BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 5, 185–194 (1984)

COMPARISON OF THE BIOAVAILABILITY OF ORAL, RECTAL AND INTRAMUSCULAR PROMETHAZINE*

TERRY L. SCHWINGHAMMER AND RANDY P. JUHL

Department of Pharmacy Practice, University of Pittsburgh School of Pharmacy, Pittsburgh, PA 15261, U.S.A.

LEWIS W. DITTERT

Department of Pharmaceutics, University of Pittsburgh School of Pharmacy, Pittsburgh, PA 15261, U.S.A.

SRIKUMARAN K. MELETHIL

Department of Pharmaceutics, University of Missouri at Kansas City School of Pharmacy, Kansas City, MO 64108, U.S.A.

FRANK J. KROBOTH

Department of Medicine, University Health Center Hospitals of Pittsburgh, Pittsburgh, PA, U.S.A.

AND VINOD S. CHUNGI†

G & W Laboratories, South Plainfield, NJ, U.S.A.

ABSTRACT

The bioavailabilities of generic and reference promethazine 50 mg rectal suppositories were compared with that of 50 mg reference oral solution (24 subjects), and all three treatments were compared with a 50 mg reference i.m. injection (six subjects). Plasma samples were assayed by an HPLC method with trifluprom azine as the internal standard. Both suppositories produced lower peak plasma concentrations (C_{max}) and longer times to peak concentration (T_{max}) than did the oral solution. There were no significant differences in the mean area under the plasma concentration–time curves (AUC) from 0 to 24 h among the three treatments. The C_{max} of the i.m. injection was significantly higher than the other three treatments, while the T_{max} of the injection was significantly shorter than the reference suppository only. The mean AUC of the injection was significantly greater than the AUCs of the other three treatments. Rectal suppositories of promethazine are more slowly absorbed than oral solutions or i.m. injections; rectal suppositories and oral solutions are less bioavailable than i.m. injections. Diminished systemic bioavailability may result from extensive first-pass hepatic metabolism that occurs after both oral and rectal dosing. There is a high degree of inter-subject variation in the bioavailability of promethazine rectal suppositories and oral solutions.

KEY WORDS Promethazine Bioavailability Rectal suppository Rectal absorption

Address reprint requests to: Terry L. Schwinghammer, Pharm. D., 239-B Victoria Building, 3500 Victoria Street, Pittsburgh, PA 15261, U.S.A.

* Source of Support: G & W Laboratories, South Plainfield, NJ, U.S.A.

† Currently with Serono Laboratories, Randolf, MA, U.S.A.

0142–2782/84/020185–10$01.00 *Received 25 July 1983*

INTRODUCTION

Promethazine is a phenothiazine derivative that has antihistaminic, antiemetic, and sedative properties. The drug is available in oral, rectal, and parenteral dosage forms. The rectal suppository is a logical alternative to oral tablets or liquid preparations of the drug in patients with nausea and vomiting. Also, the rectal route may be preferable to intramuscular administration in children or debilitated patients with decreased muscle mass. The instability of the drug and its low plasma concentration after therapeutic doses have hindered the development of analytical procedures for assaying the drug in serum or plasma. As a result, little information exists regarding the relative bioavailability of promethazine by each of these routes of administration. A high-performance liquid chromatography procedure which permits sensitive and specific determination of promethazine concentration in serum has recently been developed.[1] Using a modification of this technique,[2] we compared the single-dose bioavailability characteristics of two suppository formulations of promethazine with oral solution and parenteral preparations of the drug.

METHODS

Subject selection

Twenty-four healthy, male, non-smoking voluteers between the ages of 20 and 31 years and weighing between 61 and 87 kg (mean 78 kg) were selected for the study. All subjects were given a thorough history and physical examination including anoscopy and were found to be in good physical condition. No subject was known to be allergic to promethazine or other phenothiazine derivatives or had received phenothiazines or other sedatives within 7 days prior to the study. The protocol and consent form were approved by the human use committee of the University of Pittsburgh, and informed consent was obtained from each subject.

