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SHORT RESEARCH ARTICLES

Are doses of lamotrigine or levetiracetam adjusted during pregnancy?

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Summary

Subtherapeutic levels of lamotrigine and levetiracetam are more likely to occur during pregnancy owing to the effect of pregnancy on their pharmacokinetics. This can lead to suboptimal control of epilepsy, and guidelines recommend proactive dose adjustment in the second and third trimesters alongside therapeutic drug monitoring (TDM). This retrospective cohort study using administrative databases aimed to investigate whether prescribers adjust the dose of lamotrigine or levetiracetam during and after pregnancy and whether TDM is used to manage dose adjustment. In 460 individual pregnancies, 232 women (61.4%) had their lamotrigine dose increased in the second and third trimesters and 44 women (53.7%) had their levetiracetam dose increased. Only 57 women (12.4%) had any TDM. The dose was not always decreased postpartum, and 157 women (56.9% of those who had escalated doses during pregnancy) had dose reduced following birth. Between 2012 and 2015, 29 women had an epilepsy-coded hospital discharge during pregnancy and were more likely to have had their dose of lamotrigine or levetiracetam increased. Overall, doses of lamotrigine and levetiracetam were not increased during pregnancy in 40% of the study population, dose changes were not often guided by TDM, and doses were not always reduced postpartum.

KEY WORDS: Lamotrigine, Levetiracetam, Pregnancy, Therapeutic drug monitoring, Epilepsy, New Zealand.

An enquiry from the maternal deaths registry in the United Kingdom showed that women with epilepsy are 10 times more likely to die while pregnant compared to women without epilepsy, and sudden unexpected death in epilepsy (SUDEP) is the major cause of death in pregnant and postpartum women with epilepsy.[1] Multiple risk factors are suspected, including frequent generalized tonic-clonic seizures, poor adherence to antiepileptic drug (AED) treatment, nocturnal seizures, and early onset of epilepsy. In addition, one study investigating SUDEP observed subtherapeutic serum concentrations of one or more AEDs in 57% of the cases with postmortem serum concentrations available.[2] In New Zealand three pregnant women died from SUDEP between 2006 and 2012. The Perinatal and Maternal Mortality Review Committee (PMMRC) found that all three had suboptimal AED serum concentrations and that two of the deaths were potentially avoidable.[3]

Subtherapeutic levels of lamotrigine and levetiracetam are more likely to occur during pregnancy owing to the effect of pregnancy on their pharmacokinetics. Lamotrigine is metabolized in the liver by glucuronidation catalyzed by UDP-glucuronosyl-transferase, and during pregnancy these enzymes are induced.[4] Levetiracetam is primarily eliminated by renal excretion, and pregnancy increases renal blood flow and enhances glomerular filtration rate.[4] Consequently, there can be large increases in the clearance of lamotrigine and levetiracetam during pregnancy with an associated significant decline in the serum concentration.[5,6] There also appears to be significant interpatient and

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intrapatient variability.[7] Although a number of studies have shown worsening seizure control with declining lamotrigine concentrations,[5,7] a clear correlation between lowered levetiracetam levels during pregnancy and worsening seizure control has not been seen.[8,9]

The PMMRC recommended that all women with epilepsy be referred to specialist care during pregnancy and that consideration should be given to proactively increasing the dose of lamotrigine and levetiracetam in the second and third trimesters.[3] The New Zealand Formulary advises dose adjustment of lamotrigine be based on therapeutic drug monitoring (TDM) and suggests a possible dose increase of levetiracetam in the second and third trimesters.[10] Plasma levels normalize within 2 to 3 weeks following birth; therefore, dose adjustment is also required in this period to avoid toxicity.[11]

Our aim was to investigate whether prescribers:

- adjust the dose of lamotrigine or levetiracetam during pregnancy and postpregnancy
- monitor plasma-drug concentrations of lamotrigine and levetiracetam

Methods

This study is a retrospective cohort study using three of New Zealand's administrative databases between 2010 and 2015: the Pharmaceutical Collection, the National Minimum Dataset (NMDS; hospital events), and the Laboratory Claims Collection. Levetiracetam was included on the Pharmaceutical Schedule in 2010; therefore, we have included data from 2010 until 2015. Every person in New Zealand has a unique National Heath Index (NHI) number, an alphanumeric identifier that is used in all interactions with the health system over that person's life. This number makes it possible to link an individual's health data across a range of databases. The recording of NHIs is reliable from 2008, with 97% of all records containing an NHI.

Study population

Women who had given birth were identified by the NMDS (captures 97% of all births) and were linked by encrypted NHI to the Pharmaceutical Collection (captures 100% of community-dispensed AEDs) to determine whether they had been dispensed lamotrigine or levetiracetam in the preceding 12 months. The encrypted NHI numbers of the women identified as having been dispensed levetiracetam or lamotrigine were used to find laboratory test information in the Laboratory Claims Collection (captures 80% of laboratory requests data). Women were excluded if they had not been dispensed lamotrigine or levetiracetam in two or more trimesters.

