Teaching Course 7

Treatment of women with epilepsy - Level 1-2

Teratogenic and other considerations in the selection of antiepileptic drugs in girls and women

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Introduction and background

Efficacy, safety and tolerability are the main criteria by which antiepileptic drugs (AEDs) are selected. While there are no indications of gender differences in AED efficacy, selection of AEDs for females of childbearing potential nevertheless require special considerations. These include interactions between AEDs and contraceptive methods, teratogenic risks with AEDs, impact of pregnancy on the pharmacokinetics and possibly efficacy of AEDs.

Interactions between AEDs and contraceptives

There is a bidirectional pharmacokinetic interaction between AEDs and oral contraceptives [Reimers et al.2015]. Enzyme-inducing AEDs (carbamazepine, eslicarbazepine-acetate, felbamate, lamotrigine, oxcarbazepine, phenobarbital, primidone, phenytoin, rufinimide, topiramate at dosages >200 mg/day) may reduce the effectiveness of oral contraceptives by induction of the metabolism of the oestrogen and progestagen components, and possibly also by increasing the hepatic synthesis of SHBG, thus decreasing the unbound, active concentration of progestagen. This can affect the combined oral contraceptive, the combined contraceptive patch, the combined contraceptive vaginal ring, the progestogen only pill, the progestogen implant, and the postcoital contraceptive, and may lead to contraceptive failure and an increased frequency of unplanned pregnancies. For women that rely on these contraceptive methods, selection of a non-enzyme inducing AED may be preferable. There are, however, contraceptive methods that are unaffected by enzyme inducers, e.g. depot injections of medroxyprogesterone, hormone-releasing intrauterine systems and other intrauterine contraceptive devices. Tricycling is another alternative for
women prescribed enzyme-inducing AEDs -ie the use of a combined oral contraceptive, usually in an at least 50 µg dosage, given continuously for three sets of 21 days followed by 7 days’ pause.

Estradiol-containing oral contraceptives induce the elimination of lamotrigine leading to decline in lamotrigine serum concentrations by approximately 50%. These changes occur rapidly and lamotrigine levels rise during the pill-free week if sequential pills are used [Reimers et al 2015]. Given these effects, lamotrigine is not an optimal choice for women that use combined oral contraceptives sequentially. Pure progestagen-containing pills do not seem to affect lamotrigine serum concentrations. However, since lamotrigine can reduce slightly the bioavailability of gestagens, low dose pure progestagen pills (mini pills) might not be fully effective. It has therefore been suggested that for women taking lamotrigine, the combined contraceptive pill can be used with tricycling or continuous use to avoid fluctuations in lamotrigine serum concentrations during the pill free weeks.

**Teratogenic risks with AEDs**

A major concern in the selection of an AED for girls and young women is the risk of adverse effects on the fetus of maternal drug use in future pregnancies. Given the high rate of unplanned pregnancies this needs to be taken into account when treatment is initiated in every girl and woman. Potential adverse fetal effects include intrauterine growth retardation, major congenital malformations (MCM), impaired postnatal cognitive development, and adverse effects on behavioural development [Tomson and Battino 2012]. Since AEDs differ in their teratogenic potential, this has a major impact on drug selection.
Growth retardation

Reductions in birth weight, body length and head circumference in the offspring of women treated with AEDs have been reported in studies since the 1970’s [Tomson and Battino 2012]. Most studies report a more pronounced effect in infants exposed to polytherapy. With respect to specific AEDs in monotherapy some report carbamazepine to be associated with a small head circumference. More recent studies based on Scandinavian Health Registers have demonstrated small head circumference and increased risk of small for gestational age in association with maternal use of topiramate [Vejby et al 2014].

