Lamotrigine in pregnancy: safety profile and the risk of malformations

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ABSTRACT

The use of antiepileptic drugs in pregnancy always presents challenges to doctors and their patients as it may have deleterious effects on the developing embryo. Lamotrigine is most commonly prescribed drug among the newer antiepileptic drugs; hence, it has been selected for the present review. A number of studies pertaining to the safety of lamotrigine use during pregnancy have been reported, with differing results. Contradictory results have been reported in animals regarding lamotrigine teratogenicity, and human studies have also proven inconclusive. In many countries, human pregnancy registries are maintained to establish the safety of antiepileptic drugs during pregnancy, as all the different suggestions favour some over others, with specific antiepileptic combinations still being questioned. It is our hope that the present work may integrate the available disparate relevant facts into a directed effort towards minimising the risk of foetal compromise.

Keywords: antiepileptic drugs, drug safety, foetal malformation, lamotrigine, pregnancy complication, teratogenicity

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INTRODUCTION

Drug administration during pregnancy may result in adverse foetal effects. Hence, teratogenic screening is required and recommended. In the general population, 1% of adults and 5% of children suffer from epilepsy. Which antiepileptic should be prescribed to epileptic pregnant women? The choice drug is one that is effective, safe and free from foetal toxicity. No antiepileptic is both ideal and safe. Insufficient data has not allowed for definitive commentary concerning teratogenicity of newer antiepileptic medications (AEM), such as lamotrigine (LTG), gabapentin, tiagabine or levetiracetam. Existing suggestions also favour invariably some over others, with the efficacy of specific AEM combinations still being questioned.[1] The general practitioner's (GP) awareness of the newer antiepileptics is very variable, with gabapentin and LTG having the highest awareness rates among GPs.[2] LTG has been selected for the present study. LTG (Lamictal) was approved by the US Food and Drug Administration for use as an antiepileptic drug in 1994, and as a mood stabiliser in bipolar disorders in 2003. LTG is the most widely-used second generation antiepileptic agent.[3,4] LTG is a phenyl triazine derivative, initially developed as an antifolate agent. However, structure activity studies indicate that its effectiveness as an anti-seizure drug is unrelated to its antifolate activities.[5] Folate supplementation (0.4 mg/day) has been recommended by the US Public Health Service for all women of childbearing age to reduce the likelihood of neural tube defects, and this is appropriate for epileptic women.[6]

PHARMACOLOGY OF LAMOTRIGINE

Chemical structure

The International Union of Pure and Applied Chemistry (IUPAC) name of lamotrigine is 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine and the empirical formula is $C_9H_7C_{12}N_5$; while the molecular mass is 256.091 g/mol.

Pharmacodynamics

As described by Brunton et al, the mechanisms underlying the broad spectrum of actions of LTG are not completely understood.[6] One possibility involves LTG's inhibition of glutamate release in rat cortical slices treated with veratridine, a Na^+ channel activator. This raises the possibility that LTG inhibits synaptic release of glutamate by acting on Na^+ channels.[6] Tierny et al described that LTG is thought to interfere with neuronal sodium channels and inhibit the release of excitatory amino acids, glutamate and aspartate.[4] A decrease in glutamate release has also been reported as a mechanism of action.[3]

Pharmacokinetics

LTG is absorbed in the gastrointestinal tract and hence oral administration is employed. It is metabolised primarily by glucuronidation (Major metabolite: LTG 2-N-glucuronide) and the plasma half-life of a single dose (antiepileptic) is 15–30 hours.[6-8] Its antiepileptic doses are 100–500/day,

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bid. However, it must be noted that therapeutic range and optimum drug level have not been established.[3,4,7]

Common therapeutic uses

1. First-line drug for primary generalised tonic-clonic (includes simple partial, complex partial and secondarily generalised seizures), and as an adjuvant therapy in partial seizures (focal onset tonic-clonic, atypical absence, myoclonic, Lennox Gastaut syndrome).
2. Alternative drug for absence seizure and atypical absence, myoclonic, atonic.[3,4]

Adverse effects

Both neurological and systemic effects are seen. Common neurological side effects are dizziness, visual disturbances, diplopia, sedation, ataxia, headache and tremor. Skin rash, dyspepsia, nausea, are more frequent, while Stevens-Johnson syndrome and disseminated intravascular coagulation are rare systemic side-effects.[3,4]

Contraindications

Hepatic and renal impairment. Regarding its safety in pregnancy, proper risk benefit analysis is advised before prescribing LTG. The principal weakness of majority of the studies is that they are not conducted using randomised controlled trials. They are simply observational studies.

