Phenytoin loading doses and therapeutic drug monitoring at The Royal Melbourne Hospital: A retrospective audit

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Introduction

Phenytoin was one of the first anti-epileptic drugs available and is still widely used today. It has a narrow therapeutic index, long half-life and non-linear pharmacokinetics due to its saturable hepatic metabolism.[1-4] Its therapeutic range is well-defined at 10-20mg/L and toxicity is concentration-dependent, making it an ideal candidate for therapeutic drug monitoring (TDM).[2,5]

A major consideration for interpreting phenytoin TDM levels is a patient's albumin status, as phenytoin is approximately 90% protein bound. As such, in hypoalbuminaemia (albumin ≤35g/L) a level should always be taken concurrently to allow for adjustment using the Sheiner-Tozer equation. [1,2,6,7]

Phenytoin's use in status epilepticus requires rapid effect, thus phenytoin is often loaded. Weight-based dosing is the current standard of practice, with 15-20mg/kg the most evidence-based recommendation.[2] Intravenous loading dose levels should be taken 2-4 hours post-dose, while oral loading levels should be taken within 24 hours.

The half-life of phenytoin is approximately 22 hours, thus in the absence of loading, steady state is reached 7-10 days after first dose or a dose change. Maintenance phenytoin levels should be taken at steady state and as a trough (i.e. within 2 hours of the next dose).[8] Theoretically, given phenytoin's long half-life, a maintenance level may be appropriate if taken at least 8 hours post-dose, provided subsequent levels are taken at a comparable time.[9,10] Where dose adjustment is indicated, well-established recommendations are available.[2]

While many disparate recommendations surround phenytoin TDM, there exists no unanimously accepted, gold-standard guideline. As such, it is an area benefiting from investigation and development at the Royal Melbourne Hospital.

Aims

To retrospectively analyse phenytoin dosing and therapeutic monitoring, considering:

- Appropriate mg/kg loading dosing to achieve target steady-state plasma concentrations;
- Appropriateness of phenytoin levels in relation to adjustment for albumin and timing of levels;
- Whether doses are adjusted accordingly;
- If a patient's phenytoin level is sub- or supra-therapeutic, what is the incidence of drug interactions, renal and hepatic impairment, and obesity.

Methods

A retrospective, observational audit of all inpatients at the Royal Melbourne Hospital who had phenytoin levels taken within the year of 2018.

The patient pool was generated from pathology records for all reported phenytoin levels. Each patient's medical record was reviewed via the Electronic Contents Manager (ECM), and AUSCARE® was utilised to obtain pathology results.

Patients were screened and excluded if:

- A level had been taken in error
- There was a lack of accompanying data in ECM
- Phenytoin was being purposely weaned

The auditing tool REDCap® was used to record data for each admission and this was exported into Microsoft Excel® for analysis.

Results

How many levels?	
Recordable admissions: **123**	
Recordable levels: **339**	
Loading levels: **37**	Maintenance levels: **302**
How appropriate where the levels?	
Phenytoin levels taken completely appropriately[a]: **47** (13.9%)	
Loading: **1**	Maintenance: **46**
What about albumin?	
Phenytoin levels where patient had low albumin[b]: **267** (81.9%)	
Levels with an albumin level taken concurrently: **165** (48.7%)	
Loading: **12** (32.4%)	Maintenance: **153** (50.7%)

[a]in relation to the timing of the level and whether or not an albumin level was taken concurrently
[b]albumin ≤ 35 g/L

Table 1. Summary of phenytoin levels recorded; Appropriateness of levels; Albumin levels recorded.

Loading levels	
Loading doses recorded: **74**	
Range of mg/kg doses: **6.0 – 25.0 mg/kg**	
Loading levels taken: **37** (50.0%)	
Average mg/kg dose: **15.5 mg/kg**	
Average unadjusted level: **10.2**	Average level once adjusted for albumin: **16.5**
First loading dose level[a]	
Levels: **18**	Therapeutic levels: **10** (55.6%)
Average mg/kg dose that resulted in a therapeutic level **16.9 mg/kg**	
IV vs. Oral load levels	
IV: **34**	Oral: **3**
IV taken at appropriate time[b] **2** (5.9%)	Oral taken at appropriate time[c] **3** (100.0%)

[a]initial phenytoin load, no recent phenytoin doses prior
[b]within 4 hours of an IV load
[c]within 24 hours of an oral load

Table 2. Summary of phenytoin loading levels taken, including number of overall loads, number of initial loads, and the average mg/kg doses associated with each.