Average doses per trimester and 3 months postpartum were calculated to investigate the rate of dose escalation during the second half of pregnancy and dose deescalation postpregnancy. Tests in the laboratory claims data were recorded by date and trimester of pregnancy they were completed. Details on prescribing of other AEDs during the study period were recorded and categorized either as no other AEDs dispensed or by the number of additional AEDs dispensed. Pearson's chi-square tests were used to analyze dichotomized variables.

Results

Between 2010 and 2015, 549 women had been dispensed lamotrigine or levetiracetam in the 12 months before giving birth. After excluding 165 women who had not been dispensed either of these medicines in two or more trimesters, 384 women were included in the final sample. To avoid duplicate analyses, 20 women dispensed both lamotrigine and levetiracetam during their pregnancies were excluded. Eighty women had two infants during the study period, and 8 women had three infants born in the study period, resulting in 460 individual pregnancies.

Forty-four women (9.6%) were dispensed one other AED, and 4 women (0.9%) were dispensed two other AEDs during pregnancy.

Dose escalation

The dose was escalated in the second and third trimesters for 276 cases (60.0%), compared to 184 cases where the dose was not escalated (40.0%). Escalation varied depending on the drug the women were taking (Table 1). Overall women were significantly more likely to have their dose increased than not (Pearson chi-square $p = 0.0001$). Excluding women who had also taken another AED during pregnancy did not change the outcomes.

The proportion of women having their dose escalated during the second half of pregnancy did not significantly change over the study period of 2010–2015 (Fig. S1). More than half of the dose increases involved escalated doses that were 50% or less higher than the original dose, with the median percentage dose increase being 44%. See Fig. 1.

Monitoring

Only 57 (12.4%) women had any TDM during pregnancy, and 28 of those women (49.1%) had only a single drug concentration recorded during pregnancy. Other women had two or more concentrations recorded during pregnancy. Overall, 9 (2%) women had TDM recorded prepregnancy, 25 (5.4%) in the first trimester, 25 (5.4%) in the second trimester, and 27 (5.9%) in the third trimester. The laboratory data completeness was unknown; therefore, a sensitivity analysis was performed using records for antenatal bloods to estimate the rate of laboratory recording. In this analysis, the cases of 310 women dispensed lamotrigine during pregnancy between 2012 and 2015 were analyzed to see whether any antenatal laboratory tests were recorded. In this cohort, 257 (82.9%) of the women had at least one set of antenatal screening bloods recorded.

Table 1. Dose changes, therapeutic drug monitoring, and epilepsy-coded hospital discharges during pregnancy

	Lamotrigine	Levetiracetam	Total
Dose escalated during pregnancy			
Yes n (%)	232 (61.4)	44 (53.7)	276 (60.0)
No n (%)	146 (38.6)	38 (46.3)	184 (40.0)
Therapeutic drug monitoring (TDM) recorded			
Yes n (%)	47 (12.4)	10 (12.2)	57 (12.4)
No n (%)	331 (87.6)	72 (87.8)	403 (87.6)
Dose decreased postpartum (following dose escalation during pregnancy)			
Yes n (%)	136 (58.6)	21 (47.7)	157 (56.9)
No n (%)	96 (41.4)	23 (52.3)	119 (43.1)
Epilepsy/seizure recorded in hospital notes (between 2012 and 2015)			
Yes n (%)	21 (8.2)	8 (10.5)	29 (8.8)
TDM recorded n (%)	3	2	5 (17.2)
Dose increased n (%)	17	6	23 (79.3)
Dose decreased postpartum n (%)	8	3	11 (47.8[a])
No n (%)	234 (91.8)	68 (89.5)	302 (91.2)
TDM recorded n (%)	25	7	32 (10.6)
Dose increased n (%)	139	34	173 (57.3)
Dose decreased postpartum n (%)	87	18	105 (60.7[a])

[a]Dose decrease postpartum as a percentage of those whose dose was increased during pregnancy.

