

# Neonatal hypoglycaemia and withdrawal symptoms after exposure in utero to valproate

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## Abstract

**Aims**—To define, in a prospective study, the risk of hypoglycaemia—defined as blood glucose concentration  $< 1.8$  mmol/l—in term infants exposed in utero to valproate and to describe the withdrawal symptoms.

**Methods**—Twenty epileptic women were treated with valproate only during pregnancy and two were treated with valproate and carbamazepine. In the first trimester, the daily median dose of valproate was 1.0 g (range 0.3–4.2) and in the third trimester 1.2 g (range 0.3–4.8).

**Results**—Thirteen of the 22 infants became hypoglycaemic. One infant had eight episodes of hypoglycaemia, one had three episodes, two had two episodes, and nine had one episode each. The lowest blood glucose concentration was 1.0 mmol/l. All episodes were asymptomatic. The maternal mean plasma concentration of total valproate during the third trimester correlated negatively with blood glucose concentration one hour after delivery ( $p < 0.0003$ ) and with the development of hypoglycaemia ( $p < 0.0001$ ). There was no evidence for hyperinsulinaemia as the cause of hypoglycaemia. Ten infants developed withdrawal symptoms, which correlated positively with the mean dose of valproate in the third trimester and the concentration of the free fraction of valproate in maternal plasma at delivery ( $p < 0.02$ ).

**Conclusions**—Infants exposed to valproate in utero had a significantly elevated risk of hypoglycaemia, and withdrawal symptoms were often observed.

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Keywords: hypoglycaemia; withdrawal symptoms; valproate; blood glucose; glucose

Glucose is an essential substrate for cerebral metabolism, and neonatal hypoglycaemia can cause cerebral damage resulting in severe handicap.<sup>1-3</sup> In a previous study,<sup>4</sup> we unexpectedly found that neonates exposed in utero to valproate appeared to have an increased risk of hypoglycaemia during the first days of life, but in that study the infants were exposed to very large doses of valproate. The common occurrence of withdrawal symptoms and probably the incidence of minor abnormalities and major malformations were related to the dose of valproate. Meanwhile, it is now possible to determine routinely the free fraction of val-

proate in plasma, and the prescribed dose of valproate has been reduced considerably.

In this study, we have analysed prospectively and consecutively the incidence of hypoglycaemia in neonates exposed to valproate in utero and recorded withdrawal symptoms as well as minor abnormalities and major malformations.

## Materials and methods

During the period July 1993 to February 1997 in the county of North Jutland, Denmark, we consecutively studied all infants born to epileptic mothers treated during pregnancy with valproate alone or in combination with other antiepileptic drugs. Preterm infants (gestational age  $< 37$  weeks) and second twins were excluded, but major malformations and minor abnormalities were recorded.

During the study period, 24 500 infants were born in the county. Twenty two infants and their mothers were included. Nineteen mothers had primary generalised epilepsy and three had complex partial epilepsy (table 1). Twenty mothers received valproate alone and two both valproate and carbamazepine (table 1). The pregnant epileptic women were followed according to international standards. They were seen once a month by a neurologist, and total and free drug plasma concentrations were measured and their future antiepileptic dose prescribed. The dose was adjusted according to the prepregnancy plasma level to maintain a constant concentration of the free fraction of valproate to ensure, as far as possible, absence of seizures. The plasma concentrations were measured as fasting values at 8–10 am. The concentrations of valproate and carbamazepine were measured by immunofluorescence.<sup>5</sup>

All women were offered an obstetrical ultrasound investigation and an amniocentesis. Amniocentesis was performed in 11 cases and an ultrasound investigation in all cases. In one case a chorionic villous biopsy was performed. The concentrations of  $\alpha$  fetoprotein in the amniotic fluid and the fetal chromosome analyses were normal. No therapeutic abortions were performed. During pregnancy the women abstained from, or consumed only small amounts of, alcohol.

In three cases, pregnancy was complicated by mild hypertension or mild pre-eclampsia, which was treated with labetalol. This drug does not affect the level of blood glucose in neonates.<sup>6</sup> None of the women were treated with  $\beta$ -sympathomimetics,<sup>7</sup> and none received glucose infusions during labour.