Maintenance levels	
Maintenance levels recorded[a]: **294**	
Average unadjusted level: **9.4mg/L**	Average level once adjusted for albumin: **13.9mg/L**
Maintenance levels in the therapeutic range once adjusted for albumin[b]: 154 **(52.4%)**	
Average total daily dose that resulted in a level within the therapeutic range: **350.7mg** *(range observed 150 - 660mg)*	

[a]excludes 8 levels where the patient was not on phenytoin
[b]where adjustment was required i.e. the patient was hypoalbuminaemic (≤ 35 g/L)

Table 3. Summary of phenytoin loading levels taken, including number of overall loads, number of initial loads, and the average mg/kg doses associated with each.

Appropriateness of maintenance levels
% levels **completely** appropriate[a]: **12.5%** (36)
% levels appropriate[b]: **28.6%** (82)

[a]at steady state (7 days following dose change), as a trough (within 2 hours of the next dose), and with albumin recorded at the same time.
[b]at steady state, as a trough, and with albumin recorded within 7 days prior.

Table 4. Appropriateness of phenytoin maintenance levels.

The timing that levels were taken in relation to the previous once daily dose has been summarised below (see Figure 1). Notably, of these levels, 45% (94) were taken as a trough (22-24 hours post-dose), while 16.7% (35) were inappropriately taken within the first 8 hours of the preceding dose.

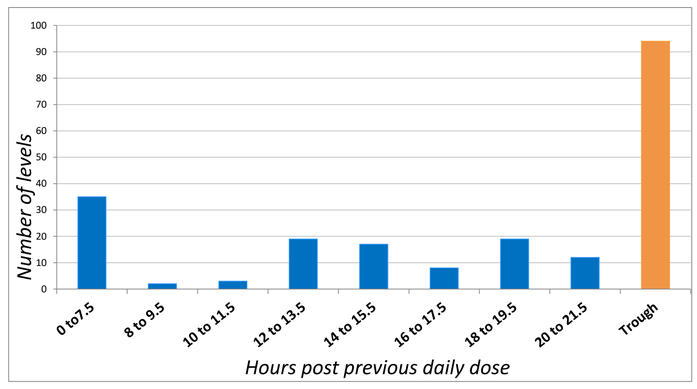

Figure 1. Timing of phenytoin levels relative to the most recent dose prior.

The appropriateness of dose adjustment for phenytoin maintenance doses has been summarised below in Figure 2.

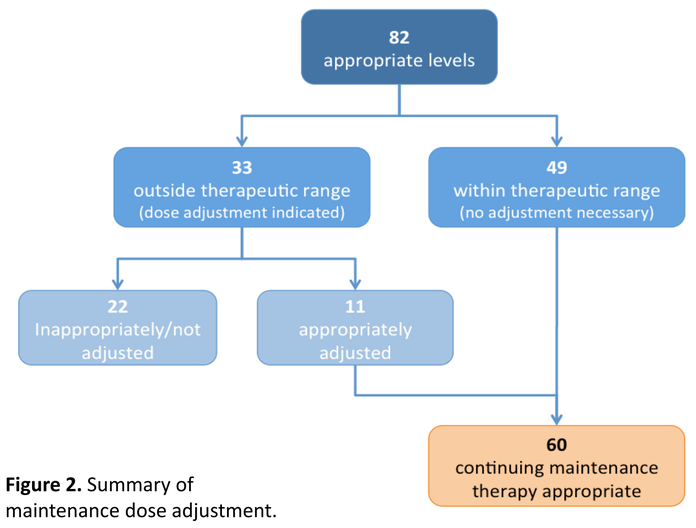

Figure 2. Summary of maintenance dose adjustment.

Conclusion

This study showed that there is room for improvement regarding phenytoin TDM at the Royal Melbourne Hospital, as 13.9% of all levels taken in 2018 were considered completely appropriate.