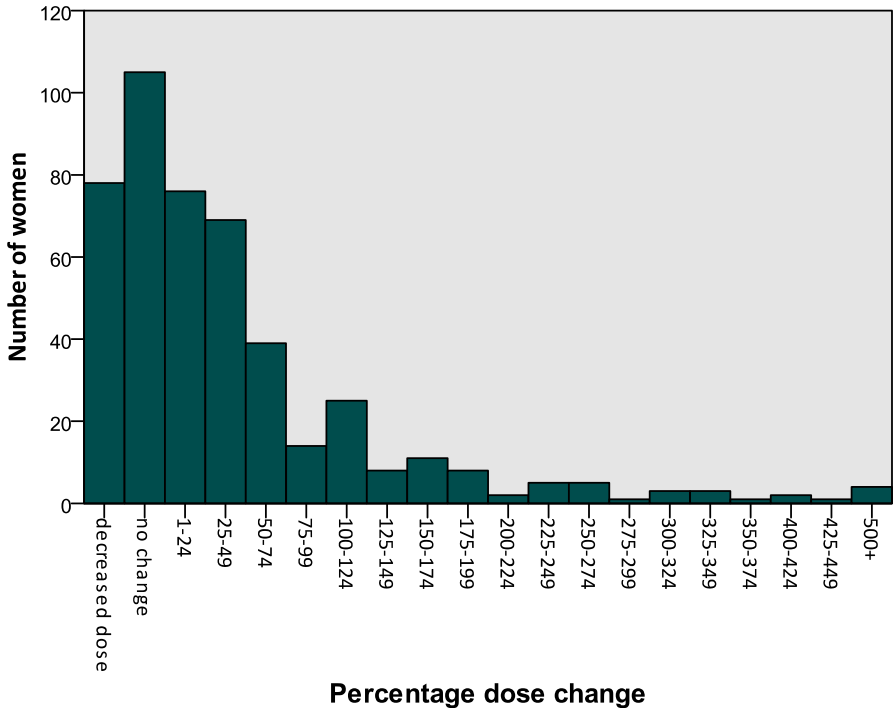

Figure 1.
Percentage change in dose from baseline.
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Dose deescalation

Of the 276 women who had their dose increased during pregnancy, 133 (48.2%) had their dose reduced postpregnancy; 70 (25.4%) had their dose increased; 49 (17.8%) had no change in their dose; and 24 (8.7%) had no postpregnancy dose (counted as a decreased dose). There was also no significant difference when comparing levetiracetam and lamotrigine: 136 women (58.6%) taking lamotrigine had their dose reduced postpregnancy compared to 21 (47.7%) of women taking levetiracetam.

Epilepsy-coded hospital notes

Between 2012 and 2015, only 29 women in the cohort had a hospital discharge record containing an ICD 10 code

for epilepsy. If we assume that these are all seizure events, then this shows that women who had a seizure were more likely to have their dose increased than those who did not (Pearson chi-square 0.021) (see Table 1). In addition, when comparing those who had any monitoring during pregnancy with those who had no recorded monitoring, there was no significant difference in the number of epilepsy-coded hospital discharges; however, the numbers are small in these groups (chi-square 0.278).

Discussion

Differing advice from guidelines on dose adjustment of AEDs complicates medicine management during pregnancy. Some guidelines advise taking baseline therapeutic drug levels either preconception or as early as possible in pregnancy and then monitoring drug levels every trimester or more frequently if seizures occur.[11] One review supports this method, finding that TDM of AED levels in pregnancy reduced seizure deterioration.[12] Other guidelines advise that dose adjustment based on clinical monitoring is sufficient.[13] The data from this study suggest that in New Zealand dose changes are made based on clinical symptoms rather than TDM, with an epilepsy-coded hospital admission being associated with an increase in AED dose. In addition, 60% of women had their dose of lamotrigine or levetiracetam increased in the second and third trimesters, but only 1 in 8 pregnant women had any recorded TDM.

An argument for using TDM to guide dose changes is to avoid worsening seizures, where the social consequences of breakthrough seizures can be significant for women, particularly if they have been seizure free for a long time. There are also significant health risks for both mother and fetus associated with poorly controlled tonic-clonic seizures.[14]

Lamotrigine drug concentrations return to baseline within the first 2 to 3 weeks following delivery.[15] This can result in symptoms of toxicity such as dizziness, ataxia, and nausea and vomiting in the first 3 to 10 days if the lamotrigine dose is not reduced.[16] The present study found that only 56.9% had their dose decreased following escalation during pregnancy. Some women had been dispensed a higher dose following pregnancy.

Although administrative data have a number of strengths, including no loss to follow-up and almost 100% coverage of the target population, results can be limited by the data available in these databases. With these datasets we had to rely on hospital discharge data for any record of seizures. More detailed clinical notes would provide a clearer picture of the effect of dose changes or TDM on seizure frequency and would provide the actual blood level results of TDM. Some recording of TDM may also be missing from the database; however, sensitivity analysis found that of all District Health Boards (DHBs), only 4 showed lower than average lab test reporting. These DHBs represented only 7% of our sample, so they are unlikely to have had a significant impact on our results. It is also possible that some women do not require dose increases during pregnancy, with one study showing that 23% of women only had minimal changes in lamotrigine clearance during pregnancy.[17] TDM during pregnancy would be useful to determine which women need their dose escalated. Diagnosis information is missing for the cases, and there is likely to be a number of women using lamotrigine for other conditions such as bipolar disorder. In this instance, although evidence regarding the dose adjustment of lamotrigine in women with bipolar disorder is limited, guidelines suggest that it is still appropriate to increase the dose of lamotrigine during pregnancy to avoid a potential relapse of symptoms of bipolar disorder.[18]

Conclusion

Pregnant women taking lamotrigine or levetiracetam in New Zealand are more likely than not to have a higher dose prescribed during pregnancy; however, this does not appear to be guided by TDM in most cases. Following pregnancy, the maintenance dose of lamotrigine or levetiracetam is not always reduced to prepregnancy levels. This potentially exposes the women and/or their babies to poorer health and pregnancy outcomes. These prescribing patterns may reflect a need for improved guidance for managing these medicines during pregnancy.

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Disclosures

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Has the dose been escalated in the second half of pregnancy (yes/no by case).