sanofi aventis

PERIODIC SAFETY UPDATE REPORT

for valproate

(Depakine®, Depakote®, Micropakine®, Valproate Sodium Irex®)

Covered period: 01-Feb-2007 to 31-Jan-2008

International Birth Date (IBD): 23-Jan-1967
Country of IBD: France
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Author(s): Delphine Mesnil, PharmD
Michel Brunet, MD
Global Pharmacovigilance and Epidemiology

Sanofi-aventis
1, avenue Pierre Brossolette
91385 Chilly Mazarin Cedex
FRANCE
Fax: 33.1.60.49.70.76

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Preferred term	Case ID
vasculitis cerebral	A01200709896
visual field defect	A01200709196
	A01200711838
	A01200800676

Autism

Cumulative experience on autism, autism spectrum disorder and Asperger's disorder:

A total of 35 cases were identified in the sanofi-aventis post-marketing pharmacovigilance database. They referred to autism (n=27), autism spectrum disorder (n=6) and Asperger's disorder (n=2).

- In 1 case, a child was exposed to divalproex orally for complex partial seizures from the age of 22 months for 6 months. She showed autistic behaviour and mental delay at the age of 5 years. Of note, at the age of 24 months the child had experienced a seizure with loss of consciousness, respiratory arrest and need of resuscitation (N119476).
- In the remaining 34 cases, the patients were exposed to valproate in utero. In 26 cases, valproate was prescribed for maternal epilepsy; in 1 case, valproate was prescribed for maternal migraine (A01 2005 03307), in 1 case valproate was prescribed for behaviour disorder (A02 2008 00288), and in the remaining 6 cases, the maternal indication was unknown.

  Seven of the 34 cases were issued from literature articles from the same author (N108441, N130000, N130004, N130005, N130007, N130010, N130057).

  - In 16 cases, autism was reported without clinical information leading to the diagnosis and there were no associated malformations (N112849, N113254, N113565, N122684, N122685, N133157, A01 2006 02941, A01 2006 02942, A01 2006 07850, A01 2006 07851, A01 2007 07311, A02 2004 01239, A02 2006 03349, A02 2007 00112, A02 2007 02452, A02 2008 00288). In 2 cases, patients were also exposed to phenytoin and/or carbamazepine in utero (A01 2007 07311, N112849). Eight of the cases were referring to siblings (N113254 and N113565; N122684 and N122685, A01 2006 02941 and A01 2006 02942, A01 2006 07850 and A01 2006 07851).
  - In 10 cases, the children presented with facial dysmorphism and developmental delay. Criteria leading to the diagnosis of autism were not provided (N108441, A01 2005 01956, A01 2005 03307, A01 2005 06142, A01 2005 08792, A02 2004 00639, A02 2005 01709, A02 2005 01880, A02 2007 01155, A02 2007 01393). Moreover concomitant treatment in utero with phenobarbital+amphetamine and carbamazepine was reported in case A02 2004 00639 and with carbamazepine in cases A01 2005 01956 and A02 2005 01880.
  - In 8 published cases, the children were described with concomitant features of Foetal Valproate Syndrome (A01 2007 09570, A01 2007 09936, N130000, N130004, N130005, N130007, N130010, N130057) and the diagnosis of autism followed DSM IV criteria or ICD-10 criteria in 7 of the cases. In 3 of these cases, the children were exposed to

concomitant antiepileptic drugs with carbamazepine or phenytoin. Two of the cases were referring to siblings (A01 2007 09570 and A01 2007 09936), described in the same article.

Conclusion: according to the National Center for Health Statistics, the prevalence of autism ranges from around 10 to 15 cases per 10,000 populations. It is noteworthy that a statement is present in the CCSI, regarding the potential association between in utero valproate exposure and a risk of developmental delay, particularly of verbal intelligence quotient. No conclusion can be drawn regarding a causal role of valproate in the development of autism in these children exposed in utero or orally to valproate. This topic will remain under surveillance by the company.

Psychomotor hyperactivity

Cumulative experience on psychomotor hyperactivity:

A total of 67 cases were identified in the sanofi-aventis post-marketing pharmacovigilance database. They referred to psychomotor hyperactivity (n=61) and attention deficit/hyperactivity disorder (n=6).

In 1 case, psychomotor hyperactivity was triggered by encephalopathy already listed in the CCSI for valproate (A04 2006 00817). It was not taken into account in this analysis.

In the remaining 66 cases, it is noteworthy that 44 cases involved children (aged between 2 and 11 years) whereas the other cases referred to neonates (n=4), infants (n=5), adolescents (n=2), adults (n=6), elderly (n=2) and unknown age group (n=3).

