Initial Therapy for Epilepsy – A Focus on Pre-menopausal Women

an interview with

James Morrow

Consultant Neurologist, Royal Victoria Hospital and Hononary Reader, Queen's University, Belfast

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Q: Women of child-bearing age and pre-menopausal women – what are the main considerations for initiating antiepileptic therapy?

Dr James Morrow: The primary considerations for antiepileptic therapy in men and women are similar vis-à-vis efficacy. Everybody wants an effective drug that will abolish seizures. The choice of drug in this respect often depends on seizure type. Balanced against this is tolerability, so the drug also needs to have few or no side effects.

Women present a special complexity in terms of tolerability because there are several issues to consider and the weighting of these issues may change over time. For example, for a young person – a teenager – going onto antiepileptic drugs (AEDs), compliance is important: a drug that is taken once or twice a day has an advantage over one that is taken many times a day.

Cognitive issues will also be important. However, as women get older it is important to consider interactions with the oral contraceptive pill, as well as fertility issues: for instance, there are some potential linkages with conditions such as polycystic ovary syndrome (PCOS). Some drugs have been shown to have a higher teratogenic potential than other drugs, and there is also evidence of a long-term risk to bone health with some AEDs. No drug as yet ticks all the boxes all the way through the various ages, so the emphasis changes over time as well as for particular individuals.

What are the risks of taking antiepilepsy medication while pregnant?

I help to run the UK Epilepsy and Pregnancy Register, which is one of four major epilepsy pregnancy registers worldwide. It has been running for 11 years now and useful information is just starting to emerge. One always has to accept the codicil that these registers are not randomised controlled trials and therefore there may be inherent biases. Nevertheless, they do seem to demonstrate that there are potential differences among the AEDs in terms of risk of major congenital malformations.

James Morrow is a Consultant Neurologist at the Royal Victoria Hospital, Belfast and Honorary Reader, Queens University, Belfast, and has been Lead Clinician in Neurology and Clinical Director of Neurosciences in Northern Ireland from 2001. He co-ordinates the Northern Ireland Epilepsy service and, in conjunction with a team of specialist epilepsy nurses, runs dedicated epilepsy clinics providing pre-conceptual advice and a joint epilepsy/obstetric service. Dr Morrow is published widely in the field of epilepsy and is the principal investigator for the UK Epilepsy and Pregnancy Register.

E: jim.morrow@belfasttrust.hscni.net

So far the spotlight has shone on sodium valproate. The UK register highlights the fact that sodium valproate is associated with a significantly higher risk of having a child with major malformation than, for instance, carbamazepine or lamotrigine.

However, one should always emphasise that, although there is a higher risk, that risk is only between 6 and 7%: in other words, a woman taking sodium valproate still has at least a 93% chance of having a perfectly normal child (better odds, incidentally, than those reported for valproate–lamotrigine polytherapy). Therefore, the results are generally reassuring, but there are differences, which raises the potential of being able to reduce risk.

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The larger issues with major congenital malformations concern delay in cognitive and behaviour development. There are studies emerging from Gus Baker's group in Liverpool, and we have a paper in the pipeline, that show that children exposed to sodium valproate *in utero* seem to have higher levels of neurodevelopmental, cognitive or behavioural delay than do other children. This is an issue that is going to emerge over the next few years and may be another reason for choosing one drug over another.

Can you elaborate on the differences between the older and newer drugs?

Carbamazepine and sodium valproate are considered the older drugs while lamotrigine is considered a new drug, but the latter has been around for 15 years. They are not true equivalents, however: women who take sodium valproate cannot easily switch to carbamazepine as the two drugs are used for different types of epilepsy.

Lamotrigine is considered an alternative to sodium valproate and has really grown in popularity in the UK. It is now considered to be one of the first-choice drugs for young women, but it has its drawbacks, namely that it is not easy to use: it has to be initiated slowly, and some people are allergic to it.