The average loading dose observed overall was 15.5 mg/kg, though there was a significant range (6.0 – 25.0 mg/kg). This was in contrast to that which produced a therapeutic level post-first dose (16.9 mg/kg), and as such, only 55.6% of initial loads resulted in a therapeutic level. Just 52.4% of all maintenance levels were in the therapeutic range, though where levels were outside of the target range, dose adjustment was relatively well performed. For both loading and maintenance dosing, the average unadjusted level was markedly lower than the adjusted, underlining the importance of taking a concurrent albumin level (only completed in 48.7% of levels).

This study presents a prime opportunity for the development of a hospital-wide phenytoin guideline and highlights the need for subsequent multidisciplinary education to standardise practice.

Acknowledgements

Study data were collected and managed using the REDCap® electronic data capture tool hosted by the Royal Melbourne Hospital Business Intelligence Unit.

References

1. MIMS Online [Internet]. New South Wales Australia: MIMS Australia Pty Ltd; 1991. Dilantin Full PI; [updated 2019 Apr 01; cited 2019 Apr 20]. Available from: https://www-mimsonline-com-au.ezproxy.lib.monash.edu.au/Search/FullPI.aspx?ModuleName=Product%20Info&searchKeyword=dilantin&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=5250001_2
2. Australian Medicines Handbook Pty Ltd. Phenytoin [Internet]. Adelaide; 2019 [cited 2019 Feb 23]. Available from: https://amhonline-amh-net-au.ezproxy.lib.monash.edu.au/chapters/neurological-drugs/antiepileptics/other-antiepileptics/phenytoin?menu=hints
3. Therapeutic Guidelines Ltd. When to measure serum concentrations of antiepileptic drugs [Internet]. West Melbourne; 2017 Nov [cited 2019 Feb 23]. Available from: https://tgldcdp-tg-org-au.ezproxy.lib.monash.edu.au/viewTopic?topicfile=epilepsy-and-seizures&guidelineName=Neurology#toc_d1e457
4. Burton M, Shaw L, Schentag J, Evans W. Applied Pharmacokinetics and Pharmacodynamics: Principles of therapeutic drug monitoring. 4th ed. Maryland: Lippincott Williams & Wilkins; 2006.p463-91.
5. Birkett D. Therapeutic Drug Monitoring. Aust Prescr [Internet]. 2997 Jan [cited 2019 Apr 24]; 20(1)9-11. Available from: https://www.nps.org.au/australian-prescriber/articles/therapeutic-drug-monitoring DOI: 10.18773/austprescr.1997.005
6. Kiang T, Ensom M. A Comprehensive Review on the Predictive Performance of the Sheiner-Tozer and Derivative Equations for the Correction of Phenytoin Concentrations. Ann Pharmacother [Internet]. 2016 Apr [cited 2019 Apr 20]; 50(4)311-25. Available from: https://journals-sagepub-com.ezproxy.lib.monash.edu.au/doi/pdf/10.1177/1060028016628166 DOI: 10.1177/1060028016628166
7. Tobler A, Hosli R, Muhlebach S, Huber A. Free phenytoin assessment in patients: measured versus calculated blood serum levels. Int J Clin Pharm [Internet]. 2016 Apr [cited 2019 Apr 20]; 38(2):303-9. Available from: https://search-proquest-com.ezproxy.lib.monash.edu.au/docview/1780100522?accountid=12528 DOI: 10.1007/s11096-015-0241-x
8. Schoenenberger R, Tanasijevic M, Jha A, Bates D. Appropriateness of antiepileptic drug level monitoring. JAMA [Internet]. 1995 [cited 2019 May 08];274(20):1622-6. Available from: https://jamanetwork-com.ezproxy.lib.monash.edu.au/journals/jama/fullarticle/391828
9. Wu M, Lim W. Phenytoin: A guide to therapeutic drug monitoring. Proceedings of Singapore Healthcare [Internet]. 2013 [cited 2019 May 01]; 22(3):198-202. Available from: https://journals.sagepub.com/doi/pdf/10.1177/201010581302200307
10. Brophy G, Tesoro E, Schrote G, Garnett W. Pharmacist impact on posttraumatic seizure prophylaxis in patients with head injury. Pharmacotherapy [Internet]. 2002 [cited 2019 May 08]; 22(2):251-5. Available from: https://accpjournals-onlinelibrary-wiley-com.ezproxy.lib.monash.edu.au/doi/epdf/10.1592/phco.22.3.251.33547