CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020007/S022

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APR - 3 1997

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Clinical Pharmacology and Biopharmaceutics Review

NDA 20-007 SE3(022) Submission Date: 05-06-96, 07-19-96 and 08-22-96
Ondansetron HCl Injection
Zofran® 2 mg/ml
Sponsor: Glaxo Wellcome Inc.
Five Moore Dr., Research Triangle Park, NC 27709

Priority:
Reviewer: Rajendra S. Pradhan, Ph.D.
Type of Submission: Application of Approval of Alternate Route of Administration

Background:

Zofran Injection is currently approved as an intravenous (IV) injection for the prevention of nausea and vomiting occurring postoperatively (PONV) or as a result of treatment with chemotherapeutic agents. Supplement -017 was submitted on June 30, 1994, requesting an approval for intramuscular (IM) administration of ondansetron injection as an alternative to IV administration. In support of this supplement, the sponsor provided a relative bioavailability study comparing IM administration with IV administration. The sponsor claimed that showing the mean area under ondansetron concentration time curve (AUC) equivalent between the two routes is sufficient information to establish IM and IV routes to have same efficacy.

The sponsor proposed a study where healthy volunteers would be randomized to receive either IM or IV ondansetron and then receive oral ipecac (to induce vomiting) syrup. The sponsor proposed this study in order to receive an approval for IM administration of ondansetron injection as an alternative to IV administration only for PONV indication. It was understood that such a study would not help the sponsor getting IM route approved for nausea and vomiting due to cancer chemotherapy indication. Dr. Fredd suggested that the firm include two IM doses to optimize their chances for showing equivalent efficacy to the IV route of administration. Dr. Fredd agreed that a single satisfactory provocative study demonstrating equivalent efficacy would obviate the need for full scale clinical trials.

As mentioned in August 17, 1994 meeting with the firm, the firm conducted a gender-balanced, double-blind, double-dummy, parallel-group study in the ipecac-induced nausea model. In this current submission NDA 20-007/S-022 the sponsor is providing the results from this efficacy study. Along with the efficacy study the sponsor has also included results of two

4/15/97 /S/

pharmacokinetic studies to compare pharmacokinetics and tolerability of ondansetron administered as a single 4 mg intravenous dose to the same dose administered by intramuscular injection. Out of these two pharmacokinetic studies one study is a pilot study and is considered secondary for the purpose of this review.

Comments:

1. In the proposed labeling change, the values for pharmacokinetic parameters, reported from study W91-016, are arithmetic means and not geometric means as reported in the study report. It was noted that the sponsor analyzed serum ondansetron concentrations in study S3AA1001 and plasma ondansetron concentrations in study W91-016. The pharmacokinetic parameter, viz. $AUC_{0-\infty}$, for study S3AA1001 was significantly higher than for study W91-016 as shown in the following table (Geo. Means and 95% CI).

Dose = 4 mg	S3AA1001 (IV)	W91-016 (IV)	S3AA1001 (IM)	W91-016 (IM)
$AUC_{0-\infty}$	156 (136, 180)	80.2 (76.5, 84.1)	161 (137, 190)	80.4 (76.9, 84.0)
Cmax	42.9 (33.8, 54.4)	65.8 (50.8, 85.2)	31.9 (26.3, 38.6)	25.5 (20.0, 32.5)

The sponsor should provide an explanation for this difference and also justify the use of pharmacokinetic parameters from study W91-016 in the labeling.

2. In a pharmacodynamic study, unless one uses doses (more than one is recommended) in the linear portion of the dose response curve, it is not possible to analyze the data for pharmacodynamic equivalence. Since the sponsor designed this study with only one dose which was at the maximum response level, this study presents serious limitations in what one can conclude about the pharmacodynamic equivalence between IM and IV doses.

The proposed labeling change should read as follows:

Proposed

In a gender-balanced pharmacodynamic study (n=56), ondansetron 4 mg administered intravenously and intramuscularly was dynamically equivalent in the prevention of emesis and nausea using the ipecacuanha model of emesis with respect ~~to one~~ sided equivalence criteria of 15%. Both treatments were well tolerated and there was no evidence of a significant difference between ondansetron administered via intramuscular or intravenous routes in either peak or weighted mean scores.

DPE-II, OCPB Corrected

In a gender-balanced pharmacodynamic study (n=56), ondansetron 4 mg administered intravenously and intramuscularly was dynamically similar in the prevention of emesis and nausea using the ipecacuanha model of emesis. Both treatments were well tolerated

Recommendation:

The 4 mg intramuscular and intravenous ondansetron injections were shown to be similar in prevention of emesis and nausea, using the ipecacuanha model of emesis. However, the Medical Officer (HFD-180) should please note that in this ipecacuanha emesis model study, IM and IV routes at 4 mg dose are neither bioequivalent nor pharmacodynamically equivalent. Please forward the text under Comments to the Sponsor as appropriate.

/S/ 3-28-97

Rajendra S. Pradhan, Ph.D.
Division of Pharmaceutical Evaluation II

FT initialed by Lydia Kaus, Ph.D. /S/ 4/3/97

cc: NDA 20-007, HFD-180, HFD-870 (MChen, Kaus, Pradhan), HFD-850 (Lesko), HFD-340 (Viswanathan), HFD-850 (Drug, Reviewer), Drug File (Millison)

Appendix I

A Study to Compare the Efficacy of 4 mg Ondansetron Intramuscular and 4 mg Ondansetron Intravenous in the Ipecacuanha Model of Emesis in Healthy Male and Female Volunteers

Protocol: 517/440(S3AA1001)

Objectives:
The primary objective of this study was to examine the relative efficacy of the intramuscular versus intravenous route of administration of ondansetron in the prevention of emesis following a single 30 ml dose of ipecacuanha in healthy male and female volunteers. Nausea assessments were to be analyzed only in the event of emetic episodes.

The secondary objective was to calculate PK parameters for IM and IV ondansetron following 4 mg doses.

Formulation:
The following formulations were used for this study

Batch Size	Route	Dosage Form and Strength	Batch Size (L)
	IV	2 mg/ml, 2 ml ampoule	
	IM	2 mg/ml, 2 ml ampoule	
	IV	placebo, 2 ml ampoule	
	IM	placebo, 2 ml ampoule	

Study Design:
This was a randomized, double blind, double-dummy, parallel group, single center study. Twenty eight adult male and twenty eight adult female subjects who were healthy and between the ages of were enrolled in the study. All enrolled subjects completed the study.

Treatments:
A: 4 mg IV ondansetron and IM placebo
B: 4 mg IM ondansetron and IV placebo
Both treatments were followed 30 minutes later by the administration of 30 ml of syrup of ipecacuanha.

Data Analysis:
The pharmacodynamics of IV and IM ondansetron were assessed by recording the number of emetic episodes experienced by each subject and the time to onset of emesis for a period of 11.5 hours after dosing with ipecacuanha. Additionally, nausea score assessments were made prior to administration of ipecacuanha and every 15 minutes for 4 hours afterwards. This included a subjective assessment of the volunteer's worst nausea score over the previous 15 minute period. Nausea scores were rated on a 0-3 scale, where 0 was no nausea and 3 was severe nausea.

The pharmacokinetics of ondansetron after administration of each treatment were assessed by measuring concentration over the 12 hour post-dose period.

Statistics of Pharmacodynamics:
The primary analysis was based on the number of subjects with emesis in each treatment group. Dose response modelling of IV ondansetron in the ipecacuanha induced model of emesis predicts a probability of no emesis of 0.976 following a 4 mg dose. A clinical criterion of ±15% for equivalent treatments was considered by the sponsor. The null hypothesis was that the probability of no emesis following 4 mg IM ondansetron is less than that of IV minus 0.15; the alternative hypothesis is that the probability of no emesis is greater than or equal to that of IV minus 0.15. The null hypothesis would be rejected in the following cases:

- if the number of emetic episodes under IV is greater than 0 and the number of emetic episodes under IM is less than or equal to that of IV, or
- if the number of emetic episodes under IV is equal to 0 and the number of emetic episodes under IM is less than or equal to 1.

peak nausea scores were summarized by counting the frequencies under each score (0-3) for each treatment group. The sponsor performed linear regression on the integer mean score response using CATMOD procedure in SAS 6.08 with treatment as independent variable.

Weighted mean score was calculated by taking the summation of nausea scores weighted by the time interval (0.25 hr). Treatment groups were compared with a two-sample t-test using the GLM procedure in SAS and with Wilcoxon two sample rank-sum test.

Results:
There was only one incidence of emesis, which occurred in the IV group, approximately 4.5 hours after dosing with ipecacuanha. Nausea data are summarized in the table below:

	Total	Peak Score Frequencies (N)				Weighted Mean ± SD
		0 (no nausea)	1	2	3 (sever)	
IV	28	18	9	0	1	0.065±0.126
IM	28	23	2	2	1	0.092±0.314
P-values IV vs IM				0.577[a]		0.677[b]
						0.239[c]

a: P-value is based on the linear regression with integer mean score response. Independent variable is TREATMENT

b: P-value is based on a two-sample t-test

c: P-value is based on Wilcoxon rank-sum test. Residuals from the two-sample t-test were not normally distributed, and so treatments were compared using the Wilcoxon rank-sum test.

The following table summarizes the pharmacokinetic parameters for IV and IM routes.