Major Congenital Malformations

In 1968 Meadow reported oro-facial clefts and other abnormalities among babies of mothers who received primidone, phenytoin, or phenobarbital (Meadow 1968). Over the more than 50 years since this first report of birth defects in children exposed in utero to AEDs, subsequent studies have confirmed higher birth defects rates among children of mothers with epilepsy. A pooled analysis of data from 26 studies reported an MCM rate of 6.1% in offspring that had been exposed to AEDs compared to 2.8% in children of untreated women with epilepsy, and 2.2% in offspring of mothers without epilepsy (Tomson and Battino 2012).

A large number of retrospective and prospective cohort studies have confirmed an increased frequency of MCMs in offspring of women treated with AEDs. The prevalence of major congenital malformations has ranged from 4% to 10%, corresponding to a two- to fourfold increase compared with the expected [Tomson and Battino 2012; Tomson et al., 2015]. Differences in treatment strategy, study populations, controls and criteria for malformations can account for the variation in outcome. More recent
population-based register studies have indicated a more limited increase in risk with AED exposure. A nation-wide Norwegian study found an overall malformation rate of 3.4% among 2,309 children of mothers taking AEDs as monotherapy during pregnancy compared to 2.9% in the general population [Vejby et al., 2014], OR 1.27 (1.02–1.59).

The critical issue for drug selection is whether there are differences in MCM risk between different AEDs. Important such differences have become apparent from prospective epilepsy and pregnancy registers during the last decade. These are observational studies that have collected thousands of pregnancies with AED use and published rates of major congenital malformations with different AED monotherapies summarized in Table 1 [Tomson et al 2015]. The prevalence of MCMs among children exposed to carbamazepine and lamotrigine is consistently fairly low, whereas rates are higher in association with valproic acid than with carbamazepine or lamotrigine. Emerging data also indicate low MCM rates with levetiracetam, whereas there are signals indicating higher risks with topiramate exposure (Table 1).

The drug dosage also needs to be considered in any comparison. A dose-effect relationship has been demonstrated for valproic acid in all three major registries, albeit with different cut-offs for the lowest risks. In the EURAP registry the lowest risk (5.6%) was observed with valproic acid doses at conception below 700 mg/day and with greater risk (24.2%) with doses of 1500 mg/day and above. In the UK Ireland Register the lowest risk with valproic acid (5%) was observed in association with doses up to 600 mg/day, and in the North American Registry at doses up to 500 mg/day. The UK Ireland Register found a dose-effect also with carbamazepine and EURAP with carbamazepine, lamotrigine and
phenobarbital, i.e. all the monotherapies included in the analysis. In earlier studies, polytherapy has been considered to be associated with greater risk for major congenital malformations than monotherapy. The risk with polytherapy, however, depends more on whether valproic acid is included in the AED combination than on the number of AEDs [Holmes et al., 2011].

The types of MCMs differ between drugs. A pooled analysis of data from 21 prospective studies looked at four different groups of MCMs (cardiac, neural tube defects, oro-facial clefts, and hypospadias) associated with monotherapy exposure to the five most commonly used AEDs in these studies (Tomson and Battino, 2012). Cardiac malformations were the most frequent of the four MCMs for carbamazepine, lamotrigine, barbiturates, and phenytoin, whereas neural tube defects were the most common for valproic acid. Cardiac malformations appeared more frequently with barbiturates than with any of the other AEDs, whereas neural tube defects and hypospadias were more prevalent with valproic acid than with the other AEDs.

Although AED exposure is the major cause of increased risk, recent data have also confirmed that individual susceptibility and probably genetic factors are of importance. In the EURAP study, parental major malformations was associated with a four-fold increase in risk of malformations in the offspring [Tomson et al., 2011]. Recent data from the UK Ireland and Australian pregnancy registers have also demonstrated that women whose last pregnancy resulted in a fetal malformation have a substantially increased risk of having further malformed foetuses if they become pregnant again while taking the same AED[Vajda et al., 2013].
Postnatal cognitive and behavioural development

