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Sodium valproate (valproic acid)

MSF welcomes the rigorous and comprehensive review undertaken by the Independent Fetal Anticonvulsant Trust (INFACT) on the risks of the administration of sodium valproate in women of childbearing age.

Currently, valproic acid (sodium valproate) is listed in the WHO Model List of Essential Medicines (EML) in two different sections: section 5 anticonvulsants/antiepileptics (oral formulations in the core list in 1979 for epilepsy/seizure, injectable formulations in complementary list in 2015 for status epilepticus) and section 24.2.2 medicines used in bipolar disorders (since 1997).

Valproate-containing medicines have been approved world-wide to treat epilepsy and bipolar disorder. They are also used off-label for other conditions.
The teratogenicity of sodium valproate is well known and documented since it was marketed in the late 1970's. Early 1980s published reports have suggested that sodium valproate exposure of the foetus during pregnancy was associated with an increased risk for congenital malformations. The definition of "fetal valproate syndrome" (FVS) including neural tube defects such as spina bifida, facial features such as cleft lip and/or cleft palate, cardiovascular abnormalities, genitourinary abnormalities, endocrine disorders, and skeletal abnormalities was made in the mid 1990's.

In 2013, the prospective observational NEAD study, involving 25 epilepsy centres in the UK and the USA, following children until 6 years of age showed that fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across a range of domains.
A British study published also in 2013 has reported a six times increased prevalence of neurodevelopmental disorders for children with a prenatal sodium valproate exposure. The most common neurodevelopmental disorder, at six years of age, for sodium valproate exposed children, was autistic spectrum disorders.
Epidemiological studies have demonstrated that children exposed to sodium valproate in utero have lower cognitive test scores than children exposed to either another anticonvulsant in utero or to no anticonvulsant in utero.
In 2019, the European Reference Network for Congenital Malformations and Intellectual Disability propose the term Fetal Valproate Spectrum Disorder (FVSD) to refer to the range of clinical and developmental effects attributed to exposure to sodium valproate in utero. Autistic Spectrum disorders, speech and language problems, memory difficulties can be observed after sodium valproate exposure during pregnancy.

EMA's position on valproate-containing medicines:

In 2018, the Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that women using sodium valproate should use effective contraception and recommended that sodium valproate use during pregnancy should be restricted to women with epilepsy who are unresponsive to other drugs.
In 2018, the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed new measures to avoid fetal exposure to valproate-containing medicines, due to the high risk of malformations and developmental problems.
The new measures include a ban on the use of valproate-containing medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available.
Valproate-containing medicines are contraindicated in any woman of childbearing age unless the conditions of a new pregnancy prevention programme are met. The programme is designed to ensure that patients are made fully aware of the risks and the need to avoid becoming pregnant. A visual warning of the pregnancy must also be placed on the packaging of the medicines and warnings be included on patient cards attached to the box and supplied with the medicine.
PRAC and CMDh agreed that despite previous recommendations aimed at better informing patients of the risks with valproate-containing medicines, women were still not always receiving the right information in a timely manner.

FDA's position on valproate-containing medicines:

In 2009, the FDA notified health care professionals and patients about the increased risk of neural tube defects and other major birth defects, such as craniofacial defects and cardiovascular malformations, in babies exposed to valproate-containing medicines during pregnancy. Healthcare practitioners should inform women of childbearing potential about these risks, and consider alternative therapies, especially if using valproate-containing medicines to treat migraines or other conditions not usually considered life-threatening.
Women of childbearing potential should only use valproate if it is essential to manage their medical condition. Those who are not actively planning a pregnancy should use effective contraception, as birth defect risks are particularly high during the first trimester, before many women know they are pregnant. A valproate Medication Guide, provided with each outpatient prescription, will explain the benefits and risks of valproate and encourage patients to discuss options with their healthcare professional.
In 2011, the FDA notified healthcare professionals that children born to mothers who take valproate-containing medicines during pregnancy have an increased risk of lower cognitive test scores than children exposed to other anti-seizure medications during pregnancy. Healthcare professionals should weigh the benefits and risks of valproate when prescribing this drug to women of childbearing age, particularly when treating a condition not usually associated with permanent injury or death. Alternative medications that have a lower risk of adverse birth outcomes should be considered.

In 2013, the FDA contraindicated valproate-containing medicines for migraine prevention in pregnant women due to decreased IQ scores in exposed children. With regard to women of childbearing age who are not pregnant, valproate-containing medicines should not be taken for any condition unless the drug is essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking valproate-containing medicines should use effective birth control.

MSF would like to draw the attention of the Expert Committee to the following points:

- According to WHO, nearly 80% of people with epilepsy live in low- and middle-income countries and three quarters of these people do not get the treatment they need as there is low availability of antiepileptic medication.
- Absence of treatment in epilepsy is associated with increased mortality and morbidity risks. The use of sodium valproate in women of childbearing age requires a careful evaluation of the benefit of treatment and the risk of teratogenic effects. The balance of risk/benefit should be systematically evaluated before prescription. Information on the risks and recommendations on contraception should be provided to all women of childbearing age. Access to contraception should be ensured.
- MSF recommends that risk/benefit balance be carefully assessed in all woman of childbearing age and in all pregnant women before initiation of antiepileptic medicines with potential teratogenic effects. In its programs, MSF recommends that women of childbearing age with epilepsy should have seizures controlled as well as possible with the minimum dose of antiepileptic medicine taken in monotherapy, wherever possible. Polytherapy and sodium valproate should be avoided if possible.
  In women of childbearing age, MSF recommends levetiracetam as drug of choice but levetiracetam is not included in the EML and therefore not widely available. In the absence of levetiracetam, carbamazepine can be an option, although it is not indicated in some forms of epilepsy (absence seizures). Lamotrigine is another option, although its initiation requires a gradual dose titration, with close follow-up difficult to implement in some settings. Levetiracetam doesn’t require any gradual dose titration, therefore no close follow-up during initiation and presents fewer drug interactions with antiretrovirals than other antiepileptic medicines. If using sodium valproate is absolutely necessary as there is no other option, an effective contraception (such as with an intrauterine device) is strongly recommended.

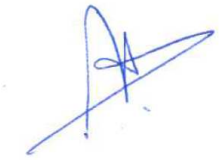
  MSF recommends that any antiepileptic treatment in pregnant women should be carefully considered and if antiepileptic medicine is necessary, initiation with sodium valproate should be avoided. If the treatment with sodium valproate was started before pregnancy, an alternative anticonvulsant should be chosen in order to replace sodium valproate.

- As some antiepileptic medicines are powerful enzymatic inducers, drug interactions between hormonal contraceptives and antiepileptic medicines may impact the birth control success in women of childbearing age, therefore contraception should be chosen according to this risk.
- In some settings, many women will not be able to access family planning, therefore an alternative to sodium valproate should be offered to all women of childbearing age in all settings.
- As levetiracetam, carbamazepine and lamotrigine, possible alternatives to sodium valproate, are not widely available, especially in low-and middle-income countries (LMICs), availability and affordability of these medicines should be promoted, in order to allow therapeutic options for the treatment of epileptic women of childbearing age.
- The inclusion of levetiracetam in the EML should be considered, and affordability and availability of various antiepileptic medicines in LMICs should be improved, in order to allow some therapeutic options for the treatment of epileptic women of childbearing age.

MSF has been using sodium valproate in its programs since 2003.

MSF urges the 23rd Expert Committee to consider all these elements when making a decision on the proposal of the Independent Fetal Anticonvulsant Trust (INFACT) regarding sodium valproate.

For Médecins Sans Frontières



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