	Treatment A 4 mg IV	Treatment B 4 mg IM	B/A
$AUC_{0-\infty}$ (ng*h/ml) Geo. LS Mean 95%CI Geo. LS Mean Ratio 90% CI	156 (136, 180)	161 (137, 190)	103 (89 - 120)
Cmax (ng/ml) Geo. LS Mean 95%CI Geo. LS Mean Ratio 90% CI	42.9 (33.8, 54.4)	31.9 (26.3, 38.6)	74% (58 -96)
tmax (h) Median Range Difference (A-B) 90% CI	0.08 (0.08, 1.00)	0.38 (0.17, 4.00)	0.17 (0.09 - 0.33)
$t_{1/2}$ (h) Geo. LS Mean 95%CI Geo. LS Mean Ratio 90% CI	4.2 (3.6, 4.8)	4.3 (3.5, 5.3)	103 (85 - 125)

λ_z (1/h) Geo. LS Mean 95%CI Geo. LS Mean Ratio 90% CI	 0.166 (0.145, 0.191)	 0.161 (0.131, 0.198)	 97 (80 - 118)

CI: Confidence Interval
LS Mean: Least squares mean

Figure 1 shows the median serum ondansetron concentration (ng/ml) versus time plot.

Comments:

1. One of the serious limitation of this study design is that there is no placebo arm. That means that one does not know if either treatment is effective at all (as 30 ml dose of ipecac syrup could very well be a dose which does not produce any emesis to begin with). This is a common limitation of all the clinical efficacy trials which do not use placebo arm and have only active control arm. However, Minton et. al.[1] has reported that in a study with ten healthy subjects (men), a dose of 30 ml syrup of ipecacuanha (British Pharmacopoeia) resulted emesis in every subject. This information was considered while reviewing the sponsor's study, thus justifying the sponsor's choice of 30 ml ipecac dose. It should be noted that the sponsor has used Ipecac syrup (USP) where as Minton et. al. used British Pharmacopoeia formulation, these two have slightly different composition (attached).

2. The sponsor has not definitively shown pharmacodynamic equivalence science the sponsor studied one dose level which was at the maximum response. One way to improve this design is to use more than just one dose level of ondansetron to get some kind of dose-response in the study.

Conclusions:

IM and IV ondansetron were shown to be similar in prevention of emesis and nausea, using the ipecacuanha model of emesis.

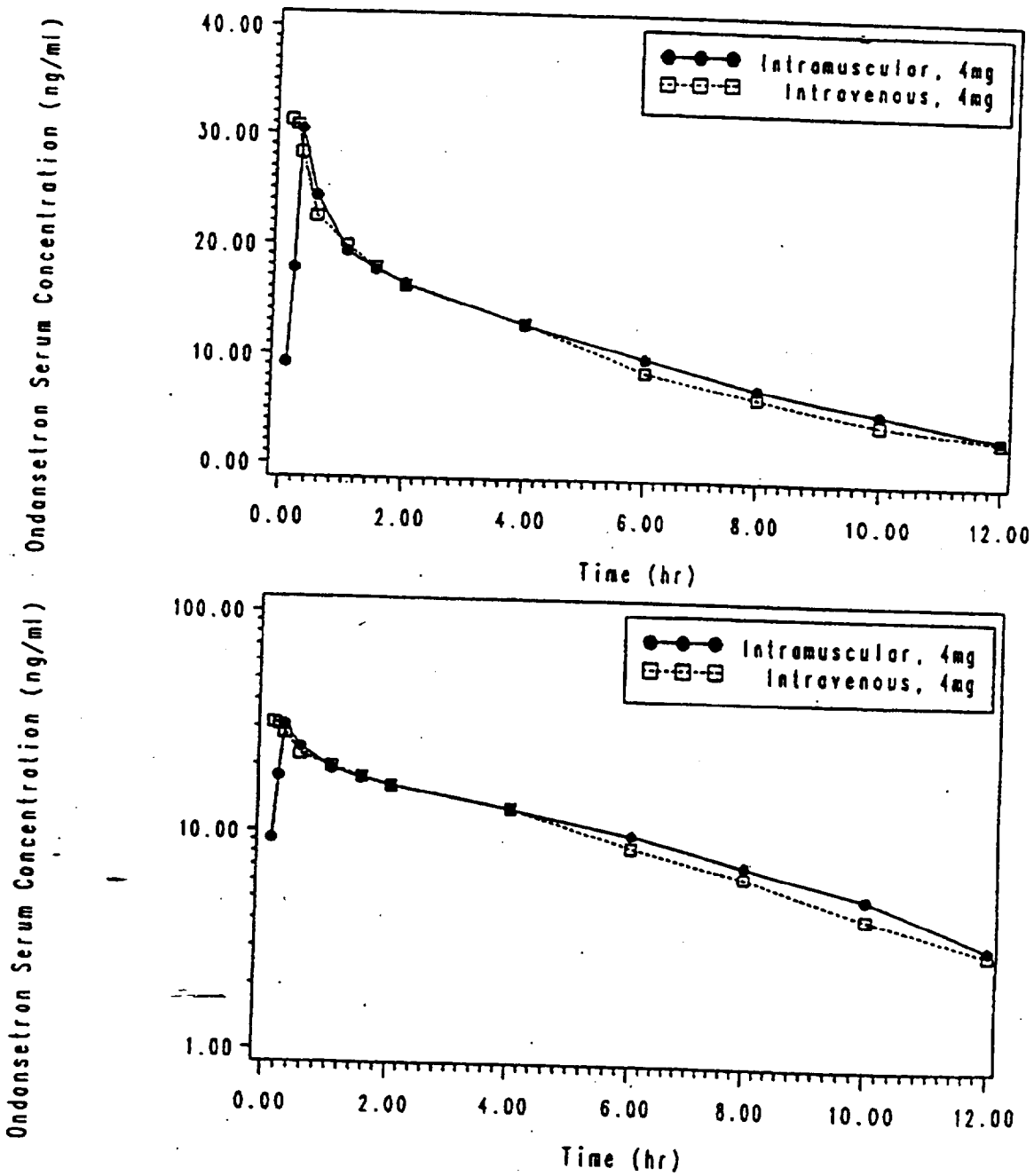
There was no evidence of a significant difference between IM and IV ondansetron in either peak or weighted mean nausea scores. However, this comparison is based on only one dose which is close to the maximum effect dose.

The overall extent of absorption as measured by $AUC_{0-\infty}$, showed no evidence of a difference between the two routes. However, it should be noted that mean $AUC_{0-\infty}$ observed in this study is almost twice that seen in study W91-016.

As expected, Cmax ~~was~~ shown to be bioinequivalent with the IM treatment mean levels being 74% to that of the IV.

[1] Minton N., Swift R., Lawlor C., Mant T., Henry J.; Clin. Pharmacol. Ther., 53-57, (1993)

Figure 1. Linear and semi-logarithmic plot of median serum ondansetron concentration (ng/mL) versus time



Column IV below *Column III*, and place as a receiver under *Column IV* a 125-mL separator containing 15 mL of 4 *N* sulfuric acid. Pass through the columns 10 mL of a 1 in 5 solution of triethylamine in the ether-isooctane mixture, followed by three 10-mL portions of a 1 in 50 solution of triethylamine in the ether-isooctane mixture. Discard *Column III*, and pass through *Column IV* 20 mL of the 1 in 50 solution of triethylamine in the ether-isooctane mixture. Shake the separator, allow the phases to separate, and transfer the aqueous extract to a 50-mL volumetric flask. Extract with two additional 10-mL portions of 0.5 *N* sulfuric acid, combining the extracts in the volumetric flask. Add 0.5 *N* sulfuric acid to volume, and mix (*emetine solution*).

Elute *Column IV* with 75 mL of chloroform, collecting the eluate in a 250-mL separator containing 150 mL of ether. Discard *Column IV*. Extract with one 20-mL, and then with two 10-mL, portions of 0.5 *N* sulfuric acid, collecting the extracts in a 50-mL volumetric flask. Rinse the stem of the separator, add the acid to volume, and mix (*cephaeline solution*).

Concomitantly determine the absorbances of the *emetine solution*, the *cephaeline solution*, and the *Standard preparation* in 1-cm cells at the wavelength of maximum absorbance at about 283 nm and at 350 nm, with a suitable spectrophotometer, using 0.5 *N* sulfuric acid as the blank.

Calculate the quantity, in mg, of emetine in the portion of Ipecac taken by the formula:

$$0.05C(A_{283} - A_{350})_U/(A_{283} - A_{350})_S,$$

in which C is the concentration, in µg per mL, of emetine in the *Standard preparation*, and the parenthetic expressions are the differences in the absorbances of the solution of *emetine* from the *Assay preparation* (U) and the *Standard preparation* (S), respectively, at the wavelengths indicated by the subscripts.

Calculate the quantity, in mg, of cephaeline in the portion of Ipecac taken by the formula:

$$0.971(0.05C)(A_{283} - A_{350})_U/(A_{283} - A_{350})_S,$$

in which 0.971 is the ratio of the molecular weight of cephaeline to that of emetine, C is as defined in the preceding paragraph, and the parenthetic expressions are the differences in the absorbances of the solution of *cephaeline* from the *Assay preparation* (U) and the *Standard preparation* (S), respectively, at the wavelengths indicated by the subscripts.

parenchyma of the xylem composed of small rectangula longitudinally elongated cells with moderately thick wall scattered bordered or simple pits; rhizome parenchyma cells than root parenchyma cells, with slightly thicker walls an nified with fairly numerous simple pits; sclereids from th zome large, rectangular, with uneven walls and large, conspi pits.

Assay for total ether-soluble alkaloids—Proceed with Pow Ipecac as directed in the *Assay for total ether-soluble alka* under *Ipecac*.