- In 4 cases, psychomotor hyperactivity or attention deficit/hyperactivity disorder occurred in neonates after exposure to valproate in utero (N110635, A01 2005 06142, A01 2005 08816, A01 2006 03307). The reactions were associated with congenital malformations and/or developmental delay in the last 3 cases.
- In 5 cases, a causal role of valproate was assessed as probable based on the recurrence of the reaction upon the reintroduction of valproate (A02 2007 01862, A06 2003 00070, N117780, N119942, N131372). In the last 4 cases, the patients were children.
- In 19 cases, a causal role of valproate could not be ruled out. However,
  - alternative aetiologies may be suggested as confounding factors in 10 cases: recurrence of seizures (A01 2004 02350), underlying brain injury (A01 2005 08090), underlying learning disability and/or psychomotor retardation (A01 2005 00701, A02 2005 00095, N101999, N104538), patient born in a context of foetal distress (A01 2003 03021), hysterical personality (A02 2006 02346), underlying liveliness (N106561), psychosis (A02 2004 00823);
  - alternative explanations were provided in 4 cases: bad compliance of valproate prescribed for schizophrenia (A02 2004 00246), concomitant carbamazepine, also suspected by the reporter (A01 2003 05910), venlafaxine withdrawal in 2 cases (A01 2003 03304, A04 2005 01098);

Preferred term	Case ID
abortion missed	A01200707942
	A04200700668
abortion spontaneous	A01200701427
	A01200711979
	A02200700682
blighted ovum	A02200702976
ectopic pregnancy	A01200712002
foetal growth retardation	A02200703701
	A02200800212
	A02200800223
intra-uterine death	A01200705834
	A01200707946
polyhydramnios	A02200700522
	A02200700770
pregnancy with contraceptive device	A01200708516
premature labour	A02200800224

Abortion spontaneous

Cumulative experience on abortion spontaneous:

A total of 75 cases were identified in the sanofi-aventis post-marketing pharmacovigilance database. Among them, 76 reactions were coded as follows: abortion (n=1), abortion spontaneous (n=54), abortion threatened (n=1), abortion missed (n=2), intra-uterine death (n=9), blighted ovum (n=1) and stillbirth (n=8).

- In 9 cases, no alternative aetiologies were mentioned. However, it was unknown if the foetus showed congenital abnormalities:
  - in 8 cases, the patient had no history of previous miscarriage or abortion and spontaneous abortion occurred during the patient's first pregnancy (A01 2006 01830, A01 2006 04856, A01 2007 07946, A02 2004 00613, A04 2007 00668, N113940, N116235, N122589). Of note, in 3 of these cases, the patients were also treated with other antiepileptics: topiramate and phenytoin (N113940), carbamazepine (N116235), zonisamide (A01 2007 07946). In case A04 2007 00668, a gemellar pregnancy was reported;
  - in 1 case, the patient had 2 miscarriages while treated with valproate and 3 pregnancies with normal term infant while valproate was continued (A01 2003 03682).
- In 22 cases, the women had histories of other:
  - spontaneous abortion in 15 cases (A01 2004 03072, A01 2004 03562, A01 2004 05451, A01 2004 05452, A01 2007 01427, A01 2007 07942, A02 2003 01633, N101036, N101262, N104624, N107457, N112941, N118567, N124417, N124465), or abortions NOS in 1 case (A01 2003 02759). Among them, the previous miscarriages had occurred also under valproate in 7 cases (A01 2004 03562, A01 2007 01427, N101036, N101262, N104624, N107457, N124417). Of note, blighted ovum was noted in case N101262 and

polycystic ovaries syndrome in case A01 2007 01427. Cases A01 2004 05451 and A01 2004 05452 referred to the same woman who had several episodes of spontaneous abortion and intra-uterine death under valproate;

- pregnancies with foetal malformations in 6 cases, under valproate (A01 2006 04857, N102131, N106630, N131201, N131204) or with no information whether previously treated with valproate (N115462). Of note, gemellar pregnancy was reported in 1 case (N106630); the second live born infant had facial dysmorphism. In 1 case, the patient had a history of miscarried foetus with encephalocele (N131204);

In 4 of these 22 cases, other antiepileptic treatments were concomitantly received: phenobarbital (N102131), lamotrigine (N104624) or gabapentin (A01 2007 07942, N124417).