Once you get past those parameters, it is generally well tolerated. However, there is evidence to suggest that blood plasma levels may drop quite precipitously, resulting in seizure breakthrough in some individuals during pregnancy. There is also evidence that it may affect and be affected by the pill, and that it may not be as effective as sodium valproate for some of the primary generalised epilepsies. Therefore, it also is not as direct an alternative to sodium valproate as was recently thought.

What about the choices available for partial epilepsy in terms of pregnancy?

Carbamazepine comes out very well with a relatively low major congenital malformation rate, but it has other problems. There is evidence in the literature to suggest that neurodevelopment delay may be associated with this drug. It also interferes with the contraceptive pill and is a hepatic enzyme inducer, so interactions are generally common. Hepatic enzyme inducers also pose a longer-term issue: they may be associated with an increased risk of osteoporosis.

> The suspicion of osteoporosis has largely been on the older hepatic-enzyme-inducing drugs such as phenytoin, phenobarbital and, to a lesser degree, carbamazepine.

In terms of drugs other than carbamazepine, lamotrigine ticks some of the boxes, but not all of them. Levetiracetam, which is one of the newest drugs, does look to be a very effective broad-spectrum AED. It does not seem to interfere with the pill and is generally well tolerated. Just last year we published some preliminary results for levetiracetam in pregnancy that are encouraging, but the numbers are not sufficient to be absolutely certain. Nevertheless, we have high hopes for this drug.

Are antiepileptics that are metabolised by the P450 system linked to an increased risk of osteoporosis?

There are papers that suggest that people with epilepsy in general have a higher risk of osteoporosis. The suspicion of osteoporosis has largely been on the older hepatic-enzyme-inducing drugs such as phenytoin, phenobarbital and, to a lesser degree, carbamazepine. However, there are other papers that suggest that osteoporosis is more common in women taking sodium valproate, which does not induce the P450 system.

Many of the papers are by necessity retrospective. A lot of them are compiled from people with epilepsy presenting with fractures, but fractures are not necessarily caused by osteoporosis. That will bring in biases within these papers. I think there is evidence to suggest that these particular AEDs may pose a risk with regard to bone health. The jury is still out on whether some are safer than others. From a theoretical point of view one might prefer not to use hepatic-enzyme-inducing drugs, but there is definitely a need for long-term controlled studies.

What about catamenial seizures?

Catamenial seizures occur in certain parts of the menstrual cycle. There are a number of studies that have published on catamenial seizures, but they remain a little controversial.

Catamenial seizures certainly exist; however, more women believe they have catamenial epilepsy than actually do. It all depends on how you define exactly what catamenial seizures are: most people define them as occurring within a few days of the menstrual period, but depending on the time period included, you can potentially include a lot of people.

There is evidence to suggest that oestrogen is a convulsive agent and progesterone is an anticonvulsive agent, so there are hormone links. There may also be an effect of fluid retention or other psychological issues around that time. There are lots of contributory factors and there are various manipulations drug-wise that can be used to deal with it.

Once catamenial seizures have been diagnosed, one of the best approaches is to try to time additional antiepileptic therapy with the expected seizures. One of the common drugs that is used is clobazam, which is given for a few days around the time of expected seizure increase.

Is there a link between antiepileptic drug choice and polycystic ovary syndrome?

There has been a lot of work by Professor Isojärvi in Finland, who highlighted an apparent increase in the incidence of PCOS in women taking sodium valproate compared with women taking carbamazepine or lamotrigine. The link is controversial.

Many of the papers were retrospective and contained quite small numbers. And again there is the issue of definition of the syndrome as opposed to purely polycystic ovaries. I think there probably is a link, but how strong that link is I could not say. A lot more work needs to be done in this area.

What kind of strategies should a doctor consider to reduce the risk of birth defects?

