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COMPARATIVE BIOAVAILABILITY OF PAPAVERINE HYDROCHLORIDE, PAPAVERINE HEXAMETAPHOSPHATE AND PAPAVERINE POLYMETAPHOSPHATE.

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ABSTRACