Quality Assurance when Using Therapeutic Drug Monitoring: A Lamotrigine Split Sample Method to Reflect Comparability

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Abstract

Purpose: Therapeutic drug monitoring can optimise patient outcomes if the Anti-Epileptic Medication (AEM) level is received in a timely fashion. When choosing a laboratory (lab) to measure levels, the treating physician must incorporate quality assurances so as to be confident that the results are reliable and concordant with results accepted from the current lab. The study aims to generate a practical example of how one can improve the use of drug monitoring in patients with epilepsy.

Methods: A split-sampling procedure was used to analyse the AEM levels reported by two different labs. The results were categorised in accordance with the physician's defined therapeutic range: sub-therapeutic: <10mg/L; therapeutic: 10-16mg/L; and supra-therapeutic: >16mg/L, to determine if categorisation varied between the labs. Results were further evaluated to compensate for absolute and/or clinically significant differences.

Results: Categories were concordant for 43/50 (86%) of results. Of the 7/50 (14%) category discordant results, five (10% of results) were not clinically significant. In only 4% (2/50) of patients was the discordance sufficient to have possibly generated a treatment modification depending upon the patient's clinical picture. Overall, the absolute difference in the levels reported by the two labs was neither significant nor statistically different.

Conclusion: Split-sampling studies are a practical way of ensuring physician confidence and demonstrating quality assurance when changing labs.

Keywords: Anti-Epiletic Medication; Laboratory; Lamotrigine; Therapeutic Drug Monitoring; Quality Assurance

Abbreviations: TDM: Therapeutic Drug Monitoring; AEM: Anti-Epileptic Medication; LTG: Lamotrigine.

Introduction

Therapeutic drug monitoring (TDM) reflects the measurement of the level of a given medication, in the blood of patients being treated with that medication, to reflect that sufficient amounts of that medication have been prescribed to achieve a desired therapeutic result. It offers a valuable adjunct to patient care [1] especially in the management of epilepsy which is a chronic condition in which antiepileptic medications offer the best form of intervention to control the seizures in the majority of patients who are prone to seizures. The value of TDM in patients with epilepsy is to determine anti-epileptic medication (AEM) blood levels, referable to a patient's state of health and wellbeing, at the time of measuring the AEM concentration [2]. Monitoring AEM levels may prevent breakthrough seizures by identifying non-compliance and may identify the offending AEM if there exists toxicity [3,4]. It follows that the more immediate the result, the better it reflects the effect of the AEM at that time [5]. Blood samples for newer AEM's, such as Lamotrigine (LTG) (branded product, Lamictal®) which is an antiepileptic medication that acts at the sodium channel to reduce the post synaptic potentiation of epileptic discharges, are not widely or immediately available St Louis, et al. [6]. As a result, some clinicians are uncertain about proper use of AEM blood level determination for newer AEM's, due to a lack of confidence if levels cannot readily be measured [6].

The laboratory (lab) that is commonly used by the clinic in this study, to assess LTG levels, required 2 weeks to provide results with no allowance for urgency, either in the face of ongoing seizures (when compliance may be in question) or at times of apparent toxicity (when dosages or drug-interactions may be highly relevant). To counter these issues, the clinic identified an alternative lab which could provide results of LTG levels within a 24-hour window, thereby enhancing the capacity to interpret such results for an individual patient.

Studies have demonstrated that results from the same sample, if analysed separately, can yield different results as these can be affected by lab techniques, methods of handling samples, reagents or equipment that is used Abdollahi, et al. [7], Phillips, et al. [8]. Such discrepancies can result in less efficient management and deny optimal patient care by contributing to unnecessary or inappropriate dose adjustments [9,10].

As a means of quality assurance, the reliability of the lab to which the clinic chooses to send its patients' samples should be critically assessed. While most reputable labs are accredited by the National Authorities of Testing, Australia (NATA) [11], it is not until there is a direct comparison between labs that the clinician can feel suitably comfortable in accepting results.

The clinic has an established idiosyncratic therapeutic range for LTG at 10-16 mg/L (40-60µmol/L) Patel, et al. [12]. Based on the results from the clinic's usual lab. Prior to switching labs, quality assurance was needed to ensure that the results of the second lab mirrored those of the first lab, to satisfy physician confidence in interpreting the results.

