Original Article

Pharmacokinetics of Phenobarbital in Microenema Via Macy Catheter Versus Suppository

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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;51:994–1001.

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

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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.

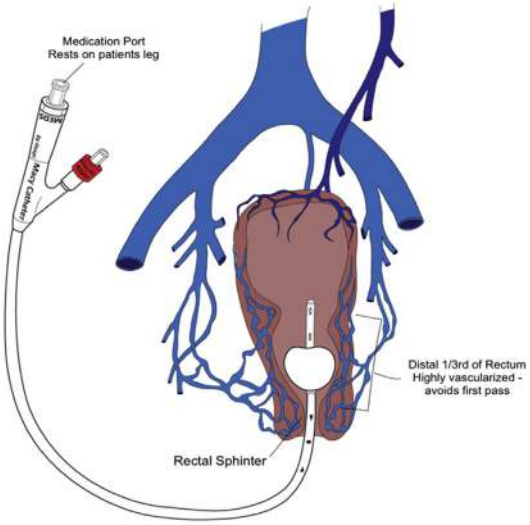

Fig. 1. Diagrammatic representation of the Macy Catheter in relation to the rectum.

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

after drug administration. All blood samples were centrifuged and the harvested plasma frozen in aliquots at −80°C for subsequent determination of phenobarbital concentrations. In addition, the level of discomfort with the specific mode of drug administration was assessed with a simple subjective numeric rating scale at the time of administration as follows: 0 = not felt at all; 1 = felt, but not uncomfortable; 2 = a little uncomfortable but not very much; 3 = uncomfortable; and 4 = hurt and painful.

All subjects were discharged from the research unit after the 12-hour blood sampling. Subjects were required to have a driver pick them up at the facility. After the appropriate washout time of one month, subjects returned to receive the second and then the third crossover drug administration according to study randomization, in Study Periods 2 and 3, respectively. The same study procedures and assessments were repeated in both Study Periods as in Study Period 1.

Plasma phenobarbital concentrations were determined at the University of Texas Health Science Center San Antonio by a validated high-performance liquid chromatography assay. Plasma (300 μL) was mixed with 50 μL of the internal standard phenytoin and 5 mL of t-butyl methyl ether. The mixture was then placed on a mechanical shaker for 15 minutes before centrifugation at 2700 rpm for 15 minutes. The organic layer was transferred to another tube and evaporated to dryness under nitrogen. The residue was dissolved in 300 μL of mobile phase (water:acetonitrile:methanol, 59:26:15 v/v) and 25 μL was injected onto a Symmetry C-12 column at 1 mL/minute. The analytical method has a linear range of 0.5−4.0 mcg/mL with a lower detection limit of 0.1 mcg/mL The intraday and interday CV of the low control sample was 3.8% and 3.5%, respectively; 2.8% and 3.4%, respectively for the medium control sample; and 4.1% and 3.8%, respectively, for the high control sample.

Because the objective of the study was to compare the differences in extent and rate of early absorption, plasma samplings were only performed for 12 hours after drug administration. The phenobarbital area under the time curve (AUC_{0-12}) was determined by trapezoidal rule. Maximal concentration (Cmax) and time to maximal concentration (Tmax) were determined by visual inspection of the concentration-time curves. Differences in AUC_{0-12} and concentrations after drug administration among the three different routes were tested for statistical significance by paired Student t-test, with 0.05 as the level of significance.

Results

Seven subjects completed all three treatment phases and two subjects completed two phases (MC-6 and suppository only). Three subjects completed only one treatment phase (two for the MC-6 phase and one for the MC-20 phase). Comfort assessment, but not pharmacokinetic analysis, was performed for these three subjects. The demographics and AUC_{0-12} values for the nine subjects completing at least two treatment phases are summarized in Table 1. All "non-completers" cited the study length as the sole reason for withdrawing from the study.