The key is planning prior to conception. If the drug therapy needs to be altered to try to minimise or reduce risk, then that must be done well in advance of the pregnancy. All too often women present already in the early stages of pregnancy, but by that stage it is inadvisable to change AED therapy because it will probably only make things worse rather than better. Organogenesis occurs within the first trimester, so by the time the AEDs have been reduced or changed the

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- Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy
- Adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy

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*Keppra® achieved high seizure-freedom rates during the following Phase III trials: Monotherapy for partial onset seizures in newly diagnosed adults (≥16 years of age): 73% (173/237) ≥6 months[2]; Adjunctive therapy for PGTC seizures in patients ≥4 years of age with IGE: 34% (27/79) during 20-week evaluation period[3]; Adjunctive therapy for myoclonic seizures in adults and adolescents (≥12 years of age) with JME: 25% (15/60) during 12-week evaluation period[4]; Adjunctive therapy for partial onset seizures in adults: 9% (23/269) during 16 - to 18-week treatment period[5]; Adjunctive therapy for partial onset seizures in children (4-16 years of age): 7% (7/101) during 14-week treatment period.[6]

References: 1. Keppra® (levetiracetam) Summary of Product Characteristics (SmPC), UCB PHARMA, S.A., January 2007. **2.** Brodie MJ, et al. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. *Neurology.* 2007;68:402-408. **3.** Morrow J, L.E.V. N01057 Study Group. Efficacy and safety of levetiracetam as adjunctive treatment in adult and paediatric patients suffering from idiopathic generalised epilepsy with primary generalised tonic-clonic seizures. Abstract presented at: 10th Congress of the European Federation of Neurological Societies; September 2-5, 2006; Glasgow, UK. **4.** Andermann E, et al. Efficacy and tolerability of levetiracetam add-on therapy in patients with refractory idiopathic generalised epilepsy. Poster presented at: 6th Asian & Oceanian Epilepsy Congress; November 16-19, 2006; Kuala Lumpur, Malaysia. **5.** Meencke H-J, et al. Assessment of a dose-response relationship of levetiracetam. *Eur J Neurol.* 2006;13:942-946. **6.** Glauser TA, et al. Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. *Neurology.* 2006;66:1654-1660.

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ABBREVIATED PRODUCT INFORMATION

NAME OF THE MEDICINAL PRODUCT: Keppra® (levetiracetam) film-coated tablets, oral solution and 100 mg/ml concentrate for solution for infusion. QUALITATIVE AND QUANTITATIVE COMPOSITION: Each film-coated tablet contains 250 mg, 500 mg, 750 mg or 1000 mg levetiracetam. Each ml of oral solution contains 100 mg levetiracetam. Each ml of concentrate contains 100 mg of levetiracetam. The 5 ml vial of concentrate contains 500 mg of levetiracetam. PHARMACEUTICAL FORM: Film-coated tablet, oral solution and concentrate for solution for infusion. Keppra concentrate is a clear, colorless, sterile solution. CLINICAL PARTICULARS: Therapeutic indications: Keppra is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy. Keppra is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. Keppra is indicated as adjunctive therapy in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalised epilepsy. Keppra concentrate is an alternative for patients when oral administration is temporarily not feasible. Posology and method of administration: Keppra therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The daily dose is administered in two equally divided doses. The total daily dose and frequency of administration should be maintained. The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. The oral solution may be diluted in a glass of water and may be taken with or without food. A graduated oral syringe and instructions for use in the package leaflet are provided with Keppra. Keppra concentrate is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion. There is no experience with administration of intravenous levetiracetam for longer period than 4 days.
Monotherapy: Adults and adolescents from 16 years of age: The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily.
Add-on therapy: Adults (≥18 years) and adolescents (12 to 17 years) weighing 50 kg or more: The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks. Elderly (65 years and older): Adjustment of the dose is recommended in elderly patients with compromised renal function (see "Patients with renal impairment" below). Children aged 4 to 11 years and adolescents (12 to 17 years) weighing less than 50 kg: The initial therapeutic dose is 10 mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. Dosage in children 50 kg or greater is the same as in adults. The physician should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.