ANIMAL EXPERIMENTATION STUDIES

Drugs that have been found to be teratogenic in man have caused similar effects in animals.[9] Marchi et al reported teratogenic effects, such as reduction in body weight and morphological changes in the brain, when LTG was administered in rats at four times the median effective dose.[10] Padmanabhan et al reported that administering LTG as a single dose of 50–200 mg/kg body weight can induce intrauterine growth retarda-tion in mice, whereas multiple doses of 25, 50, 75 mg/kg body weight cause a dose dependent increase in embryonic resorption and craniofacial malforma-tions.[11] Studies in rats and rabbits indicate that LTG crosses the placenta, yielding placental and foetal levels comparable with those of maternal plasma. No teratogenic effects were seen in animal studies using increasing doses up to 1.2 times an equivalent human dose of 500 mg/day.[12] An increase in stillbirth and postnatal deaths was noted among offsprings of rats receiving LTG at doses less than half the equivalent human dose of 500 mg/day, and this was attributed to in utero exposure to LTG. The clinical significance of these effects is still unknown.[13,14] Rats receiving up to 0.5 times an equivalent human dose of 500 mg/day produced offspring with decreased foetal folate concentrations, an effect known to be associated with teratogenicity in humans and animals.[12]

HUMAN PREGNANCY REGISTRY STUDIES

The second generation antiepileptic drugs are reported to have teratogenic effects in animals. However, data derived from human studies remains inconclusive.[6] In 1993, Richens analysed a registry of 42 pregnancies and could not reveal clear cut evidence of a relationship between LTG and teratogenesis.[15] Gentile concluded that the limited information on LTG and oxcarbazepine does not indicate a clear increase in teratogenicity.[16] Vajda et al, in their study of a human pregnancy registry of 65 cases, reported that LTGs monotherapy has so far been free of malformations, although seizure control was not a primary outcome, as they noted that more patients on LTG than on valproic acid (VPA) required dose adjustments to control seizures.[17] Ornoy reported that LTG monotherapy during pregnancy seems to be relatively safe.[18]

In a human pregnancy registry study reported by Morrow et al, there was a trend towards fewer major congenital malformations (MCMs) for LTG as compared with valproate-exposed pregnancies (unadjusted OR = 0.517, p = 0.015).[19] However, when cases were adjusted for age at birth, parity, family history of MCM, folic acid exposure, and sex of infant, the statistical significance was lost (OR = 0.589, p = 0.064). The prevalence of different types of MCM induced by LTG out of 647 cases studied, were: one neural tube defect (0.2%), one facial cleft (0.2%), four cardiac defects (0.6%), six hypospadias/ genitourinary tract defects (0.9%), three gastrointestinal tract defects (0.5%), two skeletal defects (0.3%), and four others (0.6%).[20] Regarding the dose response of LTG teratogenicity, the mean daily dose was significantly higher for those with an MCM than for those without an MCM (respectively, 352.4 mg and 250.6 mg; p = 0.005). In women taking greater than 200 mg/day doses of LTG, 5.4% (95% confidence interval [CI] 3.3–8.7) MCM rate was recorded and was no different from pregnancies exposed to 1,000 mg or less per day of valproate (5.1%, [95% CI 3.5–7.3]).[20] In a separate human pregnancy study conducted by Meador et al, a total of 333 mother/child pairs were analysed for monotherapy exposures: carbamazepine (n = 110), LTG (n = 98), phenytoin (n = 56), and valproate (n = 69), and the response frequencies of pregnancies resulting in serious adverse outcome for each antiepileptic drug were as follows: carbamazepine 8.2%, LTG 1.0%, phenytoin 10.7%, and valproate 20.3%.[20]

In another human pregnancy study, Tatum suggested that LTG may be less teratogenic to humans than other AEMs, although orofacial clefts have recently been reported.[21] Cunnington and Tennis, in their human pregnancy registry study, reported that among 414 first-trimester exposures to LTG monotherapy, 12 cases presented with major birth defects (2.9%, 95% CI 1.6–5.1), although no distinctive pattern of major birth defects was apparent among the offspring exposed to LTG monotherapy

or polytherapy.[22] They concluded that the risk of all major birth defects after first-trimester exposure to LTG monotherapy (2.9%) was similar to that in the general population and in other registries enrolling women exposed to antiepileptic monotherapy (3.3%–4.5%).[19] In September 2001, Tennis and Eldridge reported that out of 168 subjects exposed to LTG monotherapy, three experienced major birth defects (1.8%, 95% CI 0.5-5.5).[23] Perucca reported that although teratogenic effects of LTG have not been established with certainty, a positive correlation between maternal dose and rates of major congenital anomalies has been identified.[24] Tomson et al, studied the U.K. pregnancy registry and reported a higher malformation rate with valproate, 5.9% (95% CI 4.3–8.2), than with carbamazepine, 2.3% (95% CI 1.4–3.7), and LTG, 2.1% (95% CI 1.0–4.0).[25]

In general, multiple drug therapy is considered more dangerous to the foetus than mono drug therapy and, at least for VPA and LTG, there seems to be a "threshold effect".[18] Morrow et al discovered that for pregnancies exposed to multiple drug therapy with valproate and LTG (n = 141), the MCM rate was 9.6% (5.7%–15.7%), while no MCMs were recorded in pregnancies exposed to cabamazepine and LTG (n = 118; MCM rate 0.0% (0.0%–3.3%).[19] Recent pregnancy databases have suggested that valproate is significantly more teratogenic than carbamazepine, and the combination of valproate sodium and LTG is particularly teratogenic.[26]