Assay for emetine and cephaeline—

Standard preparation, *Phosphate buffer*, *Citric acid bu* and *Chromatographic columns*—Prepare as directed in the *say for emetine and cephaeline* under *Ipecac*.

Assay preparation—Transfer to a 150-mL beaker about mg, accurately weighed, of Powdered Ipecac. Add 2 mL of m sulfoxide, mix with a flattened stirring rod to assure com wetting of the powder, and allow to stand for about 30 min Add 2 mL of water and about 1 g of sodium bicarbonate, mix.

Procedure—Proceed as directed for *Procedure* in the *A for emetine and cephaeline* under *Ipecac*.

Calculate the quantity, in mg, of emetine in the portio Powdered Ipecac taken by the formula:

$$0.05C(A_{283} - A_{350})_U/(A_{283} - A_{350})_S,$$

in which the parenthetic expressions are the differences in absorbances of the solution of emetine from the *Assay pr* ration (U) and the *Standard preparation* (S), respectively, at wavelengths indicated by the subscripts, and C is as define the *Procedure*.

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Powdered Ipecac

» Powdered Ipecac is Ipecac reduced to a fine or a very fine powder and adjusted to a potency of not less than 1.9 percent and not more than 2.1 percent of the total ether-soluble alkaloids of ipecac, by the addition of exhausted marc of ipecac or of other suitable inert diluent or by the addition of powdered ipecac of either a lower or a higher potency.

The content of emetine ($C_{29}H_{40}N_2O_4$) and cephaeline ($C_{28}H_{38}N_2O_4$) together is not less than 90.0 percent of the total amount of the ether-soluble alkaloids. The content of cephaeline varies from an amount equal to, to an amount not more than 2.5 times, the content of emetine.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Emetine Hydrochloride RS*.

Botanic characteristics—Thin-walled, fairly small cork cells, the starch grains rarely simple and usually 2- to 8-compound, the single grains up to 22 µm in diameter; raphides of calcium oxalate 30 to 80 µm in length; tracheids and tracheidal vessels found in groups having very numerous, small, bordered pits; parenchyma of phelloderm filled with starch or acicular crystals of calcium oxalate, having cells thin-walled, oval with intercellular spaces;

Ipecac Syrup

» Ipecac Syrup yields, from each 100 mL, not le than 123 mg and not more than 157 mg of the tot ether-soluble alkaloids of ipecac.

The content of emetine ($C_{29}H_{40}N_2O_4$) and cep aeline ($C_{28}H_{38}N_2O_4$) together is not less than 90 percent of the amount of the total ether-soluble a kaloids. The content of cephaeline varies from a amount equal to, to an amount not more than 2 times, the content of emetine.

Powdered Ipecac	70 g
Glycerin	100 ml
Syrup, a sufficient quantity, to make	1000 ml

Exhaust the powdered Ipecac by percolation, usin a mixture of 3 volumes of alcohol and 1 volume o water as the menstruum, macerating for 72 hours and percolating slowly. Reduce the entire percolat to a volume of 70 mL by evaporation at a temperatur not exceeding 60° and preferably in vacuum, and ad 140 mL of water. Allow the mixture to stand ove night, filter, and wash the residue on the filter with

water. Evaporate the filtrate and washings to 40 mL, to this add 2.5 mL of hydrochloric acid and 20 of alcohol, mix, and filter. Wash the filter with a mixture of 30 volumes of alcohol, 3.5 volumes of hydrochloric acid, and 66.5 volumes of water, using a volume sufficient to produce 70 mL of the filtrate. Add 100 mL of Glycerin and enough Syrup to make the product measure 1000 mL, and mix.

Packaging and storage—Preserve in tight containers, preferably at a temperature not exceeding 25°. Containers intended for sale to the public without prescription contain not more than 30 mL of Syrup.

USP Reference standards ⟨11⟩—*USP Emetine Hydrochloride RS*.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Escherichia coli*.

Alcohol content ⟨611⟩: between 1.0% and 2.5% of C_2H_5OH.

Assay for total ether-soluble alkaloids—[NOTE—It is important that the ether used in this assay shall have been shown by test to be free from peroxides within 24 hours prior to use.] Transfer about 50 mL, accurately measured, of Syrup to a liquid-liquid extraction extractor, add water, if necessary, to reduce the viscosity, render the liquid distinctly alkaline with ammonium hydroxide, and extract with ether for at least 4 hours or until the extraction is complete. Use a water bath to boil the ether. Frequently disconnect the extractor from the condenser, and agitate the lower layer by raising and lowering the center tube or by other suitable manipulation. At the conclusion of the extraction period, transfer the ether extract to a separator, and rinse the extraction flask with 2 or more small volumes of ether, adding the rinsings to the separator. Complete the assay as directed in the *Assay for total ether-soluble alkaloids* under *Ipecac*, beginning with "Extract the alkaloids from the ether."

for emetine and cephaeline—

Standard preparation, *Phosphate buffer*, and *Citric acid buffer*—Prepare as directed in the *Assay for emetine and cephaeline* under *Ipecac*.

Assay preparation—Pipet 10 mL of water into a 25-mL volumetric flask. With the aid of a 20-mL pipet, add Syrup to volume, taking care to prevent contact of the Syrup with the neck of the flask above the graduation line. Insert the stopper, and mix.

Chromatographic columns—Pack a pledget of fine glass wool in the base of a chromatographic tube (25-mm × 200-mm test tube to which is fused a 5-cm length of 7-mm tubing) with the end of a tamping rod having a disk with a diameter about 1 mm less than that of the tube.

To prepare *Column I*, transfer 4.0 mL of *Assay preparation* to a 150-mL beaker, add about 1 g of sodium bicarbonate, and mix. Then proceed as directed for *Chromatographic columns* in the *Assay for emetine and cephaeline* under *Ipecac*, beginning with "add 6 g of purified siliceous earth," and prepare *Columns II*, *III*, and *IV* as directed therein.

Procedure—Proceed as directed for *Procedure* in the *Assay for emetine and cephaeline* under *Ipecac*.

Calculate the quantity, in mg, of emetine in each 100 mL of Syrup taken by the formula:

$$2.08C(A_{283} - A_{350})_U/(A_{283} - A_{350})_S,$$

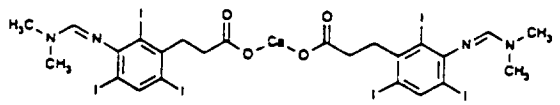
in which the parenthetic expressions are the differences in the absorbances of the solution of emetine from the *Assay preparation* (*U*) and the *Standard preparation* (*S*), respectively, at the wavelengths indicated by the subscripts, and *C* is as defined in the *Procedure*.

Calculate the quantity, in mg, of cephaeline in each 100 mL of Syrup taken by the formula:

$$0.971(2.08C)(A_{283} - A_{350})_U/(A_{283} - A_{350})_S,$$

in which 0.971 is the ratio of the molecular weight of cephaeline to that of emetine, the parenthetic expressions are the differences in the absorbances of the solution of cephaeline from the *Assay preparation* (*U*) and the *Standard preparation* (*S*), respectively, at the wavelengths indicated by the subscripts, and *C* is as defined in the *Procedure*.

Ipodate Calcium



$C_{24}H_{24}CaI_6N_4O_4$ 1233.99

Benzenepropanoic acid, 3-[[(dimethylamino)methylene]amino]-2,4,6-triiodo-, calcium salt.

Calcium 3-[[(dimethylamino)methylene]amino]-2,4,6-triiodohydrocinnamate [*1151-11-7*].

» Ipodate Calcium contains not less than 97.5 percent and not more than 102.5 percent of $C_{24}H_{24}CaI_6N_4O_4$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Ipodate Calcium RS*.

Identification—

A: *Infrared Absorption* ⟨197K⟩, dried in vacuum at 60° for 4 hours.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 1 in 100,000.

Medium: methanol. Absorptivities at 235 nm, calculated on the dried basis, do not differ by more than 3.0%.

C: Heat about 500 mg in a porcelain crucible over a flame: violet vapors of iodine are evolved.

D: Dissolve about 200 mg in 10 mL of 6 *N* acetic acid, and add 2 mL of ammonium oxalate TS: a white precipitate, which is soluble in 3 *N* hydrochloric acid, is formed.

Water, *Method I* ⟨921⟩: not more than 3.5%.

Iodide or iodine—Dissolve about 200 mg in 10 mL of 6 *N* acetic acid, add 1 mL of chloroform, and shake vigorously. Allow the layers to separate: the chloroform layer shows no violet color (*absence of free iodine*). Add 1 mL of 0.1 *N* potassium iodate, shake vigorously, and allow the layers to separate: the chloroform layer shows at most a slight trace of violet color.

Heavy metals, *Method II* ⟨231⟩: 0.003%.

Assay—Transfer about 300 mg of Ipodate Calcium, accurately weighed, to a glass-stoppered, 250-mL flask, add 30 mL of 1.25 *N* sodium hydroxide and 0.5 g of powdered zinc, and reflux the mixture for 60 minutes. Cool, wash the condenser with 20 mL of water, and filter the mixture. Wash the flask and the filter with small portions of water, adding the washings to the filtrate. Add to the filtrate 5 mL of glacial acetic acid and 3 drops of eosin Y TS, and titrate with 0.05 *N* silver nitrate VS until the entire mixture changes to a permanent pink color. Each mL of 0.05 *N* silver nitrate is equivalent to 10.28 mg of $C_{24}H_{24}CaI_6N_4O_4$.

Ipodate Calcium for Oral Suspension

» Ipodate Calcium for Oral Suspension is a dry mixture of Ipodate Calcium and one or more suitable suspending, dispersing, and flavoring agents. It contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{24}CaI_6N_4O_4$.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Ipodate Calcium RS*.