The infants were observed in the neonatal unit from the first hour of life, and every eight

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Table 1 Maternal data

Mother no	Type of epilepsy	Epileptic attack during pregnancy	Medication	Daily dose of antiepileptic drug(s) in g/24 hours + range of plasma concentrations of (total valproate) and [free valproate] in $\mu\text{mol/l}$			Poor compliance
				1st trimester	2nd trimester	3rd trimester	
1	Primary generalised		Valproate	1.0	1.0→1.5 (238–348) [29–63]	1.5 (226–338) [28–54]	
2	Primary generalised		Valproate	0.9 (310–343)	0.9	0.9→2.1 (212–362)	
3	Primary generalised		Valproate	0.6	0.6 (243)	0.6→2.1 (250–583)	
4	Primary generalised		Valproate	0.6	0.6→0.9 (247)	0.9 (298–427)	
5	Primary generalised		Valproate	1.0 (412) [27]	1.0 (306–381) [26–39]	1.0 (262–304) [29–35]	
6	Complex partial	+	Valproate	1.1	1.1	1.1→1.5 (280–319)	
7	Primary generalised		Valproate	1.0	1.0 (275–422) [38–63]	1.3 (274–408) [42–55]	
8	Primary generalised		Valproate	1.0 (122) [7]	1.0 (266–267) [27]	1.0 (146–204) [17–26]	
9	Primary generalised		Valproate	0.5 (329) [32]	0.5 (239–275) [21–25]	0.5 (222–247) [23–24]	
10	Primary generalised		Valproate	1.0 (273–290) [24–28]	1.0 (264–290) [23–38]	1.0 (174–392) [21–53]	
11	Primary generalised		Valproate	1.0 (607) [50]	1.0 (390–536) [49–56]	1.0 (251–304) [31–56]	
12	Primary generalised		Valproate	0.9 (327)	0.9 (238–309)	1.2→1.5 (334–362)	
13	Primary generalised		Valproate	0.8 (269) [18]	0.8→1.0 (281–321) [19–25]	1.0 (272–360) [35–42]	
14	Primary generalised		Valproate	1.6 (434) [20]	1.6 (373–615) [65–70]	1.6 (308–422) [30–52]	
15	Primary generalised		Valproate	1.5 (283) [20]	1.5 (249–314) [24–38]	1.5 (269–312) [29–33]	
16	Primary generalised		Valproate	1.2 (416) [55]	1.2→1.5 (287–310) [20–47]	1.5 (278–314) [30–51]	
17	Primary generalised		Valproate	1.0 (302) [20]	1.0 (223–260) [20–27]	1.0 (179–225) [19–33]	
18	Primary generalised		Valproate	0.3 (78) [3]	0.3 (77–82) [5]	0.3 (52–63) [5]	
19	Primary generalised		Valproate	0.9 (264–373) [22–40]	0.9 (236–334) [34–58]	0.9 (195–260) [31–45]	
20	Primary generalised		Valproate	1.0 (568–609) [62]	1.0 (469–537) [56–64]	1.0 (422–436) [51–69]	
21	Complex partial	+	Valproate	4.2	4.8 (22–446) [6–81]	4.8 (238–316) [44–78]	+
			carbamazepine	2.4	2.8 (6–44) [2–10]	2.8 (23–29) [7–16]	
22	Complex partial	+	Valproate	1.5 (289) [26]	1.5 (108–165) [15–26]	1.5 (123–141) [12]	
			carbamazepine	1.0 (26) [7]	1.0 (25) [5]	1.0 (22–29) [5–11]	

hours withdrawal symptoms such as irritability, jitteriness, hypertonia, seizures, and vomiting were recorded.

Glucose levels in the umbilical cord blood (mixed arteriovenous blood) as well as in capillary blood were measured at 1, 2, 4, 6, 12, 18 and 24 hours of age and then every eight hours until the 5th day of age. The samples at 1, 2 and 4 hours post partum were collected independently of feeding time. After this, samples were collected just before feeding.

Capillary blood samples were collected by heel prick on prewarmed feet into 20  $\mu\text{l}$  heparinised micropipettes containing fluoride, and immediately analysed. Glucose concentration was measured using the glucose dehydrogenase photometric method on an Hitachi 911 analyser.<sup>8</sup> The day to day combined preanalytical and analytical standard deviation was 0.15 mmol/l.

