Valproate: new measures aimed to limit exposure during pregnancy and to inform health professionals and patients.

Compared to other antiepileptics, valproate is associated with definitely higher risks for the unborn baby in case of administration during pregnancy. After first trimester exposure, the risk of malformations raises to about 10%, i.e. 3 to 4 times the basal risk of spontaneous abnormalities. In addition, neurodevelopmental disorders are observed in up to 30-40% of exposed children, with average intellectual quotients and development scores being significantly lower than in unexposed children [1]. An increased risk of autism and related disorders has been reported as well [2].

Such risks for unborn children were gradually recognized after the commercialization of valproic acid and are known since many years. The "Depakine case" in France mainly addresses the issue of the time span that separated the discovery of these risks and their consideration by drug makers and agencies. It is worth remembering that until the 1990s, very few antiepileptics were available with an effectiveness comparable to valproate, especially against "Grand Mal" epilepsy. As seizures themselves are dangerous for the fetus, drug-related risks were considered acceptable if the treatment allowed the control of epilepsy. Since then, new molecules emerged that associate good therapeutic efficacy with improved reproductive safety. Simultaneously, the risks of valproate became better appreciated. This progressively led to the current evaluation that in young female patients, the use of valproate should be limited to the small minority of cases whose disease remains poorly controlled with other anti-epileptics preferable as first-line treatment. It took time though to manufacturers, authorities, pharmacists and prescribers before they adopted this position. By the way, risks of malformations and fetal adverse effects are reported with most antiepileptics – although their actual level of dangerousness is lower than for valproate.

The EMA has recently re-evaluated the risks related to valproate exposure during pregnancy. Like European authorities, Swissmedic also strengthened the warning [3]. Both healthcare professionals and patients are to be offered a specific information booklet. The aim is to minimize the number of avoidable exposures to valproate during pregnancy, and to bring up-to-date information to all concerned patients. This comes along with a "informed consent form" to be signed by both the prescriber and the patient, aimed at documenting the communication of relevant elements to the patient.

Practically, the prescription of valproate in women of childbearing age requires effective contraception and should only be considered if

therapeutic alternatives are ineffective. Regular reassessment of the treatment is essential, especially if pregnancy comes into consideration. If valproate can not be replaced, it must at least be associated with a prevention of neuraxial abnormalities by folic acid.

References :

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