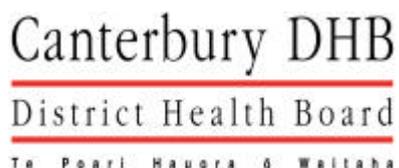


## DRUG INFORMATION

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### SAFETY OF VALPROATE IN THIRD-TRIMESTER OF PREGNANCY

#### Question:

What risks are associated with initiation of valproate at around 36 weeks' gestation as a prophylactic mood-stabiliser?

#### Answer:

It is usually recommended that valproate is avoided during pregnancy particularly during the first trimester, because of its known association with foetal malformations (Refer to enquiry on *valproate* in pregnancy).

Maternal use of valproate in pregnancy has been associated with neonatal complications such as intrauterine growth retardation, hyperbilirubinamia, hepatotoxicity, bleeding, hypoglycaemia and neonatal distress<sup>[1]</sup>.

*Hyperbilirubinaemia* has been reported in 10 infants following *in utero* exposure to valproate (nine were exposed to valproate monotherapy). Causality is difficult to establish because of the lack of evidence of this adverse effect in subsequent studies<sup>[1]</sup>.

*Hepatotoxicity* has been reported in three infants following *in utero* valproate exposure. One infant, who was also exposed to phenytoin, had normal liver function tests (LFTs) at birth but was observed to have an enlarged liver, vomiting, failure to thrive and slight icterus at two months of age. LFTs indicated cholestatic liver injury while biopsy revealed fibrosis.

One woman took valproate monotherapy (300mg or 500mg daily) during two pregnancies and produced two infants who died of liver failure. Liver atrophy and cholestasis were observed in both babies at autopsy. One of the infants also had malformations consistent with valproate exposure, hyperbilirubinaemia, hypoglycaemia, intrauterine growth retardation, hypocalcaemia and seizures at birth<sup>[1]</sup>.

*Haemorrhage*: There are rare reports of neonatal bleeding following *in utero* exposure to sodium valproate<sup>[1]</sup>. This occurred secondary to depletion of factor I (fibrinogen) which is a clotting factor that is independent of vitamin K.

*In utero* exposure to enzyme-inducing anticonvulsants (ie. carbamazepine, phenytoin, phenobarbitone) has been associated with an increased risk of neonatal bleeding<sup>[2,3]</sup>. This results from a decrease in vitamin K-dependent clotting factors (II, VII, IX & X). One of the mechanisms that may account for this is induction of foetal microsomal enzymes resulting in enhanced degradation of vitamin K<sup>[2]</sup>. Valproate is an inhibitor of microsomal enzymes and does not appear to increase the frequency of vitamin K deficiency<sup>[3]</sup>.

The manufacturer of valproate advises that the platelet count, fibrinogen plasma concentrations and coagulation status should be investigated in neonates following exposure in pregnancy<sup>[4]</sup>.

*Intrauterine growth retardation:* Some studies suggest that valproate monotherapy is associated with intrauterine growth retardation while others report normal birth weights, heights and head circumference<sup>[5]</sup>.

*Other effects:*

Two newborns exposed to valproate combination therapy were reported to have transient hyperglycaemia although no adverse effects were noted in the infant. This adverse effect has been reported in adults receiving valproic acid<sup>[1]</sup>.

Ebbesen *et al.*,<sup>[6]</sup> reported that infants with in utero exposure to valproate may be more likely to develop hypoglycemia and withdrawal reactions (irritability, jitteriness, hypertonia, seizures and/or vomiting). In this prospective study, the outcomes of 22 infants exposed to valproate alone (n=20) or with carbamazepine (n=2) were compared with 223 healthy term infants. The incidence of hypoglycaemia was significantly higher in the infants exposed to valproate compared with the control group. Thirteen of the 22 valproate-exposed neonates were reported to have asymptomatic hypoglycaemic episodes (<1.8mmol/L) which generally occurred during the first one to two hours of life (n=10) although delayed hypoglycaemia also occurred (out to 88 hours post-partum). Withdrawal reactions were reported in ten infants and commenced within 12-24 hours of delivery and persisted for up to seven days.

Conclusions:

Valproic acid is considered to be teratogenic and should be avoided in pregnancy especially during the first trimester during organogenesis. In the latter stages of pregnancy, there may be the possibility of intrauterine growth retardation, haemorrhage, hepatotoxicity, hypoglycaemia and withdrawal reactions. The risks of these adverse effects are difficult to quantify given the limited documentation in the literature and the short duration that is being considered in this case.

If the potential benefits of treatment are deemed to outweigh the risks, it would be prudent to use the lowest effective dose and administer valproate as two or three divided doses per day. The infant should be monitored for evidence of withdrawal reactions and it would be prudent to monitor clotting parameters, blood glucose concentrations and LFTs.

References:

1. Briggs GG et al. Drugs in Pregnancy and Lactation (5th ed), 1998
2. Drugdex, Micromedex database
3. Cornelissen M. et al Am J Obstet Gynecol 1993; 168:923-8
4. Epilim datasheet, Sanofi-Synthelabo (NZ) Limited
5. Iqbal MM et al. Clinical Toxicology 2001; 39(4): 381-92.
6. Ebbesen F et al. Arch Dis Child Fetal Neonatal Ed 2000; 83:F124-F129.

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