Dosage recommendations for children and adolescents:

Weight	Starting dose: 10 mg/kg twice daily	Maximum dose: 30 mg/kg twice daily
15 kg (1)	150 mg twice daily	450 mg twice daily
20 kg (1)	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg (2)	500 mg twice daily	1500 mg twice daily

(1) Children 20 kg or less should preferably start the treatment with Keppra 100 mg/ml oral solution.
(2) Dosage in children and adolescents 50 kg or more is the same as in adults. The graduated oral syringe contains up to 1,000 mg levetiracetam (corresponding to 10 ml) with a graduation every 25 mg (corresponding to 0.25 ml). A Keppra concentrate vial contains 500 mg levetiracetam in 5 ml (corresponding to 100 mg/ml).
Infants and children less than 4 years: Keppra is not recommended for use in children below 4 years of age due to insufficient data on safety and efficacy.
Patients with renal impairment: The daily dose must be individualised according to renal function. For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CLcr = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0.85 \text{ for women})$$

Dosing adjustment for adult patients with impaired renal function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	>80	500 to 1,500 mg twice daily
Mild	50-79	500 to 1,000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	<30	250 to 500 mg twice daily
End-stage renal disease patients Undergoing dialysis (1)	-	500 to 1,000 mg once daily (2)

(1) A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.
(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.
For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients. Patients with hepatic impairment: No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is <70 ml/min. Contraindications: Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients. Special warnings and special precautions for use: In accordance with current clinical practice, if Keppra has to be discontinued it is recommended to withdraw it gradually (*e.g.* in adults: 500 mg decreases twice daily every two to four weeks; in children: dose decrease should not exceed 10 mg/kg twice daily every two weeks). Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown. An increase in seizure frequency of more than 25% was reported in 14% of levetiracetam treated adult and paediatric patients with partial onset seizures, whereas it was reported in 26% and 21% of placebo treated adult and paediatric patients, respectively. When Keppra was used to treat primary generalised tonic-clonic seizures in adults and adolescents with idiopathic generalised epilepsy, there was no effect on the frequency of absences. The administration of Keppra to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection (see "Posology" above). Keppra 100 mg/ml oral solution includes methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed). It also includes maltitol; patients with rare hereditary problems of fructose intolerance should not take this medicine. Keppra concentrate contains 0.313 mmol (or 7.196 mg) of sodium per vial. To be taken into consideration by patients on a controlled sodium diet. Interaction with other medicinal products and other forms of interaction: Pre-marketing data from clinical studies conducted in adults indicate that Keppra did not influence the serum concentrations of existing antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of Keppra. As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam. A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 22% higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dosage adjustment is not required. Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low. It is expected that other medicinal products excreted by active tubular secretion could also reduce the renal clearance of the metabolite. The effect of levetiracetam on probenecid was not studied and the effect of levetiracetam on other actively secreted medicinal products, *e.g.* NSAIDs, sulfonamides and methotrexate, is unknown. Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam. No data on the influence of antacids on the absorption of levetiracetam are available. The extent of absorption of levetiracetam was not altered by food, but the rate of absorption was slightly reduced. No data on the interaction of levetiracetam with alcohol are available. Pregnancy and lactation: There are no adequate data from the use of Keppra in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Keppra should not be used during pregnancy unless clearly necessary. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus. Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. Effects on ability to drive and use machines: No studies on the effects on the ability to drive and use machines have been performed. Due to possible different individual sensitivity, some patients might experience somnolence or other central nervous system related symptoms, especially at the beginning of treatment or following a dose increase. Therefore, caution is recommended in those patients when performing skilled tasks, *e.g.* driving vehicles or operating machinery. Patients are advised not to drive or use machines until it is established that their ability to perform such activities is not affected. Undesirable effects: Pooled safety data from clinical studies conducted with Keppra oral formulations in adult patients with partial onset seizures showed that 46.4% of the patients in the Keppra group and 42.