Adverse effects of fetal exposure to AEDs on cognitive and behavioural development have been discussed in more detail in a separate contribution to this teaching course. Although very important for AED selection, it will only be discussed briefly here. Recent prospective observational studies have clearly demonstrated that exposure to valproic acid at high dose is associated with specific adverse cognitive effects, different from outcomes after exposure to carbamazepine, lamotrigine, phenytoin and probably levetiracetam. The exposed child’s IQ, corrected for maternal IQ, at age 6, was lower after exposure to valproic acid (mean 97, 95% CI 94-101) than to carbamazepine (105, 102-108), lamotrigine (108, 105-110), or phenytoin (108, 104-112). However, children exposed to valproic acid at doses below 1,000 mg/day had an IQ comparable to those exposed to other AEDs (Meador et al., 2014). A prospective study from UK, with partly overlapping cohorts with the NEAD study, confirmed a lower mean IQ in children exposed to valproic acid compared with children exposed to carbamazepine or lamotrigine, and with control children of healthy mothers [Baker et al., 2015]. The outcome in terms of the child’s IQ was also in this study dose-dependent, with no reduction in overall IQ with maternal use of valproic acid at doses <800 mg/day. However, even a low dose of valproic acid was associated with deficits in verbal abilities compared with controls.

A register-based register study from Denmark identified an association between maternal use of valproic acid during pregnancy and the risk of autism in the child [Christensen et al., 2014]. Compared with unexposed, the hazard ratio for autism spectrum disorder was 2.9 for children exposed to valproic acid, and for childhood autism 5.2. No other AED was associated with an increased risk for autism or autism spectrum disorder.
Pharmacokinetics of antiepileptic drugs during pregnancy

The pharmacokinetics of many drugs changes significantly during pregnancy, which can affect maternal seizure control as well as have consequences for fetal drug exposure [Tomson et al., 2013]. The extent to which pregnancy affects drug serum concentrations vary with the AED but also between individuals. While active drug concentrations remain fairly stable for valproic acid and carbamazepine, a pronounced decline is often seen with lamotrigine, and to a slightly lesser extent with levetiracetam and oxcarbazepine. In some patients, serum concentrations of lamotrigine decline in late pregnancy to 30% of prepregnancy levels with normalization within a few days post partum. Such alterations in serum concentrations may be associated with deterioration in seizure control (Tomson et al, 2013). Prospective data from EURAP suggest that compared to carbamazepine, and valproic acid fewer pregnancies on lamotrigine are fully controlled in terms of seizures (Battino et al., 2014).

Data on pharmacokinetics during pregnancy are lacking completely for some of the newer generation AEDs: pregabalin, lacosamide, retigabine, and eslicarbazepine acetate.

Since there is a marked individual variation in the effect of pregnancy on AED levels, monitoring drug levels is generally recommended in particular for AEDs such as lamotrigine, levetiracetam, and oxcarbazepine. When pregnancy is planned in advance, it is therefore advisable to obtain serum drug concentrations before pregnancy, when seizure control is optimal, in order to establish a reference to be used for comparison purposes.
Implications for the selection of AEDs for girls and women

The rate of unplanned pregnancies in the general population is high and the first contact with health-care providers is frequently late. Therefore, issues related to management during pregnancy will have implications for the treatment of women of child-bearing potential with epilepsy in general. Furthermore, the pharmacokinetic interactions with oral contraceptives, as well as developmental toxicity of AEDs, need to be included in the overall risk-benefit equation, which should be the basis for decisions on when and how to treat epilepsy in girls and young women. If treatment is indicated, it is particularly important in this patient group to aim at monotherapy with the lowest effective dosage. When treatment is initiated in a woman of child-bearing potential, information must be given concerning drug effects on oral contraceptives, when appropriate, as well implications in relation to pregnancy.