- Five (5) cases occurred in a context of membrane rupture (N111615), placenta abruption in twins (N115455, N115456), ectopic pregnancy (N116229), abnormal uterus ultrasound (A01 2007 11979). In the first 3 cases, valproate therapy was associated with carbamazepine. In the last case, the patient had history of foetal malformation in one child and one spontaneous abortion without antiepileptic treatment.
- In 17 cases, alternative explanations could be suggested:
  - concomitant levetiracetam therapy withdrawal one week before the reaction in a patient treated for primary generalized epilepsy (A01 2002 02864);
  - congenital abnormalities in the foetus in 12 cases: neural tube defect (N102354), pulmonary malformation (N104932), abdominal wall defect (N108156), hepatic problems NOS (N110268), foetal growth delay and multiple malformations (N119693), spine malformation (A01 2006 06072), multiple malformations (A01 2006 05594, A01 2007 05834, A02 2006 00222, A02 2006 02156, A04 2005 01039, N122584). Other AEDs were concomitantly received in some of these cases: lamotrigine (N102354), gabapentin (N110268), topiramate (N122584), lamotrigine, carbamazepine and phenytoin (A01 2006 05594). In 2 cases, the patient had a previous healthy child while on valproate throughout pregnancy (A04 2005 01039, N102354). Of note, in 1 case, maternal history included 3 previous spontaneous abortions and 1 live birth, with no information whether under treatment with valproate (A01 2007 05834);
  - bleeding NOS one month before stillbirth occurred in a gemellar pregnancy while one twin was alive but with malformation (N112580);
  - in utero death of triplets occurred during the second trimester of pregnancy. The mother had a previous uneventful pregnancy while treated with valproate (A02 2005 00302);
  - age of the 48-year-old patient (N131758);
  - stillbirth occurred just after an episode of status epilepticus (A01 2006 05560).
- No conclusion could be drawn from the information available regarding a causal role of valproate in 20 cases (A01 2004 03070, A01 2005 00110, A01 2005 01937, A01 2006 02477, A01 2006 07209, A02 2002 01993, A02 2004 02873, A02 2005 03227, A02 2007 00682, A02 2007 02976, A04 2002 00158, N109904, N110552, N111441, N111997, N115955, N117391, N118569, N121609, N121619).

The analysis focused on the 107 remaining cases.

- In 2 cases, aggression could have been triggered by other ADRs: convulsion (N132832), hyperammonaemia (N124313).
- In 2 cases, aggressive behaviour occurred after valproate withdrawal (A01 2003 05614, N128423).
- In 2 cases, aggressive behaviour occurred in children with developmental delay and multiple congenital anomalies after valproate exposure in utero (A01 2005 03969, A02 2003 03285).
- In 4 cases, a causal role of valproate was assessed as probable based on the recurrence of aggressive behaviour after reintroduction of valproate (A01 2004 04659, N104973, N103118, N124766).
- In 46 cases, a causal role of valproate could not be ruled out based on the chronology. However,
  - alternative aetiologies may be suggested as confounding factors in 19 cases: underlying brain injury (88005064), suspected paraneoplasic encephalopathy (N104486), previous episodes of aggression (A01 2006 02089, A02 2007 01238), suspected underlying depression (N100876), underlying psychosis and/or depression (A01 2004 05565, N108050, N108401), difficulty in social behaviour (N114627), stressfull family situation (N101960), underlying developmental delay or mental retardation (A01 2005 00444, N119246, N124898), Down's syndrome (A02 2006 02675), underlying autistic disorder (N108691), treatment for bipolar disorder or manic episode (A02 2002 02129, A02 2003 01279, A02 2004 00408, N130537).
  - concomitant drugs should also be considered in 6 cases: donepezil (A02 2004 02173), citalopram (A01 2002 01068), mirtazapine, zolpidem and alcohol in a context of interaction with valproate in a patient with explosive personality (A01 2005 00029), risperidone in a context of interaction with valproate (A01 2007 02241), escitalopram withdrawal (A01 2007 02308), lack of efficacy of methylphenidate administered for hyperactivity disorder (A02 2005 03116).
  - a context of valproate overdose (N108270, N108717), or an increase in daily dose of valproate (N100974, N117237, N125016) provided alternative explanations in 5 cases.
  - in 2 cases, the aggressive behaviour occurred just after administration of valproate instead of divalproex in a patient treated for bipolar disorder (A01 2007 03226) or just after a switch between two formulations of valproate (A01 2007 09014).
  - aetiological investigations, if any, were not provided in 14 cases (87005050, 89005032, 92005015, A01 2002 01646, A01 2003 01444, A01 2003 01749, A01 2004 03565, A01 2004 04345, A01 2006 06661, A02 2005 01770, N108997, N111150, N123092, N130795).
- In 18 cases, a causal role of valproate was assessed as unlikely as:
  - aggressive outbursts (A01 2004 00952), underlying intermittent explosive disorder (A01 2004 04055) and mental disability (A04 2006 00555) provided more likely aetiologies in 3 cases, in which chronology was not in favour of valproate;

Chronic overdose

- In 1 case, no reactions were reported (A01 2007 08345).
- In 1 case, the clinical picture was consistent with the side effects of valproate taken at the recommended dose or in overdose: parkinsonism (A01 2007 01951).
- In 2 cases, the clinical picture was not consistent with the reactions mentioned in the overdose section of the CCSI: bone marrow failure (A04 2007 01201), apnoea (A01 2007 10981).