Study design

A standard three-way crossover design was used to study 24 subjects randomly divided into three groups of eight. A single dose of promethazine (50 mg) was administered on three different days as a generic rectal suppository,* a reference rectal suppository,† and a reference oral solution.‡ Six of the subjects volunteered for and were selected to receive an additional treatment consisting of a 50 mg intramuscular (i.m.) injection.§ A 7-day washout period separated each study period.

---

* G and W Laboratories, Lot #2061-2.
† Wyeth Laboratories, Lot #1810924.
‡ Wyeth Laboratories, Lot #1810864.
§ Wyeth Laboratories, Lot #4811436.

Subjects were instructed not to take any medication for at least 1 week prior to and during the study and to refrain from consuming alcohol for at least 48 h prior to and 24 h following each drug administration. Subjects were required to fast for 10 h prior to and for 4 h after each dose. No food or fluids of any kind except plain water were allowed during the fasting period. Coffee, tea, soft drinks, or other caffeine-containing beverages were not allowed during the fasting and study periods. At 4 h following the dose, the subjects received a standard lunch with balanced carbohydrate, fat, and protein.

Subjects were given a saline enema 1 h prior to administration of each suppository. Suppositories were manually inserted as high into the rectum as possible and retained for at least 6 h. The oral treatment consisted of 40 ml of promethazine syrup followed by 180 ml of water. The six subjects receiving the i.m. injection were given 1 ml into the upper, outer quadrant of the right buttock.

Immediately prior to receiving each dose, an indwelling venous catheter with a heparin lock was inserted into a vein in the forearm of each subject and a 0-time blood specimen was drawn. Following drug administration, blood specimens were drawn through the catheter at 0·5, 1, 1·5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h. Plasma was separated from each sample and frozen until assayed.

Analytical methods

Plasma samples were assayed for promethazine content using an HPLC method with trifluprom azine as the internal standard.[2] The area under the plasma concentration–time curve (AUC) from 0 to 24 h was calculated using the trapezoidal rule. Plasma level data were analysed by ANOVA techniques to determine significant differences among treatments, periods, and individual subjects regarding peak plasma concentrations (C_{max}), time of peak concentrations (T_{max}), and AUC. Differences between pairs of variables were analysed using Tukey's Q value multiple range test. The mean relative bioavailabilities of the generic and reference suppositories versus the oral solution were calculated using the following equation:

$$\% \text{ Bioavailability} = \frac{AUC_{suppository}}{AUC_{solution}} \times 100$$

The relative bioavailabilities of the solution and suppositories versus the i.m. injection were calculated using the following equation:

$$\% \text{ Bioavailability} = \frac{AUC_{solution\ (suppository)}}{AUC_{injection}} \times 100$$

RESULTS

Oral versus rectal promethazine

All 24 subjects completed the oral and rectal treatment periods of the study. The mean plasma promethazine concentration–time curves resulting from

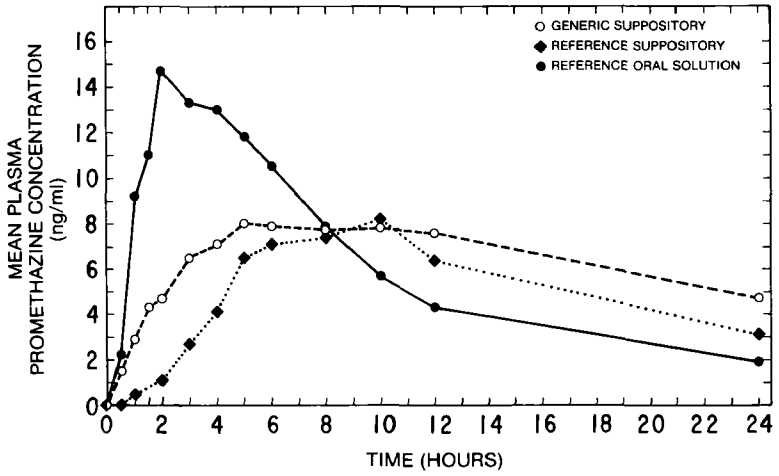

Figure 1. Mean plasma promethazine concentration versus time: oral versus rectal promethazine

administration of the generic and reference suppositories and the reference oral solution are depicted in Figure 1. Statistical analysis of the mean plasma promethazine concentration at each time point revealed that the mean plasma concentration of the reference solution was significantly greater ($p < 0{\cdot}05$) than that of the generic suppository at 1, 1·5, 2, 3, 4, and 5 h following administration. The solution produced significantly greater mean plasma concentrations than did the reference suppository at 1, 1·5, 2, 3, 4, 5, and 6 h following administration. The mean plasma concentration of the generic suppository was significantly greater than that of the reference suppository only at the 3 h time point.