Valproic acid should be avoided to women of childbearing potential unless seizures cannot be controlled by other appropriate AEDs (Tomson et al., 2016). In focal epilepsies several effective alternatives exist including carbamazepine, lamotrigine, and levetiracetam. Carbamazepine and lamotrigine have the most extensive data on safety in pregnancy. The pronounced change in drug levels during pregnancy is a disadvantage of lamotrigine and levetiracetam, in particular if drug level monitoring is unavailable. Levetiracetam has the advantage of lack of interactions with contraceptives in cases where this might be a problem. In generalized epilepsies, the alternatives to valproic acid are more limited and with less robust efficacy data. However, levetiracetam and lamotrigine are probably the most reasonable alternatives, whereas some caution is called for with topiramate considering the signals of teratogenic effects.
### Table 1.
Overall rates (%) of major congenital malformations (malformed/exposed) for different monotherapies. Data from different prospective registers

<table>
<thead>
<tr>
<th>Source</th>
<th>General population</th>
<th>Untreated epilepsy</th>
<th>Valproate</th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
<th>Phenobarbital</th>
<th>Phenytoin</th>
<th>Levetiracetam</th>
<th>Oxcarbazepine</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURAP</td>
<td></td>
<td></td>
<td>9.7% (98/1010)</td>
<td>5.6% (79/1402)</td>
<td>2.9% (37/1280)</td>
<td>7.4% (16/217)</td>
<td>5.8% (6/103)</td>
<td>1.6% (2/126)</td>
<td>3.3% (6/184)</td>
<td>6.8% (5/73)</td>
</tr>
<tr>
<td>NAAPR</td>
<td>1.1% (5/442)</td>
<td>9.3% (30/323)</td>
<td>3.0% (31/1033)</td>
<td>1.9% (31/1562)</td>
<td>5.5% (11/199)</td>
<td>2.9% (12/416)</td>
<td>2.4% (11/450)</td>
<td>2.2% (4/182)</td>
<td>4.2% (15/359)</td>
<td></td>
</tr>
<tr>
<td>UKIre</td>
<td>6.7% (82/1220)</td>
<td>2.6% (43/1657)</td>
<td>2.3% (49/2098)</td>
<td></td>
<td>3.7% (3/82)</td>
<td>0.7% (2/304)</td>
<td></td>
<td></td>
<td>4.3% (3/70)</td>
<td></td>
</tr>
<tr>
<td>AUS</td>
<td>3.3% (5/153)</td>
<td>13.8% (35/253)</td>
<td>5.5% (19/346)</td>
<td>4.6% (14/307)</td>
<td></td>
<td>2.4% (1/41)</td>
<td>2.4% (2/84)</td>
<td>5.9% (1/17)</td>
<td>2.4% (1/42)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2.
Rates of major congenital malformations (95% CI) with monotherapy with valproate, carbamazepine, and lamotrigine at different dose levels in EURAP and UK Ireland Registers

<table>
<thead>
<tr>
<th>Drug</th>
<th>EURAP</th>
<th>UK Ireland</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose range mg/d</td>
<td>Number of exposed</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 700</td>
<td>431</td>
<td>5.6% (3.60-8.17)</td>
</tr>
<tr>
<td>≥ 700 &lt; 1,500</td>
<td>480</td>
<td>10.4% (7.83-13.50)</td>
</tr>
<tr>
<td>≥ 1,500</td>
<td>99</td>
<td>24.2% (16.19-33.89)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>&lt;400</td>
<td>3.4% (1.11-7.71)</td>
</tr>
<tr>
<td>≥ 400 &lt; 1,000</td>
<td>1047</td>
<td>5.3% (4.07-6.89)</td>
</tr>
<tr>
<td>≥ 1,000</td>
<td>207</td>
<td>8.7% (5.24-13.39)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>&lt;300</td>
<td>2.0% (1.19-3.24)</td>
</tr>
<tr>
<td>≥ 300</td>
<td>444</td>
<td>4.5% (2.77-6.87)</td>
</tr>
<tr>
<td></td>
<td>≥ 400</td>
<td>&gt;400</td>
</tr>
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</table>
Disclosure:

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References

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