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IN VIVO RETENTION TIME EVALUATION OF POLYETHYLENE GLYCOL SUPPOSITORY BASES

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ABSTRACT

Ninety six (96) healthy male volunteers between the ages of 21 and 35 received two experimental polyethylene glycol suppository bases and one commercially available base. A comparison of the two experimental bases with the commercially available base indicates that the base containing polyethylene glycol 1000-4000 (65:35) is superior and that the base containing polyethylene glycol 1540-6000 (30:70) is probably comparable to the commercial product. It is concluded that these polyethylene glycols can be used as suppository bases without undue reaction.

INTRODUCTION

In ancient times many materials were utilized in preparing suppository bases, the main requirement of suppositories being that they be of such consistency as to facilitate insertion into the body orifices. Since its introduction, cocoa butter has been the most extensively used suppository base. New synthetic materials, including glycerin, gelatin, gums, kernal oil and various combinations of vegetable oils and waxes, have been developed for this use. The most useful of these substances are the polyethylene glycol (PEG) bases. Gilliam and Tomlinson (1) suggested the use of PEG bases for suppositories. Hassler and Sperandio (2) suggested three possible suppository formulations of PEG bases which were compatible with a large number of drugs. Gross and Baker (3) studies the *in vitro* release of a dye from PEG suppository bases. Several other investigators have studied the release of drugs from PEG suppository bases (4-7).

Although considerable work has been devoted to studies of these water miscible bases, little attention has been given to the assessment of their *in vivo* retention time. This is prime consideration in evaluating the efficacy of suppository bases. It is recognized that the physio-chemical factors affecting drug release rates are important parameters in suppository formulations. However, a suppository that is prematurely expelled after insertion has little or no value as a rational therapeutic dosage form.

Although insertion of a suppository may cause rectal irritation, or even stimulation of the anal sphincter, it may not result in rejection of the suppository. Polyethylene glycol supporitories are known to "sting", particularly if not moistened before insertion, because of their tendency to absorb water from the rectal mucosa. *A priori* information indicated that all of the test formulations would dissolve within one hour at rectal temperature.

It was the intent of the clinical study to determine if any of the three PEG suppository bases were expelled during a one hour post-insertion time study period and monitor any other adverse reactions occurring during the first 24 hour post-insertion period.

MATERIALS AND METHODS

Base A - Polyethylene Glycol 1540-6000 (30:70%) placebo base.

Base B - Polyethylene Glycol 1000-4000 (65:35%) placebo base.

Base C - Neocera^{R} base.

Ninety-six (96) healthy male volunteers between the ages of 21 and 35 were selected from the student population at the University of Texas at Austin. Subjects chosen for the study conformed to the weight and height standards published in the Bulletin of the Metropolitan Life Insurance Company, November-December, 1959. The range in subjects' weights did not exceed 30 kg. The following individuals were excluded from the study: subjects with a previous history of cardiac, respiratory or thyroid disease, renal or liver impairment or unusual personality characteristics. Also,

those subjects suffering from hemorrhoids or constipation, having significant physical or organ abnormalities, on maintenance drug therapy or who had a history of drug dependence were excluded from the study.

Within two (2) weeks prior to the study day, all subjects were given a complete physical at the Student Health Center. The examination included an anoscopic examination but did not include blood studies. At the time of the examination it was determined by questioning the subjects and examining their health records that they complied with the protocol. At this time the purpose of the study was explained to each subject, signed consent forms obtained and the subjects were informed of any side effects which might occur during the study (rectal irritation, cramps, instant defecation). The subjects were also instructed not to eat anything after 12 midnight prior to the study day. Water was allowed *ad lib* up to 12 midnight but no alcoholic beverages were to be consumed after supper prior to the study day. No drugs were to be taken during the two weeks preceeding the study nor any during the study. The subjects were to present themselves in a fasted state on the morning of the study. Of the 96 subjects given physical examinations, 94 reported for the study and 90 were randomly selected for the study.