The aim of this study was to determine if there existed a confounding variation in lab results for LTG between the original lab and the lab providing more immediate results. This was undertaken in the present study using the process of split sampling.

Methods

During June 2017-January 2018 inclusive, 50 blood samples were drawn from patients, attending a private neurology clinic in Sydney, Australia, who were receiving LTG as adjunctive therapy to treat their epilepsy. The samples were split and sent to two labs in Australia with each patient made aware that this approach to quality assurance was being undertaken to ensure that, should the clinic use an alternative laboratory to provide more immediate results which would better reflect the immediacy of the TDM, the results of the test would be comparable to those currently being used. All patients involved in the study gave informed consent to the study and acknowledged that it was designed to accommodate their best interests and ensured that, before changes were made, quality assurance both should and would prevail.

The LTG results reported by the two labs were collated and evaluated in the following three ways:

Category Variation

The results were categorised in an Excel spreadsheet (Table 1) in accordance with the clinic's LTG Reference Range (Table 2) to determine if such categorisation varied between the two laboratories.

Statistical Significance

Statistical Modelling Software, SPSS, was used to determine whether the results reported by the two labs were significantly different. A two-tailed 'T-test' sampling procedure was used with the following hypotheses:

Null hypothesis: H$_0$: $\mu_1 = \mu_2$

Alternative hypothesis: Ha: $\mu_1 \neq \mu_2$.

For this analysis, a P value of <0.05 was considered significant for rejection of the null hypothesis.

Clinical Significance

The compared results were further evaluated to compensate for *clinical* significance. Where results were so close to the three subcategories (namely within 1mg/L), thereby not sufficiently deviating to suggest a change in LTG regimen, this was accepted as a comparable result.

Sample	Lab 1 (mg/L)	Lab 2 (mg/L)
1	13.1	13.2
2	11.1	11.6
3	11.3	10.8
4	12.8	11.3
5	11.6	10.5
6	20.8	20.1
7	10.4	10.7
8	18.3	19.7
9	11	9.8
10	7	6.3
11	7.1	7
12	7.7	7.4
13	11.4	10.8
14	17.9	17.1
15	18.3	15.7
16	15.8	15.7
17	15.1	13.7
18	15.8	15.3
19	15.9	16.3
20	15.2	15.6
21	17.3	15.4
22	10.8	10.5
23	11	11.9
24	0.6	0.4
25	7.3	6.8
26	18.7	19.1
27	14.5	13.8
28	13.6	12.7
29	21.9	19.2
30	20.6	18.7
31	8.2	8.3
33	9.5	8.1
33	9.6	9.5
34	16.4	11.2
35	16.4	15.5
36	13.3	14.4
37	13	12.3
38	10.5	9.5
39	14.5	13.6
40	18	17.6
41	11	12.1

42	8.2	7.1
43	11.7	10.1
44	9	7.9
45	9.7	8.9
46	8.7	7.3
47	5.3	5.9
48	7.9	6.8
49	12.8	12.7
50	14.5	14.3=

Table 1: Lamotrigine levels as reported by the two laboratories.

Reference Range	Mg/L
Sub-therapeutic	<10
Therapeutic	10-16
Supra-therapeutic	>16

Table 2: Practitioner's defined therapeutic range for Lamotrigine.

Results

Category Variation

The proportions of patient samples falling within the defined therapeutic ranges were as follows:
Sub-therapeutic: 14/50=28%
Therapeutic: 25/50=44%
Supra-Therapeutic: 7/50=14%
Falling between two different ranges: 7/50=14%
Seven (14%) of the 50 samples were not concordant, with results from the two labs falling into differing categories (Sub-therapeutic, therapeutic or supra-therapeutic).