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 2.4% of the patients in the Keppra and 2.0% of the patients in the placebo groups. The most commonly reported undesirable effects were somnolence, asthenia and dizziness. In the pooled safety analysis, there was no clear dose-response relationship but incidence and severity of the central nervous system related undesirable effects decreased over time. In monotherapy 49.8% of the subjects experienced at least one drug related undesirable effect. The most frequently reported undesirable effects were fatigue and somnolence. A study conducted in paediatric patients (4 to 16 years) with partial onset seizures showed that 55.4% of the patients in the Keppra group and 40.2% of the patients in the placebo group experienced undesirable effects. Serious undesirable effects were experienced in 0.0% of the patients in the Keppra group and 1.0% of the patients in the placebo group. The most commonly reported undesirable effects were somnolence, hostility, nervousness, emotional lability, agitation, anorexia, asthenia and headache in the paediatric population. Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural and psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk was similar in children as compared to adults. Undesirable effects that resulted from Keppra intravenous use are similar to those associated with Keppra oral use. The most frequently reported adverse reactions were dizziness, somnolence, headache and postural dizziness. A study conducted in adults and adolescents with myoclonic seizures (12 to 65 years) showed that 33.3% of the patients in the Keppra group and 30.0% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effects were headache and somnolence. The incidence of undesirable effects in patients with myoclonic seizures was lower than that in adult patients with partial onset seizures (33.3% versus 46.4%). A study conducted in adults and children (4 to 65 years) with idiopathic generalised epilepsy with primary generalised tonic-clonic seizures showed that 39.2% of the patients in the Keppra group and 29.8% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effect was fatigue. Since there was limited exposure for Keppra intravenous use and since oral and intravenous formulations are bioequivalent, the safety information of Keppra intravenous will rely on Keppra oral use. Undesirable effects reported in clinical studies (adults and children) or from post-marketing experience are listed below per System Organ Class and per frequency. For clinical trials, the frequency is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Data from post-marketing experience are insufficient to support an estimate of their incidence in the population to be treated. Very common undesirable effects (≥1/10). General disorders and administration site conditions: asthenia/fatigue; Nervous system disorders: somnolence. Common undesirable effects (≥1/100, <1/10). Nervous system disorders: amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremor, balance disorder, disturbance in attention, memory impairment; Post-marketing experience: paraesthesia; Psychiatric disorders: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal; Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation; Gastrointestinal disorders: abdominal pain, diarrhoea, dyspepsia, nausea, vomiting; Post-marketing experience: pancreatitis; Hepatobiliary disorders: Post-marketing experience: hepatic failure, hepatitis, liver function test abnormal; Metabolism and nutrition disorders: anorexia, weight increase. The risk of anorexia is higher when topiramate is coadministered with levetiracetam; Post-marketing experience: weight loss; Ear and labyrinth disorders: vertigo; Eye disorders: diplopia, vision blurred; Musculoskeletal and connective tissue disorders: myalgia; Injury, poisoning and procedural complications: accidental injury; Infections and infestations: infection, nasopharyngitis; Respiratory, thoracic and mediastinal disorders: cough increased; Skin and subcutaneous tissue disorders: rash, eczema, pruritus; Post-marketing experience: alopecia: in several cases, recovery was observed when Keppra was discontinued; Blood and lymphatic system disorders: thrombocytopenia; Post-marketing experience: leukopenia, neutropenia, pancytopenia (with bone marrow suppression identified in some of the cases). Overdose: Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Keppra overdoses. There is no specific antidote for levetiracetam. Treatment of an overdose will be symptomatic and may include haemodialysis. The dialyser extraction efficiency is 60% for levetiracetam and 74% for the primary metabolite. PHARMACEUTICAL PARTICULARS: Nature and contents of container: Keppra film-coated tablets are packaged in aluminium/PVC blisters placed into cardboard boxes containing film-coated tablets of 250, 500, 750 or 1000 mg. Keppra oral solution is packaged in 300 ml amber glass bottles (type III) with a white child resistant closure (polypropylene) in a cardboard box also containing a graduated oral syringe (polyethylene, polystyrene) and a patient information leaflet. Not all pack sizes may be marketed in each EU country. Keppra concentrate is packed in glass vials (type I) with Teflon-faced stoppers and sealed with an aluminium/polypropylene flip-off cap. The vials are placed into cartons of 10 vials. Each vial contains 5 ml of concentrate. Keppra concentrate was found to be physically compatible and chemically stable when mixed with the following diluents for at least 24 hours and stored in PVC bags at controlled room temperature 15-25° C. Diluents: Sodium chloride (0.9%) injection; Lactated Ringer's injection; Dextrose 5% injection. Product with particulate matter or discoloration should not be used.

