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Hazards of Loading Doses

January 1, 2017
Mucksavage JJ, Tesoro EP. Hazards of Loading Doses. PSNet [internet]. 2017.
https://psnet.ahrq.gov/web-mm/hazards-loading-doses

The Case

A 40-year-old woman was recently discharged after a prolonged hospitalization for seizures and a cardiac arrest. Two days after discharge, she presented to the emergency department (ED) complaining of headache, abdominal pain, and diarrhea. Her stool tested positive for *Clostridium difficile* colitis, which led to admission to the medicine service. As part of the initial ED patient evaluation, the neurology fellow (seeing the patient because of her history of seizures) noted a subtherapeutic phenytoin serum level and subsequently recommended that she be re-loaded with phenytoin. The ED physician ordered the correct loading dose of intravenous (IV) phenytoin, to be administered every 8 hours for 3 doses. Unfortunately, the physician failed to order that the dose be switched back to the appropriate maintenance dose of once daily after the loading was completed, so the patient continued to receive IV phenytoin every 8 hours.

Three days after admission, the patient developed somnolence, severe ataxia, and dysarthria. These new symptoms prompted the medicine provider to evaluate the patient's hospital course and medication history. After noticing the phenytoin dosing at every 8 hours, he checked a serum phenytoin level, which returned at 3 times greater than the maximum therapeutic level. The patient's neurologic symptoms persisted for 3 days after discontinuation of phenytoin. However, no long-term harm occurred.

Investigation of the event revealed that the admitting medicine physician did notice the unusually high phenytoin dose; however, he did not question it because he assumed it was recommended by the neurology service. Apparently, the neurology consultant told the ED physician about his recommendations, but no formal consult note had been placed in the patient's chart to provide clear instructions for phenytoin dosing or monitoring.

The Commentary

by Jeffrey J. Mucksavage, PharmD, and Eljim P. Tesoro, PharmD

Loading doses are an important way to rapidly achieve therapeutic drug concentrations or to achieve an immediate clinical response. Loading doses are larger than maintenance doses and most are administered

in a single bolus, although some drugs (e.g., digoxin, amiodarone) may require multiple loading doses administered over several hours to days.(1) Drugs with shorter half-lives, such as heparin when used to treat pulmonary embolism, may also need a loading dose to attain an immediate therapeutic effect.(2)

In the case described above, it was appropriate to load phenytoin in response to a subtherapeutic serum level. However, IV phenytoin loading doses are typically given in a single, one-time dose with maintenance doses starting approximately 12 hours afterwards. Loading regimens that use multiple doses, as in this case, can be confusing and may be interpreted as maintenance doses if the number of doses or the duration is not specified or mistakenly omitted. Not only is the multiple-dose regimen potentially confusing, in phenytoin's case it is also unnecessary, since loading doses are intended to achieve therapeutic levels immediately.

For many decades, phenytoin has been used for both the treatment and prophylaxis of seizures. Although there is great clinical experience with this drug, its unusual pharmacokinetic properties and potential for drug interactions complicate its clinical use. Due to the relatively long and variable time to achieve steady state, phenytoin loading doses are commonly administered to rapidly achieve therapeutic concentrations. For phenytoin-na?ve patients, or those in whom no phenytoin concentration is detectable, simple weight-based, one-time IV loading doses generally suffice. However, in those with a detectable yet subtherapeutic concentration, more complicated calculations are required.(3)

In such situations, the calculation of the maintenance dose can also be complex. With many drugs, an increase in dose will give you a proportional increase in expected concentration. Phenytoin is an exception. Due to the nonlinear kinetics of phenytoin occurring within the therapeutic range, small changes in dose can lead to exponential increases in concentration.(4) This occurs as a result of overwhelming the hepatic metabolic enzyme activity. Additional amounts of phenytoin cannot be metabolized, resulting in a disproportional increase in concentration. If repetitive loading doses are administered, a significant increase in the concentration can ensue, resulting in clinical signs of phenytoin toxicity as experienced by this patient.

