SHOULD VALPROATE BE PRESCRIBED TO WOMEN OF CHILDBEARING AGE?

A. Guekht, Russia
Russian National Research Medical University; Moscow City hospital №8 for Neuropsychiatry

Unsurpassed efficacy and broad spectrum of valproate. Valproic acid was the first true broad-spectrum AED to become available; it is highly effective in the treatment of primarily generalized seizures, such as absence seizures, generalized tonic–clonic seizures and myoclonic seizures. In a study of standard and new antiepileptic drugs (SANAD) (Marson et al., 2007) VPA was compared with lamotrigine and topiramate for generalized and unclassifiable epilepsy; valproate was better tolerated than topiramate and more efficacious than lamotrigine, and was recommended as drug of first choice in many patients with these epilepsies.

The response to valproic acid in patients with juvenile myoclonic epilepsy is excellent. Lamotrigine has been considered as an alternative, but its efficacy has not matched that of valproic acid, and it can exacerbate myoclonic seizures, which has not been reported for valproic acid.

In addition to its place in the treatment of epilepsy, valproic acid has gained acceptance in the treatment of the ***number of conditions,*** such as affective disorders in psychiatry and the prophylaxis of migraine headaches.

In fact, ***long-term remission*** is the goal of AED treatment. Most studies report that patients with a satisfactory seizure control before pregnancy are less likely to deteriorate than patients with uncontrolled epilepsy (Vajda et al., 2008). In the treatment of epilepsy during pregnancy, maternal and fetal risks associated with uncontrolled seizures need to be weighed against the increased risk of adverse outcomes in the offspring due to maternal use of AEDs. ***Epileptic seizures in a pregnant woman may have adverse effects on the fetus, in addition to risks for the woman***. With respect to the risks to the fetus, generalized tonic–clonic seizures are especially unfavourable. (Tomson, Hiilesmaa, 2007).

For some patients, valproate is the only medication that adequately controls seizures. Such women should be informed of the potential risks associated with the use of this medication in pregnancy. If a woman taking valproate is already pregnant, it is critical that she not stop valproate without consultation with her physician, since stopping an antiepileptic drug could lead to seizures and serious consequences for both the woman and her fetus (Meador et al., 2009).

Concerns regarding the use of VPA in women of childbearing age with IGE were expressed in many studies (Crawford, 2005; Wyszynski et al., 2005; Morrow et al., 2006; Bromfield et al., 2009, Pennel, 2009). However, there was an obvious a dose-relationship for VPA, with an increased ***risk for MCMs with VPA doses only above approximately 1,000 mg/day*** (Mawer et al., 2002; Artama et al., 2005). In fact, no threshold dose at which risk significantly increased could be identified, although ***there was a strong trend toward lower risk at <750 mg/day*** (5.5% versus 15.1% for doses >750mg/day, p = 0.063) (Bromfield et al., 2008).

Several studies confirmed that intrauterine exposure to VPA ***reduces cognitive outcome*** (Adab et al., 2001; 2004; Gaily, 2004). The prospective multicenter study in the USA and the UK (Meador et al., 2009) demonstrated that in utero exposure to VPA, as compared with other AEDs, is associated with an increased risk of impaired cognitive function at 3 years of age.

However, associations between the use of valproate in pregnancy and lower IQ in the offspring are dose-dependent, so ***lower doses may be safe*** and children exposed to valproate doses <1,000 mg/day did not differ in IQ from those exposed to other AEDs (Meador et al., 2009).

Relatively low and probably safe in terms of teratogenicity and cognitive outcome for offsprings doses are used in the significant proportion of patients with IGE.

Indeed, there is a choice of new AEDs for treatment of epilepsy in patients of child –bearing age. As stated in the recent EURAP report (Tomson et al., 2011),the lowest rates of malformation with less than 300 mg per day lamotrigine and less than 400 mg per day carbamazepine was noted. Compared with lamotrigine monotherapy at doses less than 300 mg per day, risks of malformation were significantly higher with valproic acid and phenobarbital at all investigated doses, and with carbamazepine at doses greater than 400 mg per day.

However, ***alternative drugs also raise some concerns.*** For instance, pharmacokinetic alterations of LTG (Tomson, Battino, 2007; Pennell, 2008): in some patients, serum concentrations may decline in late pregnancy to 30% of prepregnancy levels with normalization

within a few days post partum. Such alterations in serum concentrations have frequently been associated with deterioration in seizure control.

Conclusion: Epilepsy has specific implications for women, both on account of the effects of epilepsy and AEDs on the reproductive cycle and on the unborn child and because of the effects of pregnancy and hormonal changes on the epilepsy. The issue of teratogenicity has received considerable attention.

The choice of AED should always be a mutual decision of the doctor and the woman of childbearing potential, based on the discussion of the risks and benefits of all the appropriate AEDs available.

It is reasonable to recommend one of the new AEDs as initial treatment of IGE. However, it should be recognized that for some patients, valproate is the only medication that adequately controls seizures. If valproate is used in a woman of childbearing potential, the lowest effective dose should be employed, as valproate's teratogenic risk is dose dependent.

Key references:

Artama M et al.. Neurology 2005; 64(11):1874-8
Marson AG et al. The Lancet 2007; 369-1016-26.
Meador KJ et al., N Engl J Med 2009 ; 360(16):1597-605
Morrow J et al. J Neurol Neurosurg Psychiatry 2006; 77(2):193-198
Pennell PB et al. Neurology 2008; 70: 2130–2136
The treatment of epilepsy / eds. Simon Shorvon, Emilio Perucca, Jerome Engel. – 3rd ed. 2009
Tomson T, Hiilesmaa V. BMJ 2007; 335: 769–773.
Tomson T. et al. Lancet Neurol. 2011 Jul;10(7):609-17
Tomson T, Battino D. Clin Pharmacokinet 2007; 46: 209–219.
Vajda FJE et al., Epilepsia 2008; 49: 172–176.
Wyszynski DF et al., Neurology 2005; 64(6):961-5.