Hypoglycaemia was defined as a glucose concentration below 1.8 mmol/l (= 32.4 mg/dl) as in our previous study,<sup>4</sup> as we have not yet found sufficient evidence to change this definition.<sup>3 9 10</sup>

Concentrations of proinsulin,<sup>11</sup> insulin,<sup>12</sup> and C peptide<sup>13</sup> in umbilical cord plasma were determined by enzyme immunoassay and radioimmunoassay.

The infants received an early feed—that is, within the first hour of life—and were thereafter breast fed about eight times a day. Breast feeding was supplemented with formula milk for an average of 2 days (range 0–6). One infant was exclusively formula fed. The main reason for supplementation was feeding problems because of withdrawal symptoms (table 2).

The following liver function tests were carried out on all hypoglycaemic infants: plasma concentrations of aspartate aminotransferase,

Table 2 Infant data

Infant no	Sex	Gestational age (weeks)	Birth weight (g)	Apgar score 1–5 minutes	Withdrawal symptoms					Treatment of symptoms	Minor abnormalities
					Irritability	Jitteriness	Hypertonia	Seizures	Vomiting		
1	f	42	2650	9–10	+	+	+		+		Ptosis, rough curly hair, epicanthic folds, hypertelorism, deep groove below the lower lids
2	m	39	2950	10–10	+	+	+		+	Phenobarbital	
3	m	42	4000	10–10		+			+		
4	f	41	3580	10–10							
5	m	41	3925	10–10							
6	f	40	3880	7–10	+	+	+				
7	m	39	3400	6–10	+	+					
8	f	41	3070	8–10	+	+	+		+		Small unusually shaped ears
9	m	42	3715	10–10							
10	m	41	3820	10–10	+	+	+				
11	f	42	4110	10–10							
12	m	38	3030	9–10	+	+					
13	m	41	4595	10–10							
14	f	39	2680	5–6	+	+	+	+	+	Phenobarbital Diazepam	
15	m	40	3960	10–10							Complete syndactyly of the right 4th–5th toe
16	m	37	3000	9–10							
17	m	38	4240	8–9							
18	f	40	3600	10–10							
19	f	38	3350	10–10							
20	m	40	3755	10–10							
21	m	39	3180	10–10	+	+	+			Phenobarbital	Small unusually shaped ears
22	m	41	3420	9–10							

alkaline phosphatase, albumin, conjugated and unconjugated bilirubin, and coagulation factors II, VII and X were measured.

At delivery, maternal plasma concentrations and umbilical cord concentrations of the free and total fractions of valproate were measured. Neonatal plasma drug concentrations were measured on the second and fourth day of age.

Written informed consent was obtained from the parents. The protocol was approved by the local ethics committees.

The statistical methods used were the Mann-Whitney rank sum test for unpaired observations, Fisher's exact test, and stepwise forward logistic regression analysis. The significance level was set at 5%.

According to the study design, three infants were excluded: two preterm infants and a second twin (first twin was infant no 16). One of the preterm infants had the following malformations: hypoplasia of the left femur, aplasia of the left fibula, and duplication of the distal part of the right thumb.

#### REFERENCE DATA

A reference group, consisting of 223 healthy term infants of appropriate size for gestational age, was studied during the first 96 hours after birth.<sup>14</sup> Capillary blood glucose concentration was measured at one of the following times: 1, 2, 4, 6, 12, 24, 48, 72, 96 hours post partum. Each infant had one measurement. In another 22 infants, glucose concentration in umbilical cord blood was measured. The blood samples were taken independently of feeding times. About 20 samples were taken at each time point from different infants. In addition, concentrations of proinsulin, insulin, and C peptide in umbilical cord plasma were determined. The infants were breast fed within the first hour of delivery and then every second or third hour. None of the infants had any neurological symptoms and none of the mothers had epilepsy.

The reference data were collected at the same hospital (Aalborg) and in the same period as the study material, and the blood glucose concentrations were determined at the same laboratory.

#### Results

Table 1 gives data on the mothers in the study. During the first trimester, the daily dose of valproate varied from 0.3 to 4.2 g (median 1.0 g) and during the third trimester from 0.3 to 4.8 g (median 1.2 g). In 10 women, the valproate dose had to be increased. During pregnancy, three women suffered from epileptic seizures and one of these women showed poor compliance.

