Comparison of Pharmaceutical Equivalence for Compounded Preparations of Pergolide Mesylate

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Results from this study show differences in potency of the active ingredient, pergolide mesylate, in the various formulations/products obtained from different veterinary compounding pharmacies. This could have important consequences both from an efficacy and toxicity standpoint. Authors' address: K. L. Maddy Equine Analytical Chemistry Laboratory, School of Veterinary Medicine, University of California, Davis, California 95617; e-mail: sdstanley@ucdavis.edu.

1. Introduction

Compounding is any manipulation of a drug formulation that produces a dosage form other than that provided for in the directions for use on the labeling of the Food and Drug Administration (FDA)-approved drug product. Formulations produced by compounding pharmacies are not subject to consistent regulatory oversight. While the guidelines for safety, efficacy, potency, stability, and purity testing of compounded preparations are largely described in the United States Pharmacopeia (USP), enforcement of these guidelines is left up to individual state pharmacy boards and can vary from state to state. Also, although many compounding pharmacies may have internal standards and guidelines for their preparations, these requirements are not uniform across the industry.

The compounding pharmacist is required to maintain various records including a reference for the formula used to prepare the compound and stability data testing to support the assigned beyond-use dating. Pharmacists should use evidence-based formulas for preparations to be used in veterinary species. Although some formula sources are proprietary, the pharmacist is still obligated to provide the veterinarian with evidence supporting the stability and potency of the compound.

Although compounding is oftentimes a necessary service for the equine veterinarian, it is important to understand when it is appropriate to use compounded products and when it is not.

In March 2007, the FDA announced that pergolide was being voluntarily withdrawn from the market because of the risk of cardiac valvulopathy associated with its use in humans. However, in addition to its use in human medicine, pergolide is especially important in equine medicine for the treatment of Cushing's disease. Therefore, in May 2007, to alleviate concerns that the recall of pergolide mesylate would result in the loss of the medication for the treatment of Cushing's disease in horses, the FDA agreed to a compromise: it would exercise "enforcement discretion as appropriate over the pharmacy compounding of pergolide," as long as certain criteria are met. Most notably, the drug can be made only with a valid prescription for an individual animal, and bulk ingredients must be clearly marked "for veterinary use only."[1]

NOTES

Table 1. Liquid Products

Pharmacy	Label	Day 0	Day 15	Day 30	Day 45	Day 60
A–25°C	1,000	960	853*	796*	769*	688*
A–8°C	1,000	1021	902	790*	831*	607*
B–25°C	1,000	847*	840*	806*	748*	614*
B–8°C	1,000	942	904	823*	755*	680*
C–25°C	1,000	833*	808*	762*	694*	556*
C–8°C	1,000	817*	794*	753*	617*	497*
D–25°C	1,000	874*	829*	741*	638*	543*
D–8°C	1,000	874*	838*	819*	741*	643*
E1–25°C	1,000	559*	512*	504*	446*	356*
E1–8°C	1,000	584*	579*	491*	400*	378*
E2–25°C	1,000	652*	601*	596*	542*	512*
E2–8°C	1,000	585*	565*	489*	412*	388*
F–25°C	1,000	926	890*	824*	780*	671*
F–8°C	1,000	970	954	854*	830*	726*

* Indicates the measured concentrations that fail to meet the FDA standard for potency.

For horses suffering from Cushing's syndrome, compounding of pergolide mesylate is necessary and beneficial for treatment of the disease.[2] However, practitioners must be cautious whenever using compounded products because they are not subject to the same regulatory oversight as FDA-approved drug products. This could ultimately lead to therapeutic failure and potentially toxic side effects. Presently, there are a number of pergolide formulations manufactured by various veterinary compounding pharmacies. The goal of this study was to assess the potency of the various products on receipt and at various times during storage, under different storage conditions.

2. Materials and Methods

Liquid, capsule, and powder formulations of pergolide mesylate from a number of different compounding pharmacies were tested. Compounding pharmacies selected for inclusion in this study were those commonly used by practitioners, with similar formulations and comparable prices ($1.00/treatment). For each product, two containers were ordered: one to be stored at room temperature and the second at 8 ± 2°C. An aliquot from each container was collected on receipt of the products (day 0), and the concentration of the active ingredient was determined immediately. After collection of the initial sample, one container of each product/formulation was stored at room temperature and one at 8 ± 2°C (refrigeration). The pergolide concentration was subsequently determined at 15, 30, 45, and 60 days after receipt for both storage conditions (room temperature and refrigeration). The samples were prepared by initially diluting the aliquots of compounded pergolide formulation with methanol and 0.04% hydrochloride acid (1:1), and the vials were capped and mixed thoroughly. The mixture was further diluted with mobile phase (1:9) to reach a final calculated concentration of 10 μg/ml. Liquid chromatography–mass spectrometry (LC-MS) methods were used for the determination of pergolide mesylate in compounded formulations. Linearity, precision, and accuracy were evaluated according to the validation guidelines of the International Conference on Harmonization and the USP for both methods. The LC-MS procedure was performed using a high-pressure liquid chromatograph with a linear ion-trap mass spectrometer.[a] Good linearity was obtained between 100 and 1500 ng/ml with a correlation coefficient of 0.99 or better. Intra-day accuracy (% of nominal concentration) was 91% and 93% for 20 and 1000 ng/ml, respectively. Inter-day accuracy (% of nominal concentration) was 99% for 1000 ng/ml, whereas the intra-day precision (% relative SD) was <2.0%. Inter-day precision (% of nominal concentration) was 1.4%.