During the entire 12-hour time period, the mean phenobarbital concentration achieved for the seven subjects completing all three treatment phases was consistently higher with the MC, regardless of the volume used to suspend the drug, as compared to the suppository. In addition, the mean concentration achieved with MC-20 was consistently higher than with MC-6 at every sampling time point (Fig. 2). The phenobarbital AUC_{0-12} (mean ± SD) achieved in these seven subjects were 82% and 46%, higher via MC-20 and MC-6 respectively (33.1 ± 4.3 mcg × hr/mL and 26.6 ± 6.2 mcg × hr/mL) than that achieved using suppository (18.2 ± 15.0 mcg × hr/mL) ($P < 0.05$). There was also less variability in the extent of drug absorption with the MC-20 and MC-6 administrations (1.4- to 1.9-fold difference, respectively) as compared to a 4.4-fold difference with

Table 1
Subjects' Demographics and Achievable Systemic Drug Exposure[a]

Subject	Sex	Age (yrs)	BMI	Weight (kg)	AUC for MC-6 (mcg × hr/mL)	AUC for MC-20 (mcg × hr/mL)	AUC for Suppository (mcg × hr/mL)
1	F	31	29.4	75.6	27.6	37.3	27.8
2	F	32	28.7	74.1	25.7	31.6	27.4
3	M	25	29.4	93.1	25.6	27.2	0.0
4	M	22	21.4	63.1	40.0	38.4	0.0
5	F	25	25.9	65.6	22.8	36.3	33.7
6	M	23	25.1	74.4	23.4	29.5	30.7
7	M	24	20.6	76.1	21.4	31.7	7.6
8	F	22	22.7	59.8	33.0	—	18.1
9	M	29	22.4	75.0	29.5	—	30.5

[a]As measured by area-under-the plasma concentration-time curve for 12 hours after drug administration (AUC_{0-12}). The first seven subjects completed all phases of the study.

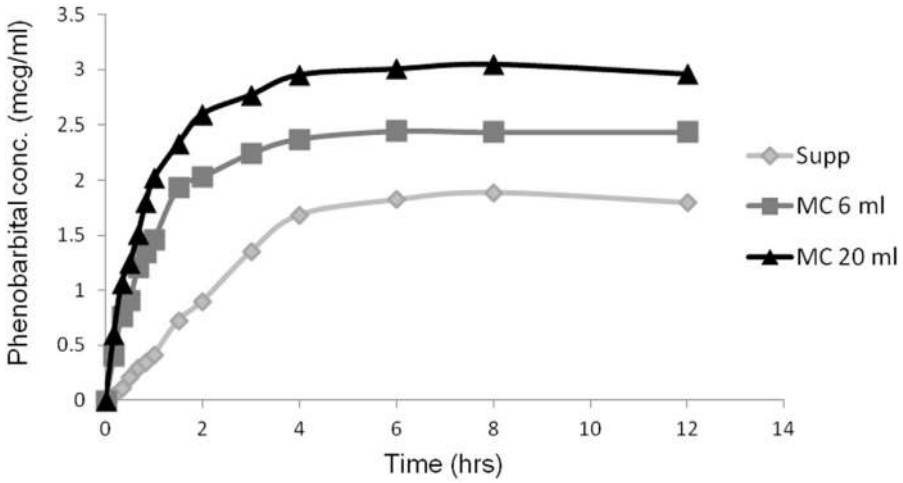

Fig. 2. Mean plasma concentration-time curve for seven study completers in the study.

drug administration via the suppository. Figure 3 shows variability of phenobarbital absorption via MC-6 (Fig. 3a) and MC-20 (Fig. 3b) administrations versus suppository for all seven subjects. When data for the two subjects who had no detectable absorption were excluded, variability is still quite high for the