A summary of other relevant pharmacokinetic data is contained in Table 1. The mean C_{max} for the generic and reference suppositories were significantly lower than that for the reference oral solution. The mean T_{max} for both the generic and reference suppositories were significantly longer than that for the reference oral solution. There were no significant differences between the generic and reference suppositories regarding either C_{max} or T_{max}. The mean AUC for the generic and reference suppositories were not significantly different from that of the reference oral solution or from each other. The generic suppository was 129·34 per cent as bioavailable as the reference suppository and 107·13 per cent as bioavailable as the reference oral solution. The reference suppository was 82·83 per cent as bioavailable as the reference oral solution.

Intramuscular promethazine

Six of the 24 subjects participated in and completed the i.m. treatment period. Figure 2 depicts the mean plasma promethazine concentration–time curves for those six subjects for all four treatments. Statistical analysis of the mean plasma promethazine concentration at each time point reveals that the mean plasma concentration of the i.m. injection was significantly greater than those produced

Table 1. Summary of pharmacokinetic data: oral versus rectal promethazine

Pharmacokinetic parameter	Generic suppository	Reference suppository	Reference oral solution	ANOVA with Tukey's Q value multiple range test G vs S	R vs S	G vs R
Mean peak plasma concentration ($ng\,ml^{-1}$)	12·10	10·24	17·30	$p<0·05$	$p<0·01$	n.s.
Mean time of peak plasma concentration (h)	6·85	8·00	2·60	$p<0·01$	$p<0·01$	n.s.
Mean AUC from 0 to 24 h ($ng\,h\,ml^{-1}$)	155·65 (±142·69)	120·34 (±109·89)	145·28 (±132·09)	n.s.	n.s.	n.s.

G: generic suppository, R: reference suppository, S: reference oral solution, n.s.: no significant difference.

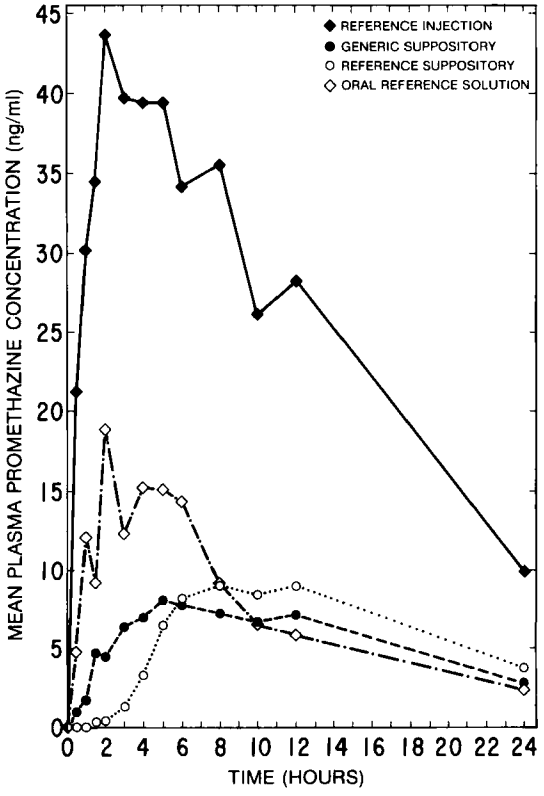

Figure 2. Mean plasma promethazine concentration versus time: intramuscular versus oral and rectal promethazine

Table 2. Summary of pharmacokinetic data: intramuscular versus oral and rectal promethazine