Table 2 gives data on the infants in the study. Fourteen boys and eight girls were included. The median gestational age was 40 weeks (range 37–42) and the median birth weight 3590 g (range 2650–4595). Fifteen infants were delivered vaginally and seven by caesarean section. Two infants (1 and 14) were small for gestational age and the latter had asphyxia. On admission to the neonatal unit all infants had a temperature > 36.5°C.

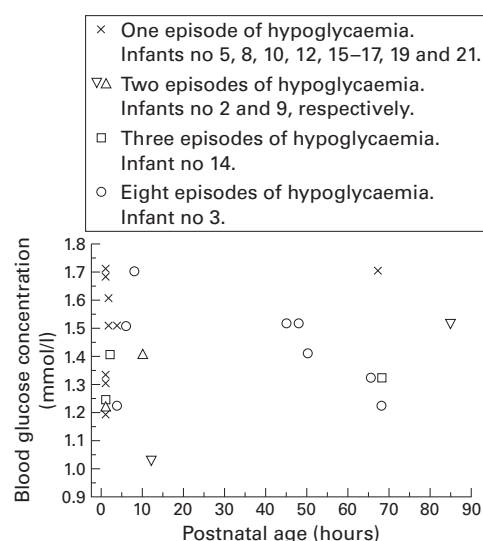


Figure 1 Scatter plot of postnatal age of hypoglycaemic episodes against blood concentration in infants exposed in utero to valproate.

In 13 of the 22 infants, blood glucose concentrations fell below 1.8 mmol/l (fig 1). In seven infants, the first episode of hypoglycaemia occurred within one hour of birth, in three within two hours, in one within four hours, in one within 12 hours, and in one within 67 hours (fig 1). Figure 2 shows the cumulated incidence of hypoglycaemia. All hypoglycaemic infants were treated with an intravenous bolus of glucose 200 mg/kg body weight, followed by a continuous infusion of glucose at a maximum rate of 2–8 mg/kg/min (median 4). The median time of infusion was 31 hours (range 25–123). Infants 3 and 14 were also treated with hydrocortisone.

The number of episodes of hypoglycaemia varied: one infant had eight, one had three, two had two, and nine each had one episode (fig 1). The lowest concentration of blood glucose measured was 1.0 mmol/l (fig 1). The hypoglycaemic infants were all asymptomatic. When neurological symptoms existed and did not disappear despite glucose infusion, we concluded that they were not related to hypoglycaemia and were recorded as withdrawal symptoms.

Figure 3 shows median concentrations of blood glucose at different times after delivery.

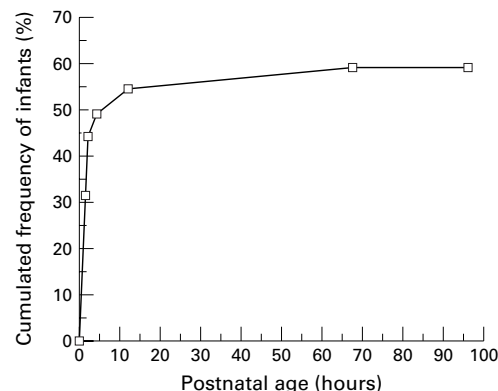


Figure 2 Cumulated frequency of infants exposed in utero to valproate who developed hypoglycaemia during the first 96 hours of age.

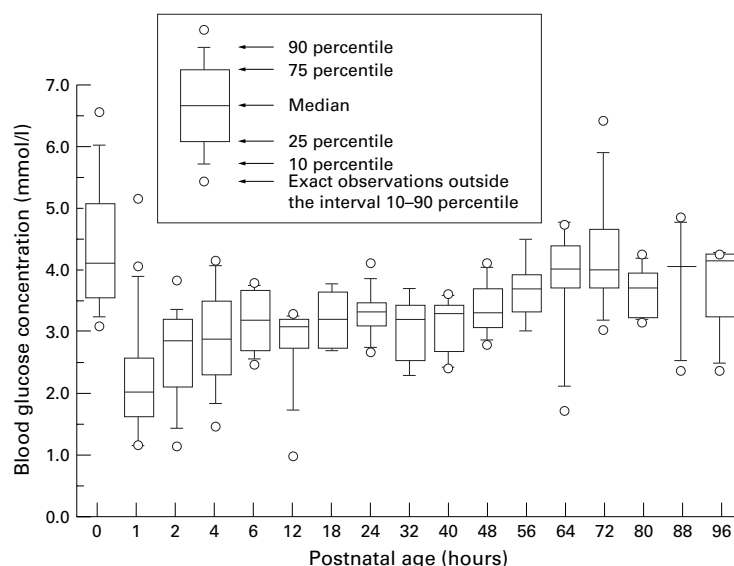


Figure 3 Blood glucose concentration in infants exposed in utero to valproate during the first 96 hours of life.

At one and two hours post partum, they were significantly lower than at delivery. The lowest concentration of glucose was seen one hour post partum (median 2.1 mmol/l, range 1.0–4.1). This was significantly ( $p < 0.01$ ) lower than in the reference group at one hour post partum (median 2.9 mmol/l, range 1.4–4.1). At two hours post partum, the difference between the two groups was nearly significant ( $p = 0.06$ ; Mann-Whitney test). Infants treated for hypoglycaemia were excluded. Correspondingly the incidence of hypoglycaemia one hour after birth was significantly higher than in the reference group ( $p < 0.05$ ; Fisher's exact test). In the valproate exposed group, seven of 22 infants were hypoglycaemic, and in the reference group only one had a low blood glucose concentration. Two hours after delivery, the incidence of low blood glucose concentration tended to be higher in the valproate treated group than in the reference group ( $p = 0.11$ ; Fisher's exact test).

The negative correlation of blood glucose concentration at one hour post partum with the dose of valproate and the plasma concentrations of valproate was investigated in a stepwise forward logistic regression analysis, with blood glucose concentration as the dependent variable and the mean dose of valproate in the third trimester, the mean concentration of free and total fractions of valproate in the third trimester, and the concentrations of free and total fractions of valproate of both mother and infant at delivery as independent variables. The analysis showed that the mean plasma concentration of the total fraction of valproate in the third trimester correlated negatively with the blood glucose concentration ( $p < 0.0003$ ) and with the development of hypoglycaemia one hour post partum ( $p < 0.0001$ ).

The median concentration of glucose in umbilical cord blood and the plasma concentrations of proinsulin, insulin, and C peptide were 4.2 mmol/l (range 3.1–6.6), 20 pmol/l

(range 7–78), 27 pmol/l (range < 5–33), and 340 pmol/l (range < 100–1041) respectively.

In the reference group, the median concentration of glucose in umbilical cord blood and the plasma concentrations of proinsulin, insulin, and C peptide were 4.9 mmol/l (range 1.9–7.4), 14 pmol/l (range 4.4–35), 24 pmol/l (range 8.6–97), and 314 pmol/l (range 116–527). There was no significant difference between the two groups ( $p > 0.05$ ; Mann-Whitney test).

In the third trimester and at delivery, the median maternal plasma concentrations of valproate ( $\mu\text{mol/l}$ ) were as follows: total fraction 285 (range 59–431) and 252 (range 14–399) and free fraction 32 (range 5–61) and 39 (range < 5–148).

The median plasma concentrations of valproate ( $\mu\text{mol/l}$ ) in the umbilical cord and neonate 26 and 73 hours after birth were as follows: total fraction 336 (range 24–589), 224 (range 18–449), and 123 (range 38–226) and free fraction 40 (range 5–87), 32 (range < 5–97), and 13 (range 3–31) respectively.

Ten infants developed withdrawal symptoms such as irritability, jitteriness, hypertonia, seizures, and vomiting (table 2). Three infants needed to be fed by tube, and one had convulsions. Withdrawal symptoms began 12–24 hours after birth and lasted two to seven days. Three infants were treated with phenobarbital, and the convulsive infant was treated with diazepam as well. The development of withdrawal symptoms correlated positively with the mean dose of valproate in the third trimester and the concentration of the free fraction of valproate in maternal plasma at delivery ( $p < 0.02$ ; Mann-Whitney test). There was a positive but statistically insignificant correlation between the mean plasma concentration of the free and total fraction of valproate in the third trimester, the maternal concentration of the total fraction of valproate at delivery, the concentrations of free and total fractions of valproate in the infant at delivery, and development of symptoms in the infant.