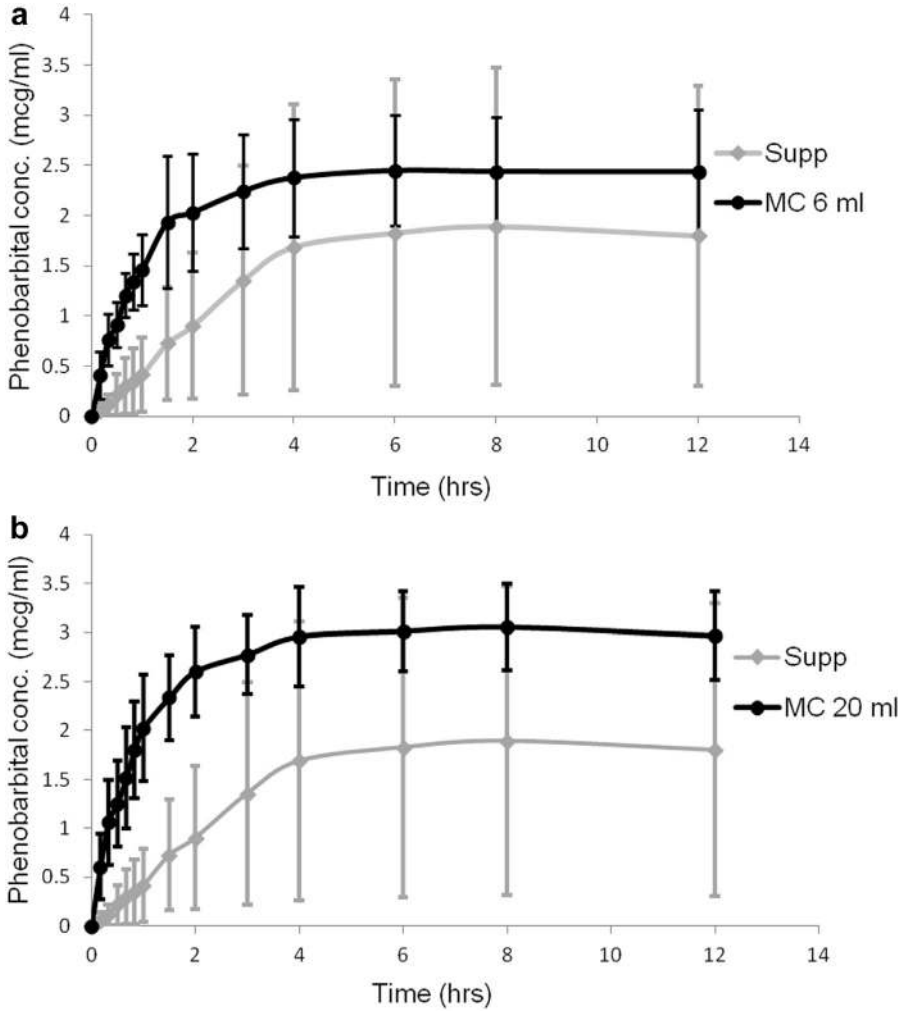

Fig. 3. Variability of phenobarbital absorption profile for seven study completers between suppository and MC-6 (a, upper panel) and between suppository and MC-20 (b, lower panel).

