Original Article

Pharmacokinetics of Phenobarbital in Microenema Via Macy Catheter Versus Suppository

Y. W. Francis Lam, PharmD, FCCP, Ansom Lam, MD, and Brad Macy, RN, BSN, BA, CHPN

Department of Pharmacology (Y.W.F.L.), University of Texas Health Science Center at San Antonio, San Antonio, Texas; WCCT Global (A.L.), Cypress, California; and Hospi Corporation (B.M.), Newark, California, USA

Abstract

Context. The oral route is compromised for nearly all patients approaching death. When agitation, seizures, or other intractable symptoms occur, a quick, discreet, comfortable, and effective alternate route for medication delivery that is easy to administer in the home setting is highly desirable.

Objectives. To characterize the early absorption profile, variability, and comfort of phenobarbital given in microenema suspensions delivered via the Macy Catheter® (MC) vs. the same dose given via suppository.

Methods. This was a randomized, open-label, crossover study comparing the early absorption profile of equal doses of phenobarbital administered rectally in three treatment phases: phenobarbital suppository and two different microenemas with phenobarbital tablets crushed and suspended in 6 mL (MC-6) or 20 mL (MC-20) of tap water.

Results. Mean plasma phenobarbital concentrations at 10 minutes were 12× higher for MC-20 and 8× higher for MC-6 compared to suppository. Concentrations achieved in 30 minutes via MC-20 took almost three hours to achieve with suppository. Mean AUC values were higher for MC-20 and MC-6 (82% and 46%, respectively) vs. suppository ($P < 0.05$). There was less variability in absorption for MC-20 and MC-6 (1.4- to 1.9-fold difference) compared to a 4.4-fold difference via suppository. MC administrations were reported as "not uncomfortable" compared to suppositories, which were reported as "mildly uncomfortable" ($P < 0.05$).

Conclusion. These results suggest phenobarbital oral tablets crushed and suspended in water and administered via the MC is superior to suppository in delivering the medication reliably and rapidly. J Pain Symptom Manage 2016;■:■−■. © *2016 The Authors. Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Key Words

Rectal administration, phenobarbital, suppository, hospice care

Introduction

Phenobarbital is a commonly used medication in hospice and palliative care. It is used for controlling terminal agitation and seizures at the end of life and can also be used for palliative sedation in patients with severe intractable suffering uncontrolled by more standard therapies. A large number of hospice patients needing symptom control are no longer able to take oral medications due to active symptoms or deterioration of physical and/or cognitive function as they approach death. The ability to give phenobarbital easily and effectively in the home setting to patients with no viable oral route could allow them to remain at home with symptoms well controlled, while avoiding in-patient admissions and allowing more patients to die in the setting of their choice. Furthermore, the ability to rapidly control agitation and seizures in the home setting could substantially decrease the burden of care on the caregiver and the hospice team, improve the quality of the death experience, and lead to an

Address correspondence to: Y. W. Francis Lam, PharmD, FCCP, Department of Pharmacology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, USA. E-mail: lamf@uthscsa.edu

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overall decrease in cost of care to the hospice agency and the health care system as a whole.

The Macy Catheter® (MC) is a relatively new FDA-cleared medical device designed for rectal administration of fluids and medications. The catheter is placed by a clinician with a procedure much like a urinary catheter placement.[1] The tip is placed just past the rectal sphincter and a small balloon is inflated to hold the catheter in place (Fig. 1). Medications and/or fluids are delivered through a medication port on the patient's leg, allowing for repeated administrations without having to reposition the patient or repenetrate the rectal vault. Stool in the rectum is not a contraindication for use unless the rectal vault is too full for insertion or the patient has diarrhea. Solid forms of oral medications known to be absorbed rectally can be crushed, mixed with water, and delivered in a microenema suspension or solution with an enteral syringe. Liquid or presuspended forms of medications are injected directly into the catheter. The catheter is flushed with 3 mL water after the medication dose.

In a retrospective chart review conducted by Macy et al. at a multisite home hospice agency, phenobarbital was administered in a microenema suspension to 26 end-stage hospice patients with agitation and two patients with seizures. Both agitation and seizures were controlled quickly and effectively.[2] The anecdotal observations were intriguing, and the investigators hypothesize that the rapid control of agitation and seizures observed may reflect a rapid absorption profile of phenobarbital when delivered to the rectum in microenema form. Because rapid absorption, dose reliability, and comfort of administration are important factors to consider in controlling severe symptoms, especially in patients who have limited time left of life, we conducted the present study to evaluate the early absorption profile of phenobarbital administered in microenema suspensions via MC in comparison to a conventional suppository dosage form, and how different fluid volume of suspensions affects absorption profile. The primary study aim was to evaluate the extent, rate, and variability of phenobarbital absorption. A secondary aim was to validate that medication administration via the MC was comfortable and to compare the degree of comfort to that experienced via suppository.

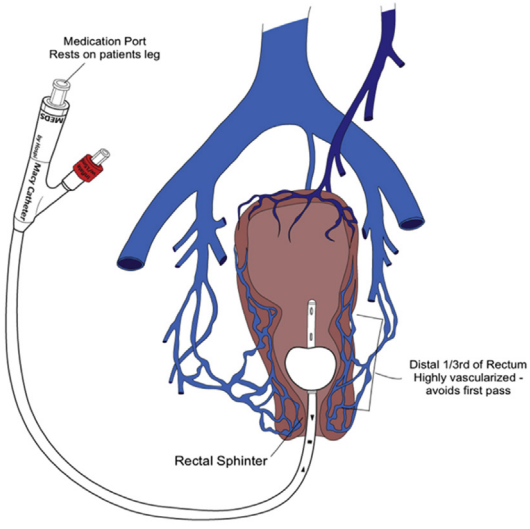

Fig. 1. Diagrammatic representation of the Macy Catheter in relation to the rectum.

Methods

After providing their informed consent, 12 healthy adult subjects were recruited for the study. The study was approved by an institutional review board for human research (Aspire IRB, Santee, CA). All subjects had a screening visit during which medical history, physical examination, and standard laboratory panels were performed to assure healthy status.

The study used a single-center, open-label, randomized, crossover design comparing the early absorption profile (first 12 hours after drug administration) of phenobarbital administered rectally via three different methods (three treatment phases), Treatment Phases 1 and 2 consisted of drug administration via the MC with phenobarbital 194.4 mg crushed and suspended in 6 mL (MC-6) and 20 mL (MC-20) of tap water, respectively. The pH of both suspensions was approximately 7 per Hydrion™ test strip analysis. Treatment Phase 3 consisted of 194.4 mg phenobarbital administered via compounded suppository. Suppositories were prepared in two batches of 100 by pulverizing two hundred 97.2 mg phenobarbital tablets (NDC: 0603-5168) and mixing with 180 gm polyethylene glycol and 7.67-gm polysorbate base. The mixture was poured into 100 molds and allowed to cool at room temperature. The first batch was used for Study Periods 1 and 2, and the second batch for Study Period 3. For each subject, a one-month washout period separated each study period.

Subjects spent the night in the research facility on the evening before Study Period 1. They were administered a bisacodyl suppository to encourage bowel movement. On the morning of the study day, subjects randomized to receive either Treatment Phase 1 or 2 had the MC placed before phenobarbital administration. Study doses of phenobarbital were given about 30 minutes later via the MC for subjects randomized to Treatment Phases 1 and 2, and via suppository for subjects randomized to Treatment Phase 3.

For each subject, 10 mL of blood was obtained through an indwelling catheter before and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours