A recognised postpartum complication is haemorrhagic disease of the newborn, which usually occurs on the second or third day postpartum^[1]. The bleeding sites most frequently affected include the intestine, umbilicus and cranium (cephalhaematoma)^[1]. Although similar, anticonvulsant-associated haemorrhagic disease of the newborn usually appears earlier, often occurring intrapartum or within the first 24 hours postpartum^[1,2]. In addition, haemorrhage tends to occur at unusual sites such as the pleural or abdominal cavities.

In each case the coagulation defect results from a decrease in vitamin K-dependent clotting factors (II, VII, IX & X).

Neonatal vitamin K

The activity of vitamin K-dependent coagulation factors in neonates is lower than in adults^[3]. This is primarily due to impaired placental transfer of vitamin K^[3]. Indeed, a high concentration gradient is required for diffusion of vitamin K to occur across the placenta^[4]. In addition, the sterile gut in the newborn means that the bacterial synthesis of vitamin K during the first few days of life is impaired.

Anticonvulsants and vitamin K

The mechanism by which anticonvulsants produce a vitamin K deficiency is not fully understood. Anticonvulsants may produce an effect that is similar to that of warfarin, namely, a competitive inhibition of the conversion of precursors to the active vitamin K-dependent clotting factors^[1]. It is also suggested that enzyme-inducing anticonvulsants may induce foetal microsomal enzymes resulting in enhanced degradation of vitamin K.

Newborn infants that have been exposed to anticonvulsants in utero are at the highest risk from vitamin K deficiency^[2]. Cornelissen observed that a biochemical marker of vitamin K deficiency, PIVKA-II (protein induced by vitamin K absence for factor II), was more frequently (significantly) detected in the cord blood of neonates exposed in utero to enzyme-inducing anticonvulsants^[2]. PIVKA-II was detected in 54% of the cord samples in the anticonvulsant group and 20% of the controls^[2]. The increased prevalence of PIVKA-II was related to treatment with phenobarbitone, carbamazepine and phenytoin, but not valproate. We note that phenytoin, phenobarbitone and carbamazepine are inducers of cytochrome P-450 isoenzymes, whereas, sodium valproate is an inhibitor of this system.

It is worth noting that whilst vitamin K deficiency is common in newborns exposed to anticonvulsants in utero, their mothers only rarely show signs of deficiency^[5].

Valproate

Rare reports of neonatal bleeding have occurred following in utero exposure to sodium valproate [6,7]. The mechanism for this however was the depletion of factor I (fibrinogen) which is a vitamin K-independent clotting factor.

As discussed, Cornelissen *et al* [2] have shown that valproate does not increase the frequency of vitamin K deficiency nor the rate of PIVKA-II detection in cord blood.

Conclusions:

Unlike the enzyme inducing anticonvulsants, phenytoin, carbamazepine and phenobarbitone, the evidence available suggests that valproate has no impact on vitamin K dependent clotting factors. Therefore, special measures for the supplementation of vitamin K in pregnant women receiving sodium valproate would appear unnecessary.

References:

1. Drugdex, Micromedex database
2. Cornelissen M *et al*. Am J Obstet Gynecol 1993; 168: 923-8
3. Cornelissen M *et al*. AM J Obstet Gynecol 1993; 168: 884-8
4. Guillaumont M *et al*. Dev Pharmacol Ther 1988; 11: 57-64 (Cited ref# 3)
5. Perucca E. Side Effects of Drugs Annual #18 1995; 60
6. Majer R *et al*. Lancet 1987; ii: 740-1
7. Bavoux F *et al*. Ann Pharmacother 1994; 28: 1307

Date prepared: January 2001

The information contained within this document is provided on the understanding that although it may be used to assist in your final clinical decision, the Drug Information Service at Christchurch Hospital does not accept any responsibility for such decisions.