BP1993

Iophendylate Injection

Definition Iophendylate Injection is a sterile mixture of stereoisomers of ethyl 10-(4-iodophenyl)undecanoate ($C_{19}H_{29}IO_2$).

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of iophendylate, $C_{19}H_{29}IO_2$ 98.0 to 101.0% w/w.

Characteristics Almost colourless to pale yellow, viscous liquid.

Very slightly soluble in *water*, freely soluble in *ethanol (96%)*; miscible with *chloroform* and with *ether*.

Identification A. When heated with *sulphuric acid*, violet vapours of iodine are evolved.

B. To 1 ml add 15 ml of *water* and 7 g of *potassium dichromate*, cool and carefully add 10 ml of *sulphuric acid*. Allow to stand until the reaction ceases, heat under a reflux condenser for 2 hours, cool, pour into 25 ml of *water* and filter. Wash the residue with a little *water*, recrystallise from 10 ml of aqueous ethanol and sublime the crystals. The *melting point* of the sublimate is about 270°, Appendix V A.

Acid value Not more than 1.5, Appendix X B.

Refractive index 1.525 to 1.527, Appendix V E.

Saponification value 132 to 142, Appendix X G. Use 1 g.

Weight per ml 1.245 to 1.260 g, Appendix V G.

Aliphatic iodine Mix 0.5 g with 10 ml of 1M *ethanolic potassium hydroxide* and boil vigorously under a reflux condenser in a water bath for 1 hour. Add 40 ml of *water* and 15 ml of *hydrochloric acid*, cool, filter and wash the residue with 10 ml of *water*. To the combined filtrate and washings add 10 ml of *potassium cyanide solution*, 5 ml of *starch mucilage* and 0.2 ml of 0.05M *potassium iodate*. A blue colour is not produced.

Free iodine *Absorbance* of a 4-cm layer at 485 nm, not more than 0.20, Appendix II B.

Assay Carry out the method for *oxygen-flask combustion for iodine*, Appendix VIII C, using 20 mg absorbed on filter paper surrounded by greaseproof paper. Each ml of 0.02M *sodium thiosulphate VS* is equivalent to 1.388 mg of $C_{19}H_{29}IO_2$.

Storage Iophendylate Injection should be protected from light.

Action and use Radio-opaque injection.

Ipecacuanha Liquid Extract

Definition Ipecacuanha Liquid Extract is prepared by extracting Ipecacuanha with Ethanol (80 per cent). It contains not less than 1.90% and not more than 2.10% of total alkaloids, calculated as emetine, $C_{29}H_{40}N_2O_4$.

Extemporaneous preparation The following formula and directions apply.

Ipecacuanha, in *fine powder*	1000 g
Ethanol (80 per cent)	a sufficient quantity

Exhaust the Ipecacuanha by *percolation* with Ethanol (80 per cent), Appendix XI F, reserving the first 750 ml of the percolate. Remove the ethanol from the remainder of the percolate by evaporation under reduced pressure at a temperature not exceeding 60° and dissolve the residual extract in the reserved portion. Determine the proportion of alkaloids in the liquid thus obtained by the Assay described below. To the remainder of the liquid add sufficient Ethanol (80%) to produce an Ipecacuanha Liquid Extract containing 2% w/v of total alkaloids calculated as emetine. Allow to stand for not less than 24 hours; filter.

The extract complies with the requirements stated under Extracts and with the following requirements.

Ethanol content 63 to 69% v/v, Appendix VIII F.

Assay To 5 ml in a separating funnel add 20 ml of *water*, 5 ml of 1M *sulphuric acid* and 10 ml of *chloroform* and shake well. Transfer the chloroform extract to a second separating funnel containing a mixture of 4 ml of *ethanol (96%)* and 20 ml of 0.05M *sulphuric acid*, shake, allow to separate and discard the chloroform layer. Continue the extraction of the liquid in the first separating funnel with two further 10-ml quantities of *chloroform*, transferring the chloroform solution each time to the second separating funnel and washing as before. Transfer the acidic liquid from the second separating funnel to the first separating funnel, make distinctly alkaline with 5M *ammonia* and shake with successive quantities of *chloroform* until *complete extraction* of the alkaloids is effected, Appendix XI G, washing each chloroform solution with the same 10 ml of *water* contained in a third separating funnel. Remove the chloroform, add to the residue 2 ml of *ethanol (96%)*, evaporate to dryness and dry for 5 minutes at 80° in a current of air. Dissolve the residue in 2 ml of *ethanol (96%)*, previously neutralised to *methyl red solution*, add 10 ml of 0.05M *sulphuric acid VS* and titrate with 0.1M *sodium hydroxide VS* using *methyl red mixed solution* as indicator. Each ml of 0.05M *sulphuric acid VS* is equivalent to 24.03 mg of total alkaloids, calculated as emetine, $C_{29}H_{40}N_2O_4$.

Preparation
Ipecacuanha Tincture

Action and use Expectorant.

Paediatric Ipecacuanha Emetic Mixture

Paediatric Ipecacuanha Emetic

Definition

Ipecacuanha Liquid Extract	70 ml
Hydrochloric Acid	2.5 ml
Glycerol	100 ml
Syrup	sufficient to produce 1000 ml

The mixture complies with the requirements stated under Oral Liquids and with the following requirements.

Content of total alkaloids 0.12 to 0.16% w/v, calculated as emetine, $C_{29}H_{40}N_2O_4$.

Identification Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 90 volumes of *chloro-*

form and 10 volumes of *diethylamine* as the mobile phase. Apply separately to the plate 2 µl of each of the following solutions. For solution (1) mix 5 ml with 10 ml of 1M *sulphuric acid*, shake with two 10-ml quantities of *chloroform* and discard the chloroform. Add sufficient 5M *ammonia* to make the aqueous solution distinctly alkaline to *litmus paper*, extract with four 10-ml quantities of *chloroform*, evaporate the combined extracts to dryness, cool the residue and dissolve it in 0.5 ml of *ethanol (96%)*. Solution (2) contains 0.1% w/v of *cephaeline hydrochloride EPCRS* in *ethanol (96%)*. Solution (3) contains 0.1% w/v of *emetine hydrochloride EPCRS* in *ethanol (96%)*. After removal of the plate, dry it at 105° to 110° for 30 minutes, allow to cool and spray with *dilute potassium iodobismuthate solution*. The principal spots in the chromatogram obtained with solution (1) correspond in colour and position to the spots in the chromatograms obtained with solutions (2) and (3). Disregard any *secondary spots*.

Assay To 25 ml in a separating funnel add 20 ml of *water* and 5 ml of 1M *sulphuric acid*, shake with three 10-ml quantities of *chloroform* and wash each chloroform extract with a mixture of 20 ml of 0.05M *sulphuric acid* and 4 ml of *ethanol (96%)* contained in a second separating funnel. Transfer the acid—ethanol mixture from the second separating funnel to the first, make the combined liquids distinctly alkaline to *litmus paper* with 5M *ammonia* and extract with successive quantities of *chloroform* until *complete extraction* of the alkaloids is effected, Appendix XI G. Wash each chloroform extract with the same 10 ml of *water*, combine the chloroform extracts, evaporate the chloroform, add 2 ml of *ethanol (96%)* to the residue, evaporate to dryness and dry the residue at 80° in a current of air for 5 minutes. Dissolve the residue in 2 ml of *ethanol (96%)* previously neutralised to *methyl red solution*, add 10 ml of 0.01M *sulphuric acid VS* and titrate the excess of acid with 0.02M *sodium hydroxide VS* using *methyl red solution* as indicator. Each ml of 0.01M *sulphuric acid VS* is equivalent to 4.806 mg of $C_{29}H_{40}N_2O_4$.

Ipecacuanha Tincture

Definition

Ipecacuanha Liquid Extract	100 ml
Acetic Acid (6 per cent)	16.5 ml
Ethanol (90 per cent)	210 ml
Glycerol	200 ml
Purified Water	sufficient to produce 1000 ml

Extemporaneous preparation The following directions apply.

Mix the Ethanol (90 per cent) and the Acetic Acid (6 per cent) with the Glycerol and 450 ml of Purified Water and add the Ipecacuanha Liquid Extract and sufficient Purified Water to produce 1000 ml. Allow to stand for not less than 24 hours; filter.

The tincture complies with the requirements stated under Tinctures and with the following requirements.

Content of total alkaloids 0.190 to 0.210% w/v, calculated as emetine, $C_{29}H_{40}N_2O_4$.

Ethanol content 24 to 28% v/v, Appendix VIII F.

Assay To 50 ml in a separating funnel add 5 ml of 1M *sulphuric acid*, shake with three 10-ml quantities of *chloroform* and wash each chloroform solution with a mixture of 20 ml of 0.05M *sulphuric acid* and 4 ml of *ethanol (96%)* contained in a second separating funnel. Transfer the acid—ethanol mixture from the second separating funnel to the first, make the combined liquids distinctly alkaline to *litmus paper* with 5M *ammonia* and extract with successive quantities of *chloroform* until *complete extraction* of the alkaloids is effected, Appendix XI G. Wash each chloroform extract with the same 10 ml of *water*, combine the chloroform extracts, evaporate the chloroform, add 2 ml of *ethanol (96%)* to the residue, evaporate to dryness and dry the residue at 80° in a current of air for 5 minutes. Dissolve the residue in 2 ml of *ethanol (96%)* previously neutralised to *methyl red solution*, add 10 ml of 0.05M *sulphuric acid VS* and titrate the excess acid with 0.1M *sodium hydroxide VS* using *methyl red mixed solution* as indicator. Each ml of 0.05M *sulphuric acid VS* is equivalent to 24.03 mg of total alkaloids calculated as $C_{29}H_{40}N_2O_4$.