Statistical Significance

Two tailed T-test sampling Procedure:
Lab 1
$s_1^2 = SS_1/(N - 1) = 939.6/(50-1) = 19.18$
Lab 2
$s_2^2 = SS_2/(N - 1) = 882.44/(50-1) = 18.01$
T-value Calculation
$s_p^2 = ((df_1/(df_1 + df_2)) * s_1^2) + ((df_2/(df_2 + df_2)) * s_2^2)$
$= ((49/98) * 19.18) + ((49/98) * 18.01) = 18.59$
$s_{M1}^2 = s_p^2/N_1 = 18.59/50 = 0.37$
$s_{M2}^2 = s_p^2/N_2 = 18.59/50 = 0.37$
$t = (M_1 - M_2)/\sqrt{(s_{M1}^2 + s_{M2}^2)} = 0.64/\sqrt{0.74} = 0.74$ The *p*-value is 0.23. A significant difference was not detected between the levels reported by the two labs.

Clinical Significance

Of the seven category discordant results (14%), four results (8%) were not of clinical significance and would not have caused any conflict in dosage or therapeutic regimen decision making for ongoing care.

Examples where slightly out of range results were not clinically significant are found in:
Sample 9: lab 1 reported 11 mg/L and lab 2 reported 9.8 mg/, both of which would be considered as low therapeutic
Sample 19: lab 1 reported 15.9 mg/L which is therapeutic, whilst lab 2 reported a level of 16.3 mg/L which is marginally above therapeutic limits; but both considered high therapeutic
Sample 35: lab 1 reported 16.4 mg/L which is slightly above therapeutic limits and lab 2 reported 15.5 mg/L, which is within therapeutic limits; both considered high therapeutic
Sample 38: lab 1 reported 10.5 mg/L which is therapeutic and lab 2 reported 9.5 mg/L which is just below therapeutic limits; both considered low therapeutic
In total, in only two samples, (4%) was there a discrepancy that may have resulted in a change of clinical management. These samples are:
Sample 21: where lab 1 reported a supra therapeutic level of 17.3 whilst lab 2 reported a therapeutic level of 15.4; and
Sample 15: lab 1 reported a supra-therapeutic level of 18.3 mg/L whilst lab 2 reported a level of 15.7 mg/L which is therapeutic.

Both results may have generated a repeat sampling depending on the patient's clinical presentation and in both cases the higher levels came from lab 1.

Discussion

It is important to ensure that AEM levels are reported and analysed in a timely fashion to increase clinical relevance. If the clinic has an established lab in which it routinely measures levels, the clinic should ensure that any alternative lab does not report significantly different results for the same test. This equates to quality control

and underpins physician confidence in interpreting the results. The results from the current study appear to show that the labs being compared provided comparable AEM levels for LTG; thereby supporting the move to the new lab, without compromising patient safety and wellbeing. The move would ensure that the two-week delay was no longer an issue and that results were reflective of the patient's current circumstances, thereby removing unnecessary doubt regarding compliance or toxicity when considering potential changes in a patient's therapy regimen. The minor discrepancy found in seven (14%) samples was insufficient to generate concern to change dosages and reinforced the notion that use of AEM levels is of value as an adjunct to clinical decision making while it does not reflect an absolute indication for change. The discrepancy found in two samples, in which one sample was therapeutic and the other, supra-therapeutic (in both cases) would be grounds for some concern, but, again, if the level was at odds with the patient's clinical history, a repeat measurement would have resulted.

A limitation of the study is the small sample size, which was restricted to 50 patients, thereby limiting the power to identify absolute difference between labs, when subjected to statistical analysis. The contrary view would be that the concordance between labs was so great (96%), for a test which is considered within the context of clinical decision-making based on patient status, that the results are sufficient to allow the clinician to change labs with a high degree of reliability.

Split sample studies, as presented in this report, offer the clinician a simple and effective means of achieving confidence when changing labs without jeopardising patient safety. This technique has generated a real example of how one can improve the use of TDM in the treatment of people with epilepsy to enhance the relevance and immediacy of the results for decisions in patient care.

Conclusion

TDM is a useful adjunct to patient care if results are processed efficiently. Split-sampling procedures are a viable method of testing whether there is a comparable difference in results before choosing to switch labs. On the basis of these data, it would seem reasonable to use lab 2 as it provides more immediate, and hence more representative, results. The reduction in time (2 weeks versus 24 hours) allows the clinician to have better control of the situation without compromising patient care or relying on flawed data.

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