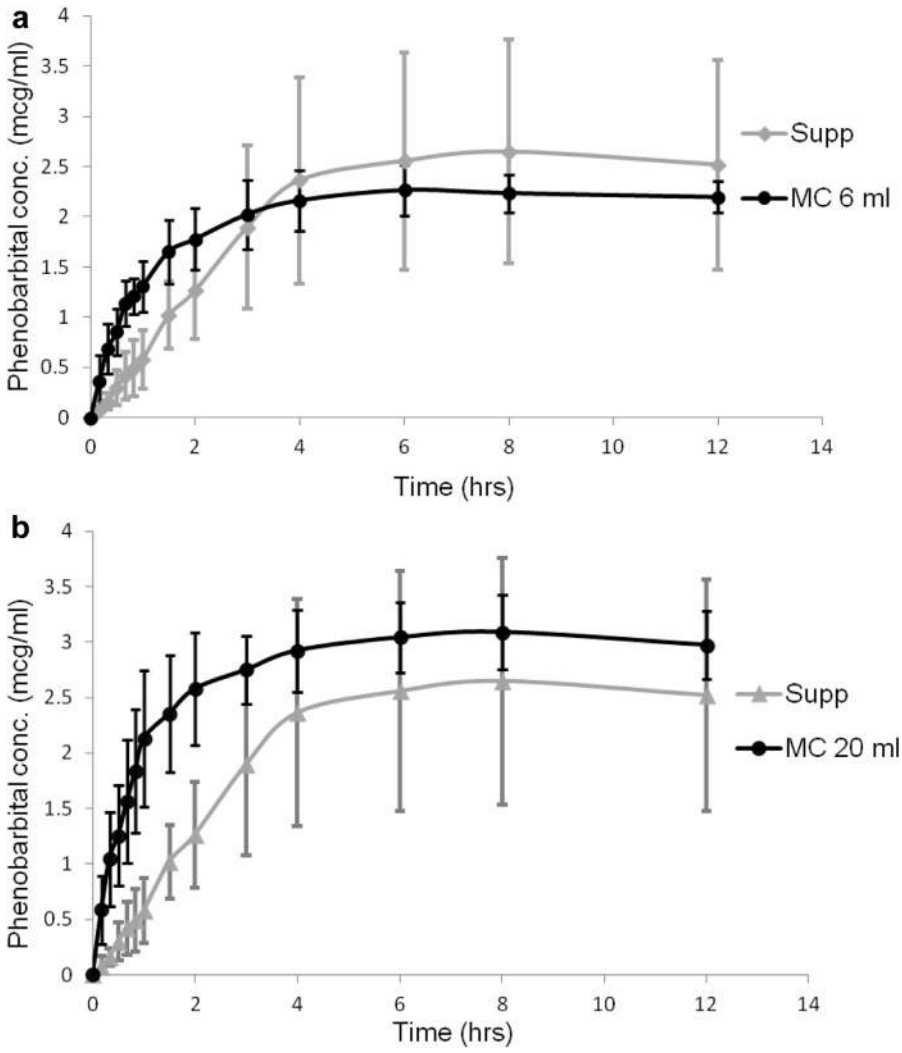

Fig. 4. Variability of phenobarbital absorption profile for five completers (excluding the two subjects with "suppository failure") between suppository and MC-6 (a, upper panel) and suppository and MC-20 (b, lower panel).

suppository compared to both MC administrations (Figs. 4a and 4b).

For the two subjects that only completed the MC-6 and suppository phases, the AUC_{0-12} and Cmax were 82% and 84.8% higher in one subject with drug delivered by MC-6 (33.0 mcg × hr/mL and 3.3 mcg/mL, respectively) vs. suppository. In the other subject, AUC_{0-12} and Cmax values were comparable between MC-6 (29.5 mcg × hr/mL and 2.8 mcg/mL, respectively) and suppository (30.5 mcg × hr/mL and 3.1 mcg/mL, respectively).

The ranges of Cmax achieved in the seven subjects who completed all three treatment phases were higher with both MC administrations (2.0 to 3.8 mcg/mL for MC-6 and 2.4 to 3.7 mcg/mL for MC-20) compared to 0.7 to 3.4 mcg/mL achieved with suppository. It is noteworthy that two of these subjects did not achieve measurable concentration after suppository administration over the entire study period. In contrast, the same two subjects achieved a Cmax of 3.7 and 2.4 mcg/mL (with MC-20), and 3.8 and 2.3 mcg/mL (with MC-6). No absorption failures occurred for any of the 16 MC dosing administrations analyzed for phenobarbital pharmacokinetics.

Significant differences in rate of drug absorption were observed in the study, being much faster for both MC-20 and MC-6 administrations compared to suppository. At 10 minutes after drug administration, mean concentrations were 12 times higher for MC-20 (0.6 mcg/mL) and 8 times higher for MC-6 (0.4 mcg/mL) compared to suppositories (0.05 mcg/mL) ($P < 0.005$). Comparable mean concentrations achieved in 30 minutes via MC-20 took almost three hours to attain with the suppository route (Fig. 2). In addition, absorption of 60% and 66% of the mean Cmax, respectively, was achieved at one hour after MC-6 and MC-20 administration. In contrast, only 22% of the mean Cmax was achieved at one hour

after suppository administration. With the suppository, less than half (47.6%) of the mean Cmax was absorbed at two hours after drug administration, as compared to 83.9% and 82.6% for MC-20 and MC-6, respectively. The rate of drug absorption was also higher for the two subjects receiving only MC-6 and suppository with 48% and 53% of the Cmax achieved in both subjects at one hour after drug administration via the MC as compared to 34% and 42.5% via suppository.

Excluding the suppository failures in two subjects who completed all treatment phases, the early absorption profile was still much more rapid via either MC method of dosing (Fig. 5). Mean concentrations at 10 minutes were 5.2× higher for MC-6 and 8.4× higher for MC-20 vs. suppository. Mean concentration achieved in 30 minutes with MC-20 took two hours to achieve with suppository. Mean AUC was higher for the MC-20 (33.3 ± 3.4 mcg × hr/mL) but comparable between MC-6 vs. suppository (24.2 ± 2.4 mcg × hr/mL vs. 25.4 ± 10.3 mcg × hr/mL). The achievable Cmax was more variable with suppository (0.7 to 3.4 mcg/mL) than with either MC-20 (2.9 to 3.4 mcg/mL) or MC-6 (2.0 to 2.6 mcg/mL).