Pharmacokinetic parameter	Generic suppository	Reference suppository	Reference oral solution	Reference i.m. injection	ANOVA with Tukey's Q value multiple range test I vs G	I vs R	I vs S
Mean peak plasma concentration ($ng\,ml^{-1}$)	11·54 (±3·94)	11·28 (±8·51)	21·84 (±14·03)	48·26 (±12·26)	$p<0·01$	$p<0·01$	$p<0·01$
Mean time of peak plasma concentration (h)	7·00 (±3·58)	8·17 (±3·37)	2·75 (±1·41)	3·00 (±1·26)	n.s.	$p<0·05$	n.s.
Mean AUC from 0 to 24 h ($ng\,h\,ml^{-1}$)	136·08 (±63·90)	146·62 (±117·70)	180·14 (±129·20)	627·13 (±156·69)	$p<0·01$	$p<0·01$	$p<0·01$

I: reference i.m. injection, G: generic suppository, R: reference suppository, S: reference oral solution, n.s.: no significant difference.

by each rectal suppository at all time points excluding the 0-h and 24-h samples. The i.m. injection produced mean plasma concentrations which were significantly greater than those of the oral solution at all time points except the 0, 0·5, 1, and 24-h samples.

A summary of the pharmacokinetic data for these six subjects for all four treatments is contained in Table 2. The C_{max} of the i.m. injection was significantly greater than that of all other treatments. The mean T_{max} of the i.m. injection and the oral solution were significantly shorter than that of the reference suppository but not of the generic suppository. The mean AUC of the i.m. injection was significantly greater than those of the other three treatments. The oral solution was 28·72 per cent, the reference suppository was 23·38 per cent, and the generic suppository was 21·72 per cent as bioavailable as the i.m. injection.

The elimination rate constant (K_{el}) was calculated for each subject following the i.m. injection. The mean K_{el} for the six subjects was $0{\cdot}07099 \pm 0{\cdot}0247\ h^{-1}$. From this information, a mean plasma half-life for the six subjects was calculated to be $9{\cdot}76 \pm 3{\cdot}41$ h.

Adverse effects

Drowsiness was the most frequent side-effect seen, occurring in 20 subjects with the generic suppository, 19 subjects with the reference suppository, and 23 subjects with the reference oral solution (see Table 3). All six subjects receiving

Table 3. Adverse effects from promethazine dosage forms

Adverse effect	Generic suppository ($n = 24$)	Reference suppository ($n = 24$)	Reference oral solution ($n = 24$)	Reference i.m. injection ($n = 6$)
Drowsiness				
mild	11	16	6	–
moderate	8	1	11	4
severe	1	2	6	2
Rectal symptoms*	15	4	–	–
Extrapyramidal reactions	–	–	1	–
Dryness of mouth	–	–	2	3
Other symptoms				
gooseflesh	1	–	–	–
abdominal cramps	1	–	–	–
chills	1	–	–	–
nausea	–	–	2	–
numb tongue	–	–	1	–
headache	–	–	1	–
lightheadedness	–	–	1	2

* Rectal burning, irritation, spasms, and/or urge to defecate.

the i.m. injection reported moderate to severe drowsiness. Fifteen subjects reported rectal burning, irritation, spasms, and/or urge to defecate after receiving the generic rectal suppository. Only four subjects complained of rectal symptoms after receiving the reference rectal suppository. The difference in the number of rectal symptoms between the suppositories may have been due to differences in the suppository bases used. The generic suppository contained a synthetic fat base, while the reference suppository base consisted of cocoa butter. One subject experienced an extrapyramidal reaction characterized by tremors and rigidity 24 h after receiving the oral solution; treatment with diphenhydramine resulted in complete resolution of symptoms. Other mild side-effects occurring after each treatment are listed in Table 3.

DISCUSSION

Promethazine is commonly used for pre-operative sedation and to treat nausea and vomiting. Parenteral or rectal administration is often undertaken when the oral route is not feasible. An extensive hepatic first-pass metabolism has been reported to occur after oral administration of promethazine.[3] It has been suggested that rectal dosing may escape this first-pass elimination, leading to higher plasma levels when the drug is administered by rectal suppository than when it is given orally.[4] A sensitive and specific assay for promethazine has only recently been developed, and therefore few studies have been done to compare the relative bioavailabilities of the drug by each of these routes. Moolenaar *et al.* compared the rate of absorption and bioavailability of promethazine from rectal and oral dosage forms.[5] The rate and extent of absorption from a suppository formulation were significantly less than that seen after administration of an oral solution and a 5 ml enema of the drug. These results cannot be extrapolated to the clinical setting, however, since both rectal formulations were prepared specifically for the study and are not commercially available. Wallace *et al.* determined promethazine concentrations in serum after a 50 mg oral and rectal suppository dose which were administered successively to a single patient after a 1 week washout period.[1] The C_{max} of the oral dose was approximately twice as high as that of the rectal dose. No other pharmacokinetic analysis was presented in that report.