On the morning of the study the subjects were randomly divided into nine (9) groups of ten (10) subjects each and a total of thirty (30) subjects assigned to each of three (3) floors of the study center. A random schedule was devised such that thirty (30)

subjects each received one of the three bases being tested. The suppositories were pre-moistened and inserted by a physician in a series of ten (10) on each floor until the study was completed. The time of insertion was noted on the consent form and on a tag which was affixed to each subject. Each group was assigned a monitor to insure that the subjects remained standing for 30 minutes, after which they were ambulatory for the remaining hour of the study period. The subjects remained under the direction of the monitor for one hour post-insertion time. Any adverse reactions occuring during the study period were recorded by the monitor. The monitor also examined the stools of any subjects who defecated during the study period for the presence of any suppository material and the condition of the stools. The subjects were instructed to report any unusual events or adverse reactions occuring within 24 hours post-insertion.

RESULTS AND DISCUSSION

The results are illustrated in Tables 1, 2, 3 and 4. Table 1 is a summary of the adverse reactions reported by the subjects and monitors during the first 24 hours post-insertion. Tables 2, 3 and 4 illustrate the percentage of adverse reactions and/or expulsion of the suppositories during the first hour and twenty-four hours post-insertion.

The results indicate that base A may be just as good as base C. Base A had one rejection during the study period and one additional reported rejection 3 hours post-insertion as compared to 2

TABLE 1

SUMMARY OF ADVERSE REACTIONS REPORTED BY SUBJECTS AND MONITORS DURING THE FIRST 24 HOURS POST-INSERTION

BASE A	OBSERVATION
Subject #27	Subject reported a defecation 3 hours post-insertion and a portion of the intact suppository appeared in the fecal matter.
Subject #80	Subject reported abdominal cramps 1.5 hours post-insertion accompanied by defecation. No suppository was observed in the feces.
Subject #84	Monitor reported an 18 minute post-insertion defecation. The stools were hard and a portion of the suppository appeared in the feces. Subject reported discomfort for 3 hours post-insertion.
Subject #85	Subject reported a slight gas-like pain 40 minutes post-insertion but no defecation occurred during the study period.
BASE B	
Subject #44	Monitor reported subject became faint 13 minutes post-insertion. Subject was allowed to sit down and assumed standing position 10 minutes later. The subject completed the study and no defecation occurred during the study period.
Subject #58	Subject reported excess gas during the study period and that diarrhea occurred 2 hours post-insertion. One dose of paregoric alleviated the diarrhea.
BASE C	
Subject #26	Subject reported rectal discomfort during first 24 hours post-insertion which disappeared within 48 hours.
Subject #32	Monitor reported defecation occurred 34 minutes post-insertion. Subject had small amount of soft feces and a portion of the suppository was observed.
Subject #33	Monitor reported defecation occurred 33 minutes post-insertion. Subject had small amount of hard stools and a portion of the suppository was observed.

TABLE 2

PERCENT OF SUBJECTS REPORTING ADVERSE REACTIONS AND/OR EXPELLING SUPPOSITORY DURING FIRST 24 HOURS POST-INSERTION

BASE A	BASE B	BASE C
13	7	10

TABLE 3

PERCENT OF SUBJECTS EXPELLING SUPPOSITORY DURING FIRST 24 HOURS POST-INSERTION

BASE A	BASE B	BASE C
6.67	0.00	6.67

TABLE 4

PERCENT OF SUBJECTS EXPELLING SUPPOSITORY DURING FIRST HOUR POST-INSERTION

BASE A	BASE B	BASE C
3.33	0.00	6.67

rejections of base C during the study period. The 3 hour post-insertion rejection, reported by the subject, seems questionable since preliminary *in vitro* studies indicated this base dissolves in less than one hour at rectal temperature. Base A had 2 additional adverse reactions as compared to one for Base C. Both

bases had a 6.67% rejection, while Base A had an additional 6.67% reported adverse reactions as compared to 3.33% for base C. It is felt that the slight gas-like pain reported by subject 85, who had base A, is of such a minor nature that there is practically no difference between these two bases.

Base B showed a 0% rejection and 6.67% of adverse reactions. Subject 44, who became faint during the study after receiving base B, did not report any discomfort due to the base but admitted being apprehensive about having a suppository inserted. It appears that base B is superior to base C.

Since there are no statistics available on what rejections or adverse reactions might occur *in vivo*, it is felt that base C, a commercially available product, is a valid base for the decision as to the success of bases A and B.

SUMMARY AND CONCLUSIONS

A comparison of two experimental PEG suppository bases, with a commercially used PEG base, indicates that the experimental bases are at least equivalent to the commercial product.

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