There were a total of 19 MC drug administrations and nine suppository administrations performed in the study. Data was collected on comfort of insertion for all administrations. Based on the five-point numeric subjective rating scale described in the section Methods, 18 of the 19 MC insertions (95%) were reported as "not uncomfortable" (Rating 1) by the subjects. Only one subject reported "mildly uncomfortable" (Rating 2). On the contrary, only three of the nine suppository insertions (33%) were reported as "not uncomfortable," five reported the insertion as "mildly uncomfortable" (56%), and one patient reported the insertion as "uncomfortable" (Rating 3). Other than the different levels of discomfort, there were no adverse events reported for any of the subjects.

Discussion

The rectal route of administration is a good alternative for patients when the oral route is not a viable option. It is especially beneficial in patients with advanced illness or those at end-of-life.[3] Many medications administered rectally are absorbed quickly and effectively through the rectum. The rectal mucosa is highly vascularized and medications delivered to the distal third of the rectum partially avoid the first pass effect through the liver (Fig. 1), allowing for greater bioavailability of many medications than that achieved with the oral route.[3–6] Our study demonstrates that phenobarbital oral tablets crushed and suspended in water and administered via the MC is superior to suppository in delivering the medication reliably, rapidly, and comfortably.

Our data are consistent with that of Moolenaar et al. who demonstrated that phenobarbital in both sodium and acid forms mixed in a 20 mL aqueous microenema solution consisting of 0.5% methylcellulose and distilled water is well absorbed rectally, with practically complete absorption at 6.5 hours after drug administration.[7] They further demonstrated that drug absorption from microenema solution was faster than from suppositories. In another study, Graves et al. compared rectal and intramuscular absorption of 5 mg/kg sodium phenobarbital and found no significant difference in total AUC between the two routes of administration.[8]

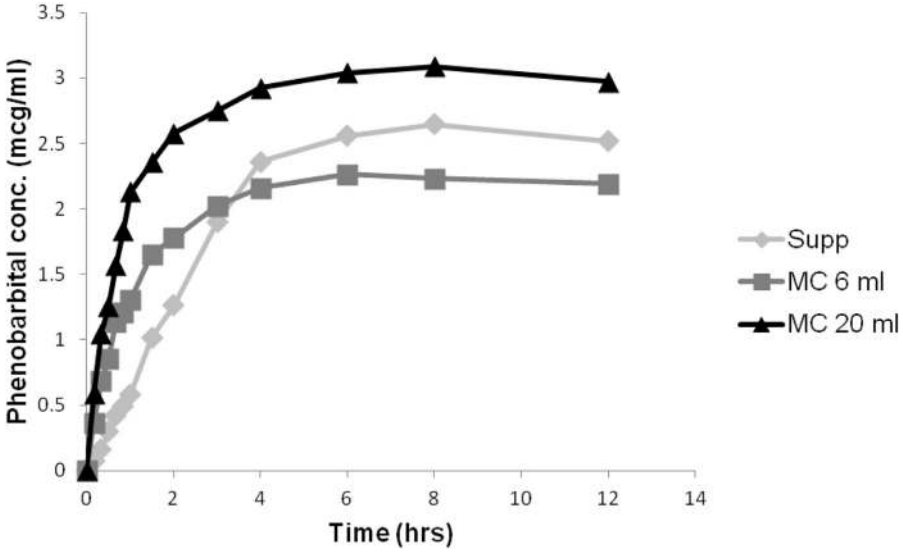

Fig. 5. Mean plasma concentration-time curve for five completers (excluding the two subjects with "suppository failure").

Enabling quick and easy rectal administration of readily available oral forms of medications could have practical importance in keeping patients comfortable at home, while decreasing the burden of care on caregivers and the health care system as a whole. This is the first study to evaluate the early absorption profile, reliability of dose delivery, and comfort of administration of phenobarbital oral tablets given in microenema form with the MC, a pragmatic and easy method of administering medications that could be easily used by a caregiver in the home setting.

Drug absorption from suppository can be variable depending on the method of preparation and the presence of stool in the rectal vault.[5] Based on anecdotal experience, a suppository, if actually placed in a mass of stool, may provide minimal medication bioavailability. Two of nine subjects (22%) in our study who received suppositories had no detectable phenobarbital concentrations at any point after administration. It is not known why these suppositories failed to be absorbed. All suppositories were prepared the same way for the study, so it is unlikely that it was a dose uniformity issue or preparation failure. One possibility could be suppository placement near or in a mass of stool.