Liver function tests, except unconjugated bilirubin, gave normal results, except for one infant (no 14) with asphyxia, who had elevated plasma aspartate aminotransferase activity (162 U/l; normal value < 90 U/l).

None of the infants had major malformations. Four infants had minor abnormalities (table 2). The facial features of infant 1 were characteristic of fetal valproate syndrome.<sup>15</sup>

## Discussion

In this study, the median dose of valproate given to the pregnant epileptic women was significantly lower than in our previous study<sup>4</sup>: median dose 1.0 g (range 0.3–4.2) in the first trimester and 1.2 g (range 0.3–4.8) in the third compared with 1.5 g (range 0.0–4.8) and 2.5 g (range 0.9–6.6) respectively. In this study, only one patient was treated with more than 2.1 g valproate daily. Some 90% of the women were treated with valproate alone compared with 65% in the previous study.<sup>4</sup>

In our previous study on 17 infants, hypoglycaemia was found in four. Blood



glucose was measured in nine infants because of neurological symptoms, but the symptoms persisted in spite of glucose infusion. These findings suggested that exposure to valproate in utero may cause neonatal hypoglycaemia. However, blood glucose concentration was not measured systematically, and therefore the risk of hypoglycaemia could not be predicted.

In this study, we systematically determined blood glucose concentration in infants of epileptic women during the first 96 hours after birth. Some 59% (13 of 22) developed hypoglycaemia and in all cases it was asymptomatic and moderate, the lowest blood glucose concentration measured being 1.0 mmol/l. Hypoglycaemia was more common during the first few hours after birth, but was seen as late as 88 hours post partum. Hypoglycaemia in these infants of epileptic mothers seems to be more common than in mature infants of diabetic mothers,<sup>16 17</sup> in which the cause is known to be hyperinsulinaemia.<sup>18</sup>

Repeated episodes of hypoglycaemia were seen in four of the infants, with a maximum of eight episodes. Lucas *et al*<sup>5</sup> found that the number of separate days in which hypoglycaemia (plasma glucose concentration < 2.6 mmol/l) occurred in preterm infants was strongly related to a reduced mental and motor development score and to an increased incidence of cerebral palsy at 18 months of age. During episodes of hypoglycaemia, ketone bodies generated from fatty acids may be an alternative substrate for cerebral metabolism, but valproate inhibits this ketogenesis.<sup>19 20</sup> Thus hypoglycaemia in infants exposed to valproate in utero may be hypoketotic. Impaired psychomotor development is often seen in infants of epileptic mothers treated during pregnancy with valproate.<sup>4 15 21 22 23</sup> One of the causes may be unrecognised hypoglycaemia.

In one of the infants in this study (no 14), there could have been an alternative cause of the hypoglycaemia, as the infant was both small for gestational age and asphyxiated.

In this study, neonatal hypoglycaemia was defined as a blood glucose concentration < 1.8 mmol/l as in our previous study. Other investigators define hypoglycaemia as a blood glucose concentration < 2.2 mmol/l or < 2.6 mmol/l.<sup>24</sup> If we had defined hypoglycaemia in this way, the values would have been 77% (17 infants) and 91% (20 infants) respectively.

In the reference group, blood glucose concentration was determined after delivery in 223 infants. Only one of these had a low blood glucose concentration (1.4 mmol/l) at 1 hour of age. Compared with this, blood glucose concentration was significantly lower at 1 hour of age and the incidence of hypoglycaemia significantly higher in the valproate exposed group. Similar but statistically insignificant correlations were found two hours post partum.

Confirmation that valproate exposure in utero is the cause of hypoglycaemia would require a study in which infants not exposed to valproate in utero were included and the blood glucose concentrations measured at the same times as in the exposed infants. Such a study

was impossible to carry out. We therefore compared the group of infants exposed to valproate and their incidence of hypoglycaemia with a group of healthy term infants of appropriate size for gestational age, although there may be alternative causes of hypoglycaemia in the infants exposed to valproate. This was seen in the infant who was both small for gestational age and asphyxiated.