Although the use of loading doses can be problematic, the literature reveals surprisingly little documentation of harm from loading doses. A retrospective review of loading dose misadventures was performed by the British National Health Services, which identified 2 deaths associated with phenytoin during 5 years of data collection.(5) One case mirrored the case above, in that it involved inadvertent continuation of loading doses as a maintenance regimen. Overall, there were 61 nonfatal cases of phenytoin incidents out of 1165 total reported errors involving loading doses. Phenytoin was listed as the fourth leading drug associated with loading dose incidents, behind only warfarin, amiodarone, and digoxin.

Another analysis of adverse events associated with loading doses was subsequently performed by the Pennsylvania Patient Safety Advisory.(6) This analysis spanned 8 years of data and reviewed errors in prescribing, dispensing, and administering loading doses reported to a state-wide adverse events reporting system. In total, 580 adverse events were reviewed, and 79% of these reached the patient. Fifteen (2.6%) were deemed serious events, including 2 patient deaths. Vancomycin, clopidogrel, and phenytoin were the top three medications associated with loading dose adverse events. In a limited review of the reported events, three loading dose error subtypes were identified: loading dose omitted or delayed (25.5%), wrong

loading dose given (15.2%), and loading dose given multiple times (7.1%).(6) Interestingly, a published vignette included in the analysis describes a patient who was administered multiple loading doses of phenytoin due to a miscommunication during the transfer of care from the emergency department to the intensive care unit. This event occurred despite multiple computer alerts for duplicate dosing.

Some strategies have been recommended to decrease errors associated with loading doses.(7,8) From an organizational perspective, these include identifying drugs that have the greatest risk of causing harm, limiting the number of drugs on formulary that require loading doses, assisting clinicians with calculations via order sets or worksheets, improving communication, and fostering error reporting. The individual clinician can also verify whether administering a loading dose is warranted and ordered correctly.(8) Furthermore, clinicians should ensure they have all of the data necessary to calculate patient-specific loading doses.(8) Since transitions of care are prone to medication errors, proper medication reconciliation procedures and handoffs are important strategies to reduce the risk of inadvertent loading dose continuation.(7) In addition, computerized prescribing systems should have checks in place that flag potential dosing errors and provide correct dosing recommendations. Computerized provider order entry systems should separate orders for loading doses and maintenance doses to ensure clarity of intent.

This case illustrates the confusion that can surround the use of loading doses, particularly with phenytoin. It also shows how poor documentation of recommendations from consultants can lead to adverse consequences. While the urgency of patient care precludes waiting for every recommendation to be documented in the medical record prior to implementation, it is critical that recommendations are communicated in writing and properly referenced if needed. Drug regimens with an unusual dose or frequency should be verified directly with the initiating service (in this case, the neurologist) rather than with the ordering prescriber, who may not be familiar with the nuances of dosing specialized medications. Consulting with a clinical pharmacist is also highly encouraged for assistance in dosing high-risk medications.

Take-Home Points

- Intravenous loading dose regimens for phenytoin should be restricted to a single dose.
- Unusual dosing should always be questioned and verified directly with the initiating service; proper documentation with appropriate referencing is essential to avoid confusion.
- Computerized prescribing systems should have dosing checks in place that not only flag potential dosing errors, but also provide correct dosing recommendations.
- Orders for loading doses and maintenance doses should be separated in computerized order entry systems to ensure clarity of intent.
- The prescribing and administration of loading doses should be clearly communicated between clinicians, particularly around transitions of care.

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This project was funded under contract number 75Q80119C00004 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The authors are solely responsible for this report's contents, findings, and conclusions, which do not necessarily represent the views of AHRQ. Readers should not interpret any statement in this report as an official position of AHRQ or of the U.S. Department of Health and Human Services. None of the authors has any affiliation or financial involvement that conflicts with the material presented in this report. View AHRQ Disclaimers