MARKETING AUTHORISATION HOLDER: UCB PHARMA, S.A. Allée de la Recherche 60 B-1070 Bruxelles Belgium.
MARKETING AUTHORISATION NUMBER(S): EU/1/00/146/001-030
DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 29 September 2000
Date of last renewal: 08 July 2005
FULL PRESCRIBING INFORMATION including Summary of Product Characteristics is available from UCB PHARMA, S.A.
DATE OF REVISION OF THE TEXT: January 2007

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pregnancy will already have passed that period. Therefore, the key is pre-conception planning.

From my point of view, the first thing I would do would be to review the diagnosis because as many as 20% of people attending hospital with a diagnosis of epilepsy may ultimately turn out not to have it. Furthermore, in some cases there is an argument for saying that people who have epilepsy but who have not had a seizure for some considerable time may no longer need their drugs. Therefore, this might be a time to consider drug withdrawal or at least rationalisation to reduce drug load, particularly for people on polytherapy.

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All of the studies agree that polytherapy carries a much higher risk of foetal malformations than does monotherapy, so it is worth trying to reduce therapy to one drug. For some of the drugs – particularly sodium valproate and lamotrigine – it is worth considering dose as well, which may be relevant in the degree of relative risk.

It is also good practice to prescribe folic acid: studies carried out in the general population suggest that it may protect against neural tube defects, and we extrapolate this into the epileptic population. There is no direct evidence that folic acid actually protects our population group; moreover, the neural tube defects that are seen – particularly with sodium valproate – are slightly different from those in the general population: they tend to be lower and involve folding rather than canalisation, for example. Therefore, in terms of the question of whether folic acid protects the unborn child, we do not actually know. Initial results from our study hint that maybe it does not have this protective effect and maybe this is a special group, so we need to be looking at some other mechanism. I would advocate that, until evidence says completely the opposite, it is a good idea to prescribe folic acid.

For unplanned pregnancies where pre-conception planning has not been possible, what are the options?

At the present time, the general practice is that if somebody presents who is already pregnant, AEDs should not be changed because to do so would actually involve taking two drugs for a period of time, which carries an even greater risk. Furthermore, by the time the patient can come off the drug of concern, she would be through the first trimester and organogenesis.

However, it is important to consider that the brain develops throughout the whole of the pregnancy. If one particular AED is found to be associated with neurodevelopmental delay, that would indicate a rethinking of this strategy and there would be a cause for changing a patient's regimen during pregnancy – but we are not there yet.

At the pre-conception planning stage, is there much difference between new and old therapies?

The latest UK National Institute for Health and Clinical Excellence (NICE) guidelines indicated there was not. However, there is. All of the registries that have published and other preceding evidence would suggest that women taking sodium valproate have a higher risk of a major malformation in their child, particularly at higher doses. In these patients one would think about seeing if they can be withdrawn from the medication, have their AED switched or at the very least have their dose reduced.

However, this is difficult, because altering the medication may result in seizure breakthrough and loss of ability to drive. I live in Northern Ireland, which is a rural community where driving is very important. Therefore, women will often go away and weigh up their choices: despite the fact that there is increased risk with the drug, they may decide to stick with it because it is working well for them, they tolerate it well and available evidence indicates that changing the drug reduces the risk only by a relatively small amount. The aim is to empower the women to make that choice themselves.

And in summary?

We are living in an era in which information regarding AEDs – as well as the number of AEDs – is increasing all the time. Therapy and management of epilepsy for pre-menopausal women is improving. However, because of the increased number of AEDs and the gathering of huge amounts of information, it is an increasingly complex task. Many patients will benefit from the input of a specialist and/or a specialist epilepsy nurse to try to guide them through these issues and help them with their choices, many of which are likely to change over time. ■

All of the studies agree that polytherapy carries a much higher risk of foetal malformations than does monotherapy, so it is worth trying to reduce therapy to one drug.

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