3. Results

LC-MS analysis of all formulations immediately on) arrival yielded highly variable results, with the actual concentration of many of the products differing from the concentration listed on the label. In addition, testing determined that many of the powders and capsule formulations were not uniformly distributed throughout the containers or capsules, suggesting imprecise formulation of these products by the compounder. Furthermore, storage conditions did seem to have an effect on stability of the different formulations, and in many cases, the liquid formulations seemed to be unstable in the aqueous vehicle in which they were formulated.

Statistical analysis by analysis of variance showed a significant difference for the label claimed concentration and the results obtained for several products tested on day 0. In addition, there were notable differences in pergolide mesylate concentrations between the two containers of the same product, which were ordered on the same date from the same compounding pharmacy (Tables 1 and 2). For stability analysis, pergolide concentrations on days 15, 30, 45, and 60 under the different storage conditions are expressed as percent change compared with day 0.

Table 2. Capsules and Tablets Products

Pharmacy	Label	Day 0	Day 15	Day 30	Day 45	Day 60
A Powder–25°C	1,000	321*	266*	203*	153*	116*
A Powder–8°C	1,000	1,213*	1179*	1118*	996	904
A Caps–25°C	1,000	995	977	891*	837*	753*
A Caps–8°C	1,000	939	910	870*	827*	766*
B Powder–25°C	1,000	1,056	1059	1039	984	737*
B Powder–8°C	1,000	1,092	1074	960	899	865*
D Powder–25°C	1,000	472*	355*	335*	309*	271*
D Powder–8°C	1,000	1,093	1060	1021	974	803*
E Powder–25°C	1,000	325*	321*	283*	240*	201*
E Powder–8°C	1,000	283*	271*	255*	222*	211*
E Caps–25°C	1,000	710*	683*	627*	548*	513*
E Caps–8°C	1,000	723*	704*	713*	647*	597*
F Caps–25°C	1,000	993	981	911	877*	833*
F Caps–8°C	1,000	961	952	914	885*	859*

* Indicates the measured concentrations that fail to meet the FDA standard for potency.

4. Discussion

Pergolide mesylate is commonly used in veterinary medicine for the treatment of Cushing's disease in horses. With the only FDA-approved formulations withdrawn from the market because of adverse side effects in humans, veterinarians are forced to turn to compounding pharmacies to procure this compound. However, although the FDA has permitted compounded formulations to be used in the treatment of Cushing's disease in the horse, there is very little regulatory oversight in the manufacture of these products. The purpose of the study described here was to assess the potency of different formulations of pergolide mesylate obtained from various veterinary compounding pharmacies. In addition, stability of the compound was determined at 15, 30, 45, and 60 days after receipt of the drug when stored at room temperature and under refrigeration.

Initial concentrations of pergolide in all formulations were highly variable between products, with many having concentrations well below the label claim. Perhaps even more perplexing was the high degree of variation in pergolide concentrations between two containers of the same product ordered from the same pharmacy on the same date. Presumably, these concentrations would be equivalent on delivery of the pharmaceutical product. Final assessment on product stability was difficult to determine, because 16 of 28 (57%) of tested products did not meet the FDA requirement for potency at the onset of the study. If one can disregard this concern, the products appearing to be the most stable are the solid materials (powders and capsules). Only 3 of 14 (21%) of the liquid products were above the required potency after 15 days, and all products were subpotent by 30 days. Conversely, the solid products showed better stability, with five of seven products that started at acceptable potency still at >90% after 30 days (the other two products were only slightly below the required potency). The only solid product meeting the potency requirement after 60 days was determined to be 120% of the target potency concentration at the outset of the study.

Previous work by Davis et al.[3] showed that pergolide mesylate in an aqueous vehicle stored with exposure to light at 25°C or without light exposure at 37°C demonstrated excessive degradation within 14–21 days of preparation, respectively. This study showed a more rapid degradation with storage at 8°C with no products maintaining potency at 30 days. Overall, the aqueous solutions stored at 8°C and 25°C both degraded; however, the solutions stored at 8°C had a statistically higher potency than solutions stored at 25°C after 30 days of storage ($p < 0.05$, data not shown). The solid formulations showed better stability of the pharmaceutical product than the aqueous solutions. Only 4 of 14 (28%) solid products were above the required potency after 45 days, but 3 of the 4 were stored at 8°C.

To insure effective therapeutics, veterinarians should be vigilant and thorough when selecting a compounder. Compounded medications should be prepared in a state-licensed facility, with strict quality control measures, by an experienced pharmacist who adheres to USP guidelines for good compounding practices. Whenever possible, FDA-approved products are preferable because manufacturers of approved drugs have to use Good Manufacturing Practices. These products deliver the drug exactly as the label specifies with excellent quality to perform optimally.

References and Footnote

1. FDA-CVM works to address concerns about pergolide supplies. *J Am Vet Med Assoc* 2007;231:20–21.
2. Muñoz MC, Doreste F, Ferrer O, et al. Pergolide treatment for Cushing's syndrome in a horse. *Vet Rec* 1996;139:41–43
3. Davis JL, Kirk LM, Davidson GS, et al. Effects of compounding and storage conditions on stability of pergolide mesylate. *J Am Vet Med Assoc* 2009;234:385–389.

[a]Thermo Scientific, San Jose, CA 95134.