Overdose NOS

- In 1 case, no reactions were reported (A01 2007 05561).
- In 1 case, the clinical picture was consistent with the side effects of valproate taken at the recommended dose or in overdose: thrombocytopenia (A01 2008 00470).
- In 1 case, the clinical picture was not consistent with the reactions mentioned in the overdose section of the CCSI: neuroleptic malignant syndrome in a context of multiple drug overdose (A01 2007 04600).

6.3.29 Reports of misuse, abuse and dependence

No relevant data were collected during the reference period.

6.3.30 Reports of use in a context of pregnancy or lactation

Ninety six (96) case reports of exposure during pregnancy or lactation were reported during the reference period of this report.

Use in a context of pregnancy

Ninety six (96) cases of exposure to valproate in a context of pregnancy were received during the reference period (Appendix 9).

- Congenital anomalies were reported in 28 cases. Valproate was administered during the whole pregnancy in 14 cases, during the first trimester in 2 cases and during an unspecified timeframe in 4 cases. In 8 cases, pregnancy was terminated by elective abortion.
- Congenital anomalies associated with developmental delay were reported in 8 cases. Valproate was administered during the whole pregnancy in 5 cases and during an unspecified timeframe in 3 cases.
- Developmental delay was reported in 3 cases. In all cases, valproate was administered during the whole pregnancy.
- Autism, autism spectrum disorders and Asperger's syndrome were reported in 7 cases (A01 2007 07311, A01 2007 09570, A01 2007 09936, A02 2007 01155, A02 2007 01393, A02 2007 02452, A02 2008 00288). In all the cases, valproate was administered during the whole pregnancy (see cumulative experience in Section 6.3.17, "Nervous system disorders").
- In 1 case, the baby was born with Down's syndrome (A01 2007 07765).

- Neonatal or infancy disorders were reported in 5 cases: fatal metabolic acidosis (A01 2008 00325), personality disorder and abnormal behaviour (A02 2008 00240), respiratory arrest, decreased heart rate, metabolic disorder, acidosis, muscle twitching (A01 2007 08001), neonatal respiratory distress syndrome (A02 2007 02691, A02 2008 00216).
- Intra-uterine death was reported in 2 cases (A01 2007 05834, A01 2007 07946).
- Spontaneous abortion, missed abortion and/or blighted ovum were reported in 6 cases (A01 2007 01427, A01 2007 07942, A01 2007 11979, A02 2007 00682, A02 2007 02976, A04 2007 00668) (see cumulative experience in Section 6.3.18, "Pregnancy, puerperium and perinatal conditions").
- 2 cases of induced abortion with no reported ADR in the foetus/embryo were reported (A01 2007 06018, A01 2007 06516).
- In 3 cases, no events were reported and neonates were born healthy (A01 2007 01854, A01 2007 02415, A01 2007 13963).
- In 14 cases, the pregnancies were still on-going or the final outcome of the pregnancy was not reported (A01 2007 03955, A01 2007 07566, A01 2007 13839, A01 2007 14024, A01 2008 00925, A02 2007 00554, A02 2007 00555, A02 2007 00699, A02 2007 01204, A02 2007 01707, A02 2007 02144, A02 2007 02294, A04 2007 00761, A04 2007 01334).
- In 17 cases, reactions occurred in the mothers treated with valproate during pregnancy: neutropenia and thrombocytopenia (A02 2007 03059), pancytopenia, agranulocytosis and post-partum haemorrhage (A02 2008 00219), nausea (A02 2008 00077), diarrhoea, vomiting, decreased blood electrolytes and confusional state (A04 2007 01835), accidental overdose without reaction (A01 2007 08345), pre-eclampsia, epilepsy and intra-uterine infection (A01 2007 04072), convulsion, vision blurred and urinary tract infection (A01 2007 08072), grand mal convulsion (A04 2007 00147), ectopic pregnancy (A01 2007 12002), polyhydramnios (A02 2007 00522, A02 2007 00770), premature labour (A02 2008 00224), suicidal ideation (A01 2007 06577), decreased vitamin B6 and decreased blood folate (A02 2007 00550, A02 2007 00552), decreased blood folate (A02 2007 00551), decreased vitamin B6 (A02 2007 00553), the last 4 cases were published in the same article.

Use in a context of lactation

No case reports of exposure during lactation were reported during the reference period of this report.

6.3.31 Reports of use in special patient groups

No relevant data were collected during the reference period.