In the valproate exposed group, the infants often received breast milk supplemented with formula milk, usually because of feeding problems caused by withdrawal symptoms, but in the reference group none of the infants received supplements. Supplements must have tended to prevent hypoglycaemia in the valproate exposed group, but in spite of this, the incidence of hypoglycaemia was found to be very high.

Preterm infants were excluded for the following reasons: they often receive infusions of glucose immediately after birth; they are often hypoglycaemic because of prematurity; they often have complicating diseases; the amount of blood required for measurement is relatively large compared with the infant's blood volume.

In the valproate exposed group, blood glucose concentration one hour after birth was found to correlate negatively with the mean plasma concentration of total valproate in the third trimester.

In conclusion, the exposure to valproate in utero (and consequently in the first days after birth) was the cause of hypoglycaemia, and the infants exposed to valproate had a significantly higher risk of developing hypoglycaemia, and the repeated episodes of hypoglycaemia occurred often. We recommend that blood glucose is repeatedly and routinely measured, especially in the first hours after birth, in infants exposed in utero to valproate.

To investigate if hypoglycaemia could be due to hyperinsulinism, we measured concentrations of proinsulin, insulin, and C peptide in umbilical cord blood. These concentrations and those of blood glucose were not significantly different from those measured in umbilical cord blood of the reference group of normal healthy term infants. Another argument against hyperinsulinism being the cause of hypoglycaemia is that the infants with hypoglycaemia were infused with glucose at a median rate of 4 mg/kg/min (range 2–8)<sup>25 26</sup> and they had a normal birth weight<sup>27</sup> and did not resemble infants of diabetic mothers.<sup>28</sup> In conclusion, we found no evidence for hyperinsulinism<sup>29</sup> as the cause of hypoglycaemia in infants exposed in utero to valproate.

Valproate can affect synthesis in the liver.<sup>19 30–33</sup> Thus an increased plasma concentration of ammonium<sup>19 33</sup> and a decreased concentration of  $\beta$ -hydroxybutyrate,<sup>19</sup> albumin, fibrinogen,<sup>30</sup> and carnitine<sup>19 31</sup> have been found in children treated with valproate for febrile convulsions or epilepsy. Similar depletion of neonatal fibrinogen caused by valproate has been described.<sup>32</sup> Valproate given to infant mice led to reduced liver glycogen.<sup>34</sup> Administration of valproate was found to inhibit

mitochondrial  $\beta$ -oxidation of fatty acids in humans and rats,<sup>35</sup> and patients with enzymatic  $\beta$ -oxidation defects often have neonatal hypoglycaemia<sup>36, 37</sup> as the result of decreased gluconeogenesis. This is in accordance with the hypoketonaemia of children treated with valproate.<sup>19, 20</sup> In isolated rat hepatocytes, valproate inhibits gluconeogenesis.<sup>38</sup> Therefore decreased gluconeogenesis caused by valproate seems to be well documented, but because hypoglycaemia in infants exposed in utero to valproate is seen in this study as early as within the first few hours after birth, decreased gluconeogenesis is considered to be a contributory cause at the most. The most important cause of hypoglycaemia may therefore be reduced liver glycogen and/or impaired glycogenolysis.

Although the maternal dose of valproate was reduced and the frequency of monotherapy increased in this study, the incidence of major malformations and minor abnormalities was lower than in the previous study.<sup>4</sup> In that study, five of 17 infants had major malformations and nine had minor abnormalities compared with one of the three excluded infants with major malformations and four of the 22 study infants with minor abnormalities in this one. The reduced incidence of major malformations and minor abnormalities seems to confirm the dependence on the dose of valproate, which is in accordance with our previous study and the study of Jäger-Roman *et al.*<sup>21</sup>

Ten infants had neurological symptoms such as irritability, jitteriness, hypertonia, seizures, and feeding problems. These symptoms correlated positively with the dose of valproate as in the previous study,<sup>4</sup> as well as with the maternal concentration of the free fraction of valproate at delivery. The symptoms began 12–24 hours after birth and were regarded as withdrawal symptoms, because they did not disappear after infusion of glucose. In one case, asphyxia may have been an alternative cause of the neurological symptoms. Thus withdrawal symptoms are often seen in infants exposed in utero to valproate in commonly recommended doses, as also reported by Koch *et al.*<sup>22</sup>

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