When ipecacuanha wine is prescribed or demanded, Ipecacuanha Tincture shall be dispensed or supplied.

Iron Dextran Injection

Definition Iron Dextran Injection is a sterile colloidal solution containing a complex of iron(III) hydroxide with dextrans of weight average molecular weight between 5000 and 7500.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of iron, Fe 4.75 to 5.25% w/v.

Content of dextrans 17.0 to 23.0% w/v.

Characteristics A dark brown solution.

Identification A. Add 5M *ammonia* to 0.2 ml of the injection previously diluted to 5 ml with *water*. No precipitate is produced.

B. Mix 1 ml with 100 ml of *water*. To 5 ml of this solution add 0.1 ml of *hydrochloric acid*, boil for 30 seconds, cool rapidly, add 2 ml of 13.5M *ammonia* and 5 ml of *hydrogen sulphide solution*, boil to remove hydrogen sulphide, cool and filter. Boil 5 ml of the filtrate with 5 ml of *cupri-tartaric solution RI*; the solution remains greenish in colour and no precipitate is produced. Boil a further 5 ml of the filtrate with 0.5 ml of *hydrochloric acid* for 5 minutes, cool, add 2.5 ml of 5M *sodium hydroxide* and 5 ml of *cupri-tartaric solution RI* and boil again; a reddish precipitate is produced.

C. To 1 ml add 20 ml of *water* and 5 ml of *hydrochloric acid* and boil for 5 minutes. Cool, add an excess of 13.5M *ammonia* and filter. Wash the precipitate with *water*, dissolve in the minimum volume of 2M *hydrochloric acid* and add sufficient *water* to produce 20 ml. The resulting solution yields reaction B characteristic of *iron salts*, Appendix VI.

Acidity pH, 5.2 to 6.5, Appendix V L.

Arsenic To 5.0 ml in a Kjeldahl flask add 10 ml of *water* and 10 ml of *nitric acid* and heat until the vigorous evolution of brown fumes ceases. Cool, add 10 ml of *sulphuric acid* and heat again until fumes are evolved, adding *nitric acid* dropwise at intervals until oxidation is complete. Cool, add 30 ml of *water*, bring to the boil and

PHARMACODYNAMICS AND DRUG ACTION

Ipecacuanha-induced emesis: A human model for testing antiemetic drug activity

In a double-blind, randomized, parallel-group study, five groups of 10 healthy men received single 5-minute infusions of 8 mg, 4 mg, 1 mg, 0.25 mg, or 0.1 mg ondansetron (as hydrochloride dihydrate) 30 minutes before oral administration of 30 ml syrup of ipecacuanha. Emetic episodes and nausea (100 mm visual analog scale) were assessed over an 8-hour period. There were no emetic episodes after 8 or 4 mg ondansetron. Seven, nine, and 10 subjects vomited after 1 mg, 0.25 mg and 0.1 mg ondansetron, respectively, with median times to onset of 62, 31, and 37 minutes. Median peak nausea scores were 0 mm for both 8 and 4 mg ondansetron and 30, 53, and 26 mm for 1, 0.25, and 0.1 mg ondansetron. Adverse events were mild. This model showed a close correlation with clinically effective doses of ondansetron. It may be successfully and safely used to assess the antiemetic potential of 5-HT_3-receptor antagonists in healthy subjects. (CLIN PHARMACOL THER 1993;54:53-7.)

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Ondansetron, a highly selective 5-HT_3-receptor antagonist is effective in the treatment of nausea and emesis resulting from the therapeutic use of cytotoxic regimes[1-6] and radiotherapy in malignant disease.[7,8] It is also effective in the prevention and treatment of postoperative nausea and vomiting.[9-16]

Controversy exists regarding the site of action of 5-HT_3-receptor antagonists.[17] Their site may be peripheral[18] at abdominal visceral afferent neurons,[19] or central[20] within the area postrema of the brain,[21] or a combination of both.

There has been no healthy human model for testing the antiemetic properties of 5-HT_3-receptor antagonists. However, work in ferrets[22] has shown that emesis induced by syrup of ipecacuanha is antagonized by pretreatment with ICS 205-930, a 5-HT_3-receptor antagonist, but not by fluphenazine, a dopamine receptor antagonist. Until recently, the mechanism of action of syrup of ipecacuanha, an emetic containing the principal active ingredients emetine and cephaeline[23] and widely used as an emetic in the management of poisoning, has not been fully understood, although emetine is believed to act through both peripheral and central mechanisms (reviewed by Costall et al.[22]). However, recent data[22] would indicate an effect through 5-HT receptors and one that is antagonized by 5-HT_3-receptor antagonists.

If the use of this model were to be extended to humans, it might enable the antiemetic activity of new 5-HT_3-receptor antagonists to be evaluated in healthy volunteers at a very early stage and enable dose predictions to be made before introduction to patients.

Syrup of ipecacuanha is a safe and effective experimental method of inducing emesis in healthy subjects.[24,25] A preliminary study showed that a standard

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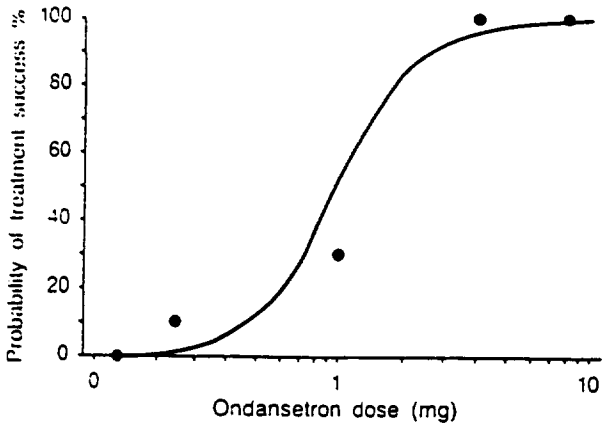

Fig. 1. Probability of prevention by ondansetron of ipecacuauha-induced emesis in healthy volunteers. Each *data point* represents the percentage of each group of 10 volunteers who did not experience emesis. Estimated ED_{50} for protection against emesis: 1.27 mg (SE, 0.29 mg; correlation coefficient, 0.867).

8 mg dose of ondansetron was effective in preventing ipecacuanha-induced emesis in healthy subjects and that it markedly reduced nausea.[26] The aim of this study was to establish an antiemetic dose response to ondansetron with use of this model.

METHODS

Clinical methods. Five groups of 10 healthy male volunteers, aged 18 to 35 years, participated in a double-blind, randomized parallel-group study. Subjects with histories of gastrointestinal or any underlying medical disorders were excluded, and all volunteers were required to have no abnormality shown by clinical and laboratory examinations. Permission for the study was granted by Guy's Hospital Ethics Committee (London, England). Subjects were required to avoid strenuous exercise, alcohol, and any medication for 48 hours before the study day, while residents in the research unit, and for a further 5 days. Subjects were not permitted to drive on the day of discharge.

Subjects came to the research unit, had laboratory safety tests, and fasted from midnight. Consumption of water for hydration was permitted. The next morning, subjects received a single 25 ml 5-minute intravenous infusion of 0.9% sodium chloride solution containing either 8, 4, 1, 0.25, or 0.1 mg ondansetron as hydrochloride dihydrate. Thirty minutes after the start of the infusion they received an oral dose of syrup of ipecacuanha (British Pharmacopoeia), 30 ml in 200 ml water, to be consumed within 1 minute.

The time to onset, number of emetic episodes, and duration of emesis were recorded for each subject. An *emetic episode* was defined as a single vomit or retch or any number of continuous vomits or retches. Emetic episodes were, by definition, separated by the absence of vomiting or retching for at least 1 minute. Nausea was assessed, by subject rating, with a 100 mm visual analog scale (VAS) before dosing with syrup of ipecacuanha and at 10, 20, 30, 60, 90, 120, 180, 240, 360, and 480 minutes after syrup of ipecacuanha. The 100 mm VAS was as follows:

I am not at all nauseated ——————— I have never felt so nauseated

Subjects were allowed sips of water for 2 hours after syrup of ipecacuanha. They were allowed water freely from 2 hours and coffee and a light lunch from 4 hours if they wished. After 4 hours subjects were allowed a normal diet, but smoking and alcohol were prohibited. They remained in the research unit until the following morning when final laboratory safety checks were made. Adverse events were monitored throughout.

Statistical methods. The following variables were analyzed: time to onset and duration of emesis (in minutes), number of emetic episodes, peak and weighted mean nausea scores (in millimeters). The latter were obtained by evaluating the area under the time curves with trapezoidal integration and dividing by the length of time over which the measurements were made.

For each variable, the values on the 8 and 4 mg doses were compared with each of the lower doses. In the analysis of the time to emesis, values on the 1 mg dose were also compared with the lower doses. Comparisons were made between doses by use of the Wilcoxon rank sum test. Subjects who did not experience emesis had their time to onset of emesis ranked at >300 minutes and duration ranked at 0 minutes. All analyses were performed with use of SAS version 6.04 (SAS Institute, Cary, N.C.)