We compared the bioavailability of a generic promethazine suppository with the standard reference suppository, oral solution, and i.m. preparation. The lower mean C_{max} and longer mean T_{max} of the test and reference suppositories in comparison to the reference oral solution indicates that both suppositories are more slowly absorbed than the oral solution. The mean AUC of the generic suppository was slightly higher than, and that of the reference suppository was slightly lower than, the mean AUC of the reference oral solution. These differences were not statistically significant, and therefore the systemic bioavailabilities of these three preparations are comparable. Examination of individual data revealed a wide variability among subjects in the rate of

absorption and extent of bioavailability of both suppositories. In some individuals, absorption appeared to continue throughout much of the sample period. Therefore, calculation of elimination rate constants and plasma half-lives for individual subjects was not possible. There was also considerable inter-subject variability in the above parameters with the oral solution.

The mean C_{max} produced by the i.m. injection was approximately two-fold higher than that produced by the oral solution and four-fold higher than that of the suppositories. The mean T_{max} of the injection was approximately equivalent to that of the oral solution and about one-third that of the suppository formulations, indicating that the suppositories are also more slowly absorbed than the i.m. injection. The mean AUC of the i.m. injection was approximately three times that of the oral solution and the suppositories. Furthermore, the mean plasma concentration at the last time point measured (24 h) was two to three times higher for the i.m. injection than for the oral solution and suppositories, although this difference was not statistically significant. These differences indicate that both suppository formulations and the reference oral solution are less bioavailable than the i.m. preparation. Extensive first-pass hepatic metabolism may account for the lower bioavailability of the oral solution relative to the i.m. injection. The slower rate of absorption from the rectal suppositories may result in even more extensive first-pass metabolism than is seen after oral dosing.[6] The nature of the suppository base or use of other additives may also be partly responsible for a reduction in the rate of absorption and the extent of bioavailability of rectal suppositories.[4] There is no evidence from this study to support the contention that use of a rectal suppository will escape hepatic first-pass metabolism.

Because of inter-subject variation in suppository and oral bioavailability, the relative bioavailabilities of these dosage forms in any given patient is difficult to predict. In terms of the mean amount necessary to produce similar plasma levels, an i.m. dose of approximately 17 mg would be comparable to a 50 mg dose of the oral solution or either suppository.

The plasma levels necessary for adequate anti-emetic or sedative efficacy are not known; however, the lower rate of absorption of the suppositories relative to the other two formulations may result in a slower onset of action. The lower peak concentrations seen with the suppositories also resulted in a lower incidence of side-effects that may be related to peak levels (e.g. drowsiness). Since the present studies used only normal healthy volunteers, it cannot be established whether a decreased intensity of therapeutic effect would also have resulted from use of suppository or oral formulations. Because a saline enema was administered prior to each rectal dose, actual plasma levels achieved clinically may be even lower and more variable than those reached in this study.

REFERENCES

1. J. E. Wallace, E. L. Shimek, S. C. Harris and S. Stavchansky, *Clin. Chem.*, **27**, 253 (1981).
2. S. Melethil, A. Dutta, V. Chungi, and L. Dittert, *Analytical Letters*, **16**, 701 (1983).

3. C. J. DiGregorio and E. Ruch, *J. Pharm. Sci.*, **69**, 1457 (1980).
4. A. G. de Boer, F. Moolenaar, L. G. J. de Leede and D. D. Breimer, *Clin. Pharmacokinet.*, 7, 285 (1982).
5. F. Moolennar, J. G. Ensing, B. G. Bolhuis and J. Visser, *Int. J. Pharm.*, **9**, 353 (1981).