DRUG MONITORING

Petrenaite et al retrospectively reviewed 11 pregnant women on LTG monotherapy.[27] A significant decrease in the ratio of plasma LTG concentration-to-dose (65.1%) was observed during the second trimester (TM2) ($p = 0.0058$), this was followed by a decrease of 65.8% during third trimester (TM3) ($p = 0.0045$), compared to pre-pregnancy values. Five patients experienced seizure deterioration during pregnancy. The pharmacokinetic changes display marked inter-patient variation, which stresses the importance of evaluating each patient individually by closely monitoring LTG concentrations until full term.[27] Harden concluded that LTG levels can be expected to decline by 65%–90% during pregnancy.[28] This is a greater decline than has been seen with other AEMs, and this information alerts the practitioner to monitor the patient carefully during pregnancy, both clinically and through the use of serum levels. It also reinforces the need to document LTG levels in women of childbearing potential in anticipation of pregnancy.[28] de Haan et al suggested that frequent LTG level monitoring and appropriate dose adjustments are advised in the periods before and during pregnancy, as well as after delivery, especially for women on LTG monotherapy.[29] Adab suggested that changes in LTG clearance are particularly marked, with increases in each trimester and a significant fall in plasma concentrations, leading to subsequent breakthrough seizures in some women. LTG concentrations may also rise precipitously after delivery, leading to symptoms of toxicity.[30] Regular monitoring of AEMs has been advocated in each trimester and shortly after delivery, with appropriate adjustment of dosage to avoid seizure precipitation during pregnancy or symptoms of toxicity after birth. Frequent monitoring has been recommended for LTG.[30] Tomson et al suggested that valproate, when administered with LTG, seems to reduce the induction of LTG metabolism associated with pregnancy.[31]

Evidence gathered from human studies indicate that LTG crosses the placenta. Ohman et al reported a decrease in plasma level of LTG as pregnancy progressed.[32] The ratio of dose to plasma concentration was 5.8 times higher at delivery and 3.6 times higher in late pregnancy.[12] The ratio of umbilical cord to maternal plasma levels was 1.2, indicating extensive placental transfer of LTG.[32] Castel-Bronca et al reported that LTG plasma levels may be good indicators of LTG levels in the brain, and that higher response intensities could be expected with the higher doses of LTG, since efficacious concentrations are maintained for a longer period.[33] Johannessen and Tomson suggested that, for the newer AEMs that are metabolised (felbamate, LTG, oxcarbazepine, tiagabine and zonisamide), pharmacokinetic variability is just as relevant as for many of the older AEMs.[34] Therefore, therapeutic drug monitoring is likely to be useful in many clinical settings for the newer AEMs.[34] Although human pregnancy registry reports are available, better randomised controlled trial of human studies regarding LTG therapy are required to determine foetal risk.[35]

FOLIC ACID SUPPLEMENTAION

LTG has antifolate properties, although this is not involved in its antiepileptic mechanism. Folate deficiency is an important factor in causing teratogenicity related to altered endogenous metabolism. Various hypotheses regarding the pathogenic mechanism of folate deficiencies manifesting as birth defects has been reported. The effect of the addition of folic acid to LTG therapy was investigated by Ali et al.[36] They concluded that the combination of LTG and folic acid significantly reduced depression, while enhancing the effects on memory and seizure threshold at the same time. LTG does not affect the seizure and memory threshold. LTG is a dihydrofolate reductase inhibitor, and it decreases foetal folate levels in rats. Therefore, folic acid supplementation should be considered for all women of child-bearing potential taking LTG.[35]

Sabers et al reported that the most frequent AEMs used were LTG 35% (n = 51), oxcarbazepine 25% (n = 37) and valproate 20% (n = 30).[37] Out of 147 cases studied, 74% (n = 109) received monotherapy, and folic acid

supplementation was administered to 118 patients (80%) during the first trimester. They concluded that treatment with LTG during pregnancy might be relatively safe, as the risk of malformations was 2.0% in women treated with LTG, whereas the overall risk of malformations among newborns in the AEM-exposed group was 3.1% (n = 4). Candito et al reported a case where while receiving LTG treatment, a patient pregnant with triplets suffered a double foetal neural tube defect.[38] Plasma homocysteine, folate, vitamins B12 and B6 (pyridoxal phosphate), and red cell folate level samples were obtained and analysed for one month, while she was receiving folic acid therapy during the second trimester of pregnancy. Mutations involved in homocysteine metabolism and linked with folate metabolism were found during analysis. While LTG therapy has not been associated with significant changes in serum folate, periconceptional folic acid supplementation is recommended, along with vitamins, B12 and B6, when their plasma values indicate deficiencies.[38]

CONCLUSION

The higher costs of the newer AEMs may inhibit their wider use, especially in poorer countries.[39] LTG teratogenicity has been reported in animals, although results from human studies have proven inconclusive. There is a need to appraise the possibility of minimising foetal toxicity caused by drugs. To achieve this, an elaborate prospective evaluation is warranted. This present study is an attempt to elucidate and establish a viable LTG safety profile for use during pregnancy, so that risks of foetal malformations can be minimised.

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