Table I. Number of subjects who experienced emesis on each dose of ondansetron (n = 10 subjects per dose)

Ondansetron dose	*No. of subjects experiencing emesis*
8 mg	0
4 mg	0
1 mg	7
0.25 mg	9
0.1 mg	10

Table II. Emetic episodes after each dose of ondansetron (n = 10 subjects per dose)

Ondansetron dose	Time to onset emesis (min)	Duration of emesis (min)	No. of emetic episodes
8 mg	>300	0	0
4 mg	>300	0	0
1 mg			
Median	62**	3**	1***
Range	38->300	0-224	0-7
0.25 mg			
Median	31**	22***	2***
Range	17->300	0-143	0-10
0.1 mg			
Median	37***	9***	2***
Range	15-267	1-211	1-5

Significance of difference from 8 and 4 mg doses: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

RESULTS

The number of subjects experiencing emesis at each dose is shown in Table I. Emesis did not occur in subjects receiving the 8 or 4 mg doses of ondansetron but did occur in seven, nine, and 10 subjects after 1, 0.25, and 0.1 mg doses of ondansetron, respectively. These findings were fitted to a dose-response model with use of nonlinear least-squares regression (Fig. 1). The correlation coefficient for the fit was 0.867 ($p < 0.001$).

A significantly shorter median time to emesis was observed on the 1 mg (62 minutes), 0.25 mg (31 minutes), and 0.1 mg (37 minutes) doses compared with the 8 and 4 mg doses (<300 minutes; Table II). The difference between the 1 mg and the lower doses was also significant. A significantly higher median duration of emesis was observed on the 1 mg (3 minutes, 0.25 mg (22 minutes), and 0.1 mg (9 minutes) doses compared with the 8 and 4 mg doses (0 minutes; Table II). A significantly higher median number of emetic episodes was observed on the 1 mg (one episode), 0.25 mg (two episodes), and 0.1 mg (two episodes) doses compared with the 8 and 4 mg doses (no episodes; Table II).

There was no difference in median weighted mean nausea score between the 8 and 4 mg doses (0 mm; Table III). A significantly higher weighted mean nausea score was observed on the 1 mg (5 mm), 0.25 mg (6 mm), and 1 mg (6 mm) doses compared with the 8 and 4 mg doses (Table III). There was no difference in median peak nausea score between the 8 and 4 mg doses (0 mm; Table III). A significantly higher median peak nausea score was observed on the 1 mg (30 mm), 0.25 mg (53 mm), and 0.1 mg (26 mm) doses compared with the 8 and 4 mg doses.

Adverse events occurred predominantly in those subjects who experienced emesis, and all adverse events were classified as mild. These included five reports of abdominal discomfort and two of diarrhea. Six episodes of headache, five episodes of lightheadedness, and four episodes of lethargy were reported. Flecks of blood were seen in the vomit of one subject and some blood staining in another. No subject required antiemetic rescue medication.

Table III. Nausea scores after each dose of ondansetron (n = 10 per dose)

Ondansetron dose	Weighted mean nausea score (mm)	Peak nausea score (mm)
8 mg		
Median	0	0
Range	0-2	0-30
4 mg		
Median	0	0
Range	0-11	0-20
1 mg		
Median	5**	30**
Range	0-20†	0-100††
0.25 mg		
Median	6***	53***
Range	0-15††	2-69†††
0.1 mg		
Median	6***	26***
Range	1-10††	8-97†††

Significance of difference from 8 mg (*) and 4 mg (†) doses: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; †$p < 0.05$; ††$p < 0.01$; †††$p < 0.001$.

DISCUSSION

This study, conducted in healthy subjects, has shown that both 4 and 8 mg intravenous doses of ondansetron prevented ipecacuanha-induced emesis, whereas efficacy was progressively reduced with the lower doses. The emetic episode data correlate well with the current clinical use of ondansetron. Clinical

trials have shown that both 8 mg[9-11,13-15] and 4 mg[13] single intravenous doses of ondansetron are effective in the prevention of postoperative nausea and vomiting. Only partial efficacy has been shown with a 1 mg dose for both prevention[13] and treatment of this condition.[12] The approved intravenous dose of ondansetron for the prevention and treatment of postoperative nausea and vomiting is 4 mg in the United Kingdom.

There was a dose response to the nausea parameters estimated in this study. Both median weighted mean and median peak nausea scores were zero for the 4 and 8 mg doses and were higher for the 1, 0.25, and 0.1 mg doses. However, the pattern for the lower doses was not clear-cut and may reflect the variability of response and subjectiveness of these measurements. Again, clinical studies have shown a comparable dose response for nausea, with similar efficacy using 4 and 8 mg doses.[13]

The dosing regimens for ondansetron in the prevention of emesis induced by cytotoxic chemotherapy and radiotherapy are more complex. However, the lowest recommended single intravenous dose of ondansetron in chemotherapy-induced emesis is 8 mg.[2,27,28] It therefore appears that the anti-emetic potency of ondansetron assessed by this model correlates better with clinical efficacy in postoperative nausea and vomiting than with chemotherapy-induced emesis. A plausible explanation is that some chemotherapy regimens are more potent emetic stimuli than syrup of ipecacuanha.

This study was designed after a pilot study in which 8 mg ondansetron prevented emesis in 19 of 20 subjects and substantially reduced nausea in the remaining subject.[26] These data, coupled with other studies showing the effectiveness of ipecacuanha in inducing emesis in healthy subjects[24,25] and patients,[29] obviated the requirement for a placebo dose in this study. The avoidance of a placebo limb in clinical trials of emesis is considered by some to be more ethically acceptable.[30]

This study has shown that ipecacuanha-induced emesis is a safe and representative model for testing the antiemetic potential of 5-HT_3-receptor antagonists. Adverse events were all mild, predictable, and predominately of a gastrointestinal nature.[31] In two subjects, very small quantities of blood were observed after emesis: these episodes were self-limiting and not considered to be of importance. Syrup of ipecacuanha is widely used in the induction of emesis in cases of accidental or deliberate self-poisoning and has a good safety record.[32,33] Serious adverse events, including significant hematemesis caused by esophageal tears, are exceedingly rare.[34,35]

In conclusion, we suggest that this ipecacuanha model of emesis could be safely and effectively used for characterization of the dose-response relationship of new 5-HT_3-receptor antagonists. Such methods should enable the definition of an effective dose range for a candidate drug in healthy volunteers before its introduction to patients. With the advent of highly effective 5-HT_3-receptor antagonists, the administration of suboptimal doses of antiemetic, in dose-ranging studies with a new candidate, is undesirable for patients, particularly for those receiving chemotherapy and radiation treatments.

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Bioavailability of IM Ondansetron 4 mg

Study#: W91-016 Volume: 3

Objectives: To estimate the systemic availability and pharmacokinetics (PK) of an IM dose of ondansetron 4 mg in a 2 ml volume.

To assess the tolerability of an IM dose of ondansetron 4 mg in a 2 ml volume.

Formulations: For the IM injection, the approved 2 mg/ml injection formulation was used . For the IV injection, the reference preparation was diluted to 8 mg/20 ml

Design: Double-blind, two-way crossover with a washout period of at least six days between doses.

Study Dates: Between 11-21-91 to 12-13-91.

Subjects: Seventeen subjects were entered into the study with sixteen completing both phases. All subjects were healthy male caucasians

Treatments: Each subject received ondansetron 4 mg as a single IV infusion over 5 min and IM injection on two separate study days. Blinding was achieved by administration of an intravenous or IM placebo on each of the study days. The IM injection sites were randomized to the lateral compartment of the left and right thighs.

Study Procedures: Blood samples were collected for analysis prior to dosing and at 5, 10, 20, 40, 60, 90 and 120 min and 3, 4, 6, 8, 10, 12, 20 and 24 hours after dosing.

The tolerability of the IM injection were rated by the subjects on a four point scale ranging from 'no pain felt' to 'severe pain' 1, 5, 15 and 60 min after dosing.

Results:

Figure 1 to 5 show comparison of ondansetron PK between IM and IV routes.

Parameter	IM	IV
AUC* (ng*h/ml)	80.4	80.2
Cmax* (ng/ml)	25.5	65.8
tmax+ (h)	0.17	0.08
λ_z# (1/hr)	0.228	0.240

+ = Median (range)

* = Geometric mean (95% CI)

= Arithmetic mean (95% CI)

The treatment comparisons for the above parameters are tabulated below:

Comparison	Estimate	90% CI	p-value
IM/IV AUC	100%	(95 - 106)	0.936
IM/IV Cmax	39%	(29 - 52)	<0.001
IM-IV tmax	0.13	(0.08 - 0.17)	0.002
IM-IV λ_z	-0.012	(-0.030-0.006)	0.272

The following table shows the assessed pain data for the ondansetron IM and IV injection.

		4 mg IM/IV placebo	4 mg IV/IM placebo
# of subjects		16	16
1 minute	None Mild Moderate Severe	10 6 0 0	3 7 4 2
5 minute	None Mild Moderate Severe	13 3 0 0	8 7 1 0

15 minute	None Mild Moderate Severe	15 1 0 0	13 3 0 0
60 minute	None Mild Moderate Severe	16 0 0 0	16 0 0 0

Conclusions:

The systemic exposure of the subjects to ondansetron following a 4 mg IM injection was same as that following a 4 mg IV injection.

The IM ondansetron injections were well tolerated, with lower pain scores recorded after ondansetron IM than placebo IM.