It is noteworthy to mention that there were no absorption failures for any of the 16 MC-delivered doses that had pharmacokinetic analysis in this study. All MC-delivered doses achieved a Cmax of at least 2 mcg/mL, compared with suppositories in which two subjects had no drug absorption, and one only achieved a relatively low Cmax of 0.71 mcg/mL.

Medications administered as aqueous liquid formulations are generally absorbed more quickly than the same medication administered via suppository.[4,9] Another possible reason contributing to absorption failure from suppository in two study subjects, and low Cmax of 0.7 mcg/mL in the third subject, could be due to limited fluid volume in the rectum resulting in inadequate dissolution of the medication. In this study, increasing the amount of water to suspend phenobarbital resulted in a faster and better absorption profile, and decreased dose variability. For the seven subjects who completed all three treatment phases, mean phenobarbital concentrations at 10 minutes were 12 times higher for MC-20 (0.6 mcg/mL) and 8 times higher for MC-6 (0.4 mcg/mL) compared to suppositories (0.05 mcg/mL). Phenobarbital administered via suppository took eight hours to attain concentrations achieved in one hour via MC-20 and 1.5 hours via MC-6. The extent of absorption as measured by AUC_{0-12} were 82% and 46% higher with MC-20 and MC-6, respectively, than with suppository. Variability in extent of absorption was also correlated with the amount of water used to suspend phenobarbital, with a 1.4-fold difference among subjects for the MC-20, a 1.9-fold difference for the MC-6, and a 4.4-fold difference for the suppository. Based on our findings, the suppository could not be recommended for rapid and reliable absorption of medication. The differences in rate and extent of absorption could be clinically significant when quick and effective control of symptoms is needed, as terminal patients are many times quite dehydrated making absorption of medication from suppository even more challenging. If absorption is delayed significantly via suppository, degradation of the medication could occur by bacterial metabolism, decreasing the overall bioavailability of the drug.[3]

Caregivers are many times reluctant to use suppositories due to invasion of privacy and embarrassment issues. Suppositories can also be physically uncomfortable when administered as demonstrated in this study. Based on a 0 to 4 rating scale, subjects assessed administration of phenobarbital via suppositories to be "mildly uncomfortable" (mean = 1.77) compared to administration via the MC as "not uncomfortable" (mean = 1.0) ($P < 0.05$). Although mild discomfort may be considered an acceptable tradeoff when treating active severe symptoms, repeated uncomfortable procedures could disturb or awaken calm patients and escalate agitated or painful states, negating symptom control efforts. In addition, suppository administration involves repositioning of the patient with each dosing, which could be painful and agitating for a patient and difficult for elderly or disabled caregivers.

A primary limitation of our study is related to generalizability of the findings from healthy young volunteers to a very ill and generally older patient population. Further research is needed to better define the potential role of microenema-delivered medications via the MC. Determination of the optimal volume for suspending medications should be further studied. Characterization of the absorption kinetics of frequently used palliative drugs that have not been well studied rectally, such as haloperidol and dexamethasone,[3,4,6,10] will assist clinicians in developing a formulary for palliative medications that can be given effectively in microenema form. Clinical assessment of symptom control and tolerability of the MC, as well as ease and acceptability of use in the home and inpatient hospice settings would be beneficial. Studies on the effectiveness of the MC as a tool to facilitate discharge from higher acuity settings or avoid admission into these settings would further our understanding of the role of the MC in end-of-life care.

Conclusion

The absorption kinetics of MC-administered phenobarbital microenemas were superior to compounded

phenobarbital suppositories, including rate of early absorption, overall absorption, variability, and comfort of administration. Based on these findings, the use of compounded phenobarbital suppositories may produce unreliable and delayed results for managing agitation, seizures, or intractable suffering. Furthermore, based on our findings of the correlation between increased fluid and increased absorption/decreased variability, the practice of inserting solid tablets directly into the rectum without dispersing them in water may provide even worse results than that of suppositories. On the other hand, the administration of microenemas with a rectal access device such as the MC could play an important role in the rapid control of symptoms related to agitation, seizures, and intractable suffering in the home setting, allowing more patients to die peacefully in the environment of their choice.

Disclosures and Acknowledgments

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