14. FIGURES

FIGURE 1

MEDIAN PLASMA ONDANSETRON CONCENTRATIONS

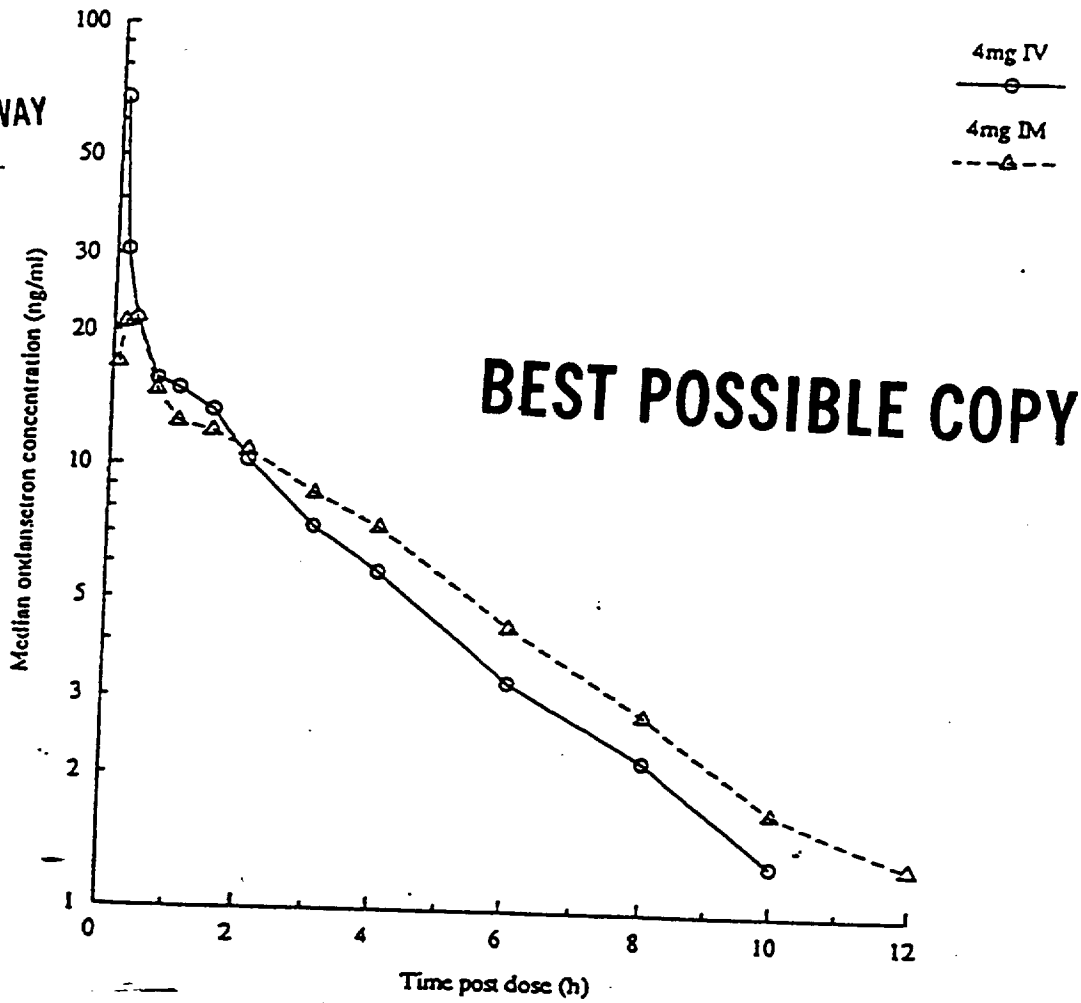


FIGURE 2

COMPARATIVE PLOT OF AUC_{∞} VALUES AFTER ONDANSETRON 4mg IM AND IV

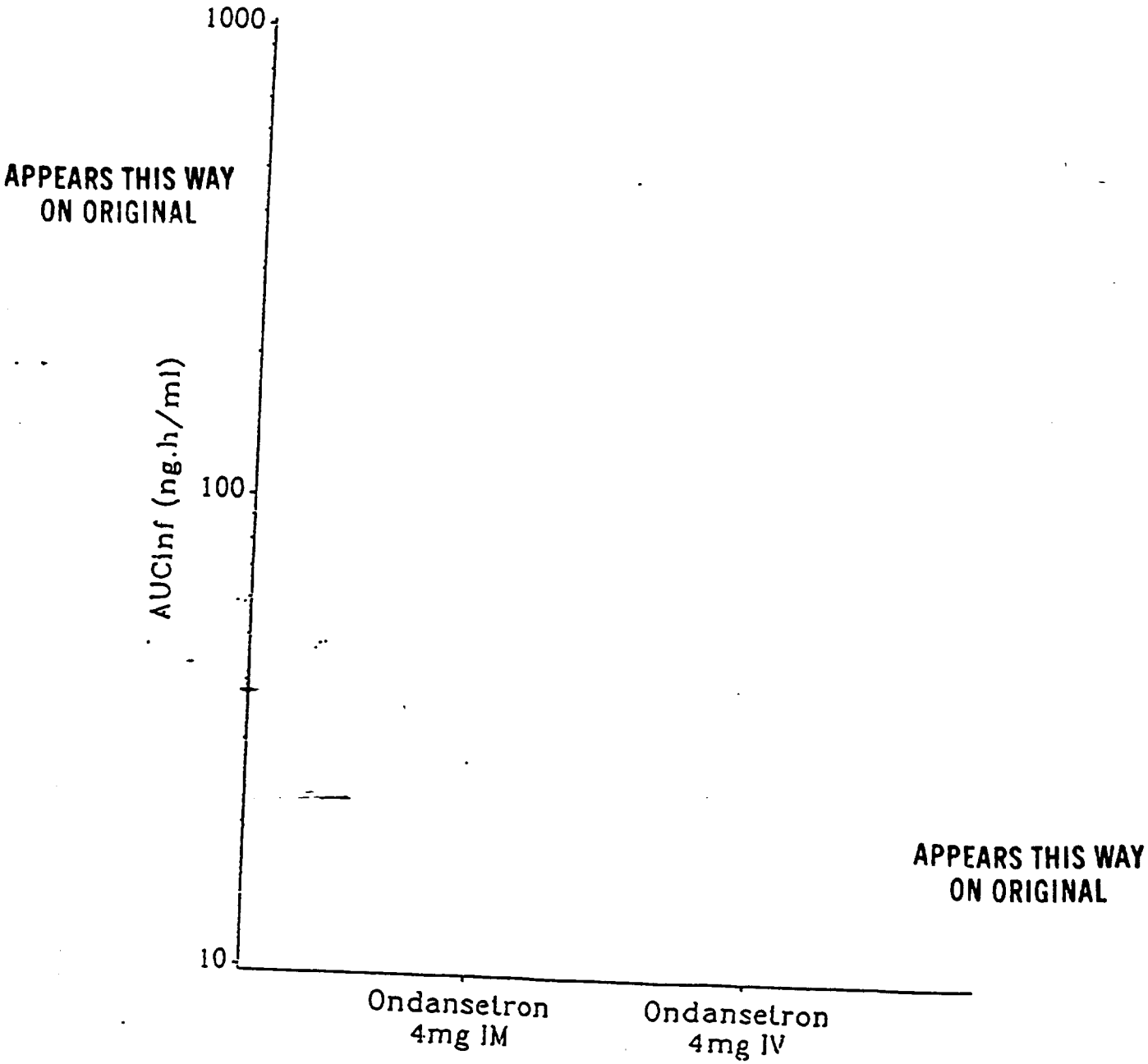


FIGURE 3

COMPARATIVE PLOT OF C_{max} VALUES AFTER ONDANSETRON 4mg IM AND IV

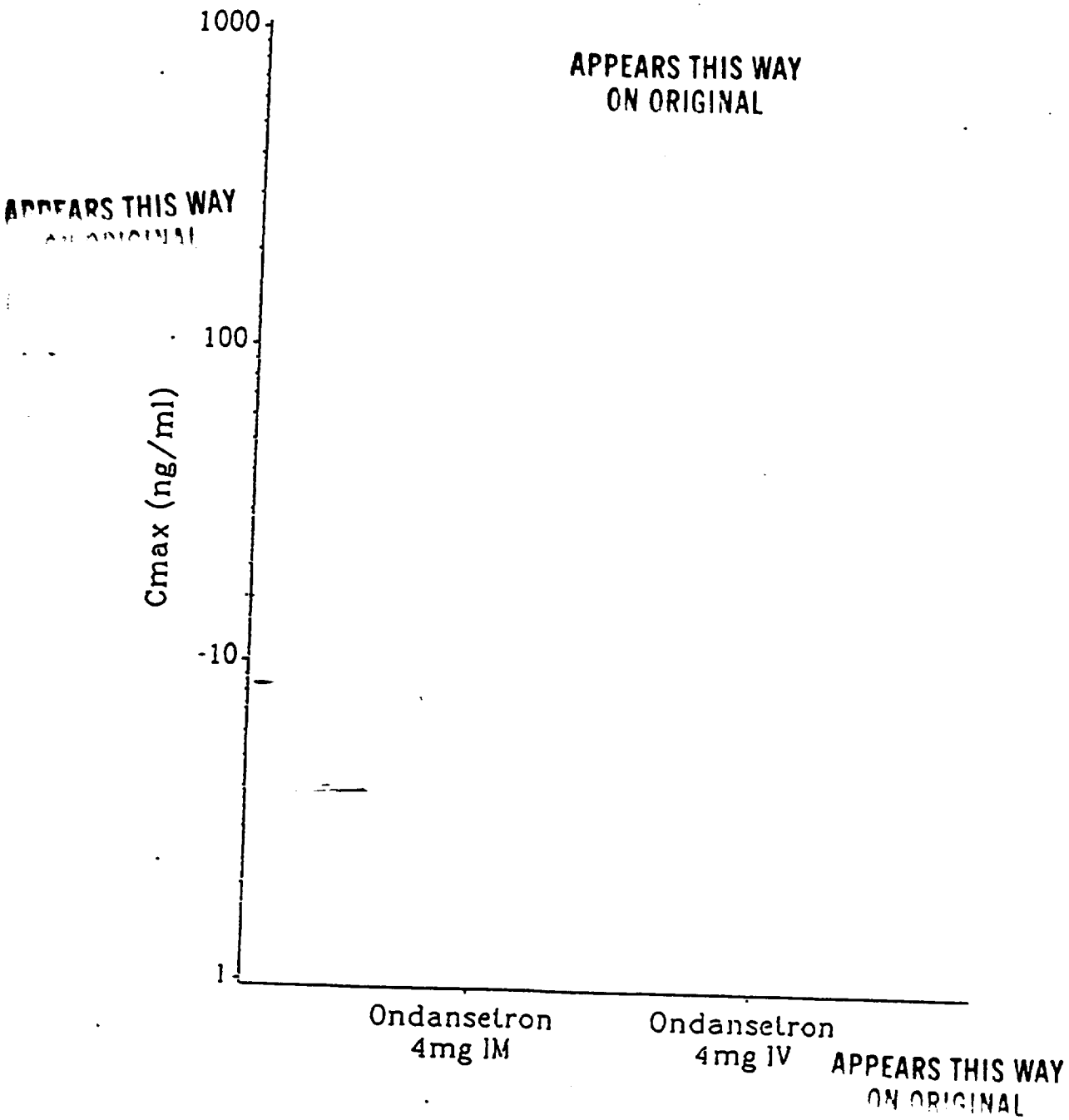


FIGURE 4

COMPARATIVE PLOT OF t_{max} VALUES AFTER ONDANSETRON 4mg IM AND IV

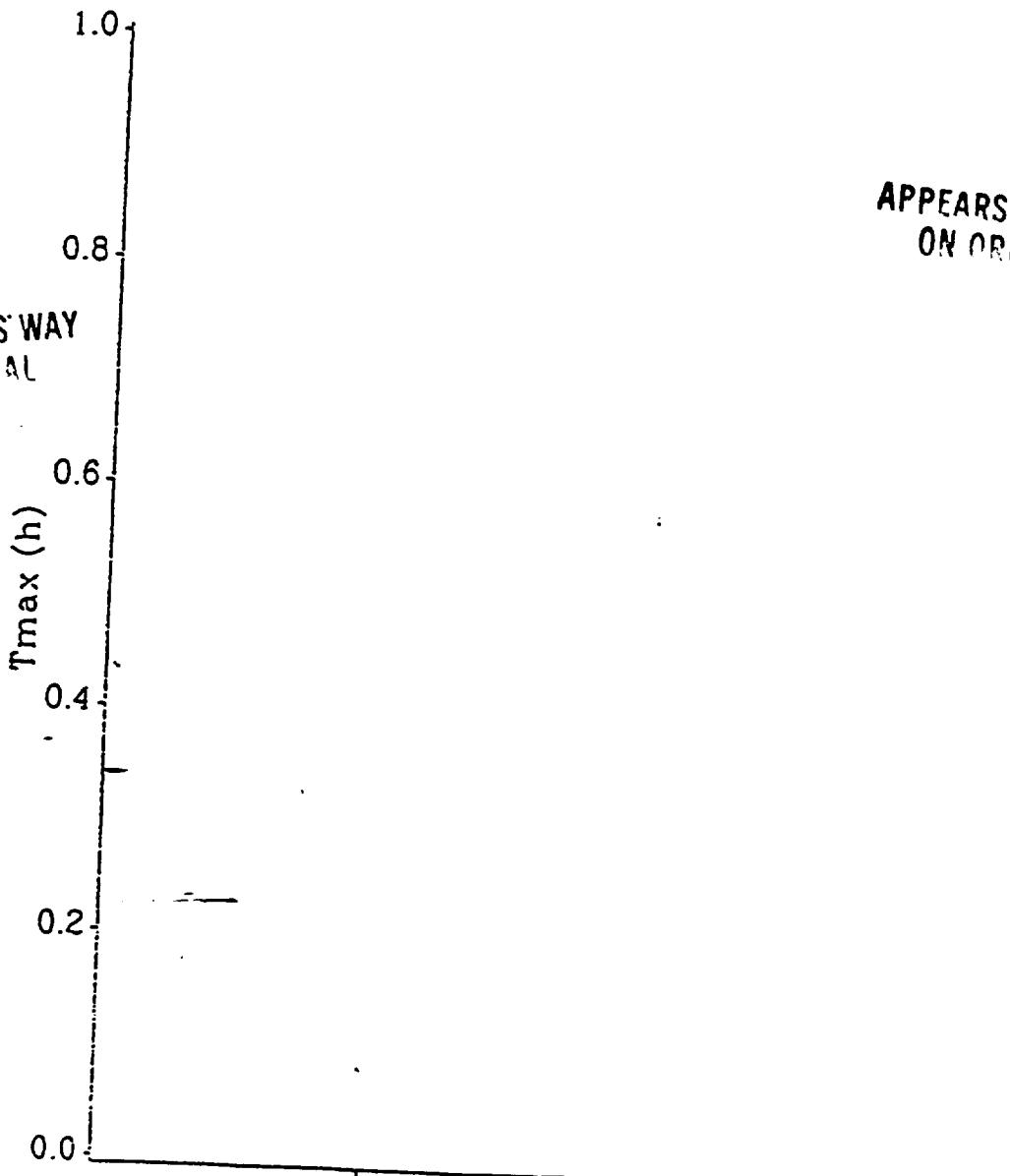
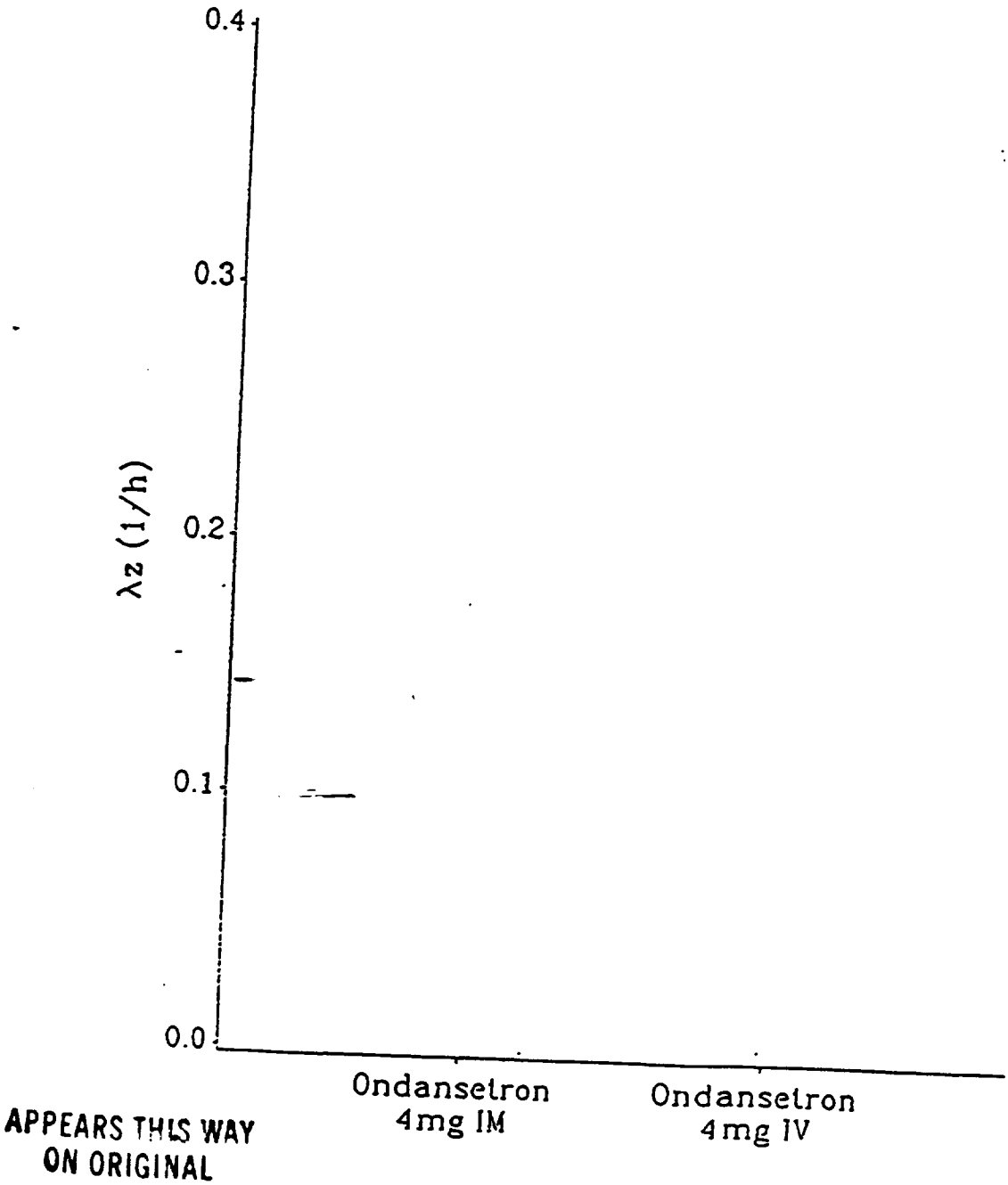


FIGURE 5

COMPARATIVE PLOT OF λ_z VALUES AFTER ONDANSETRON 4mg IM AND IV

APPEARS THIS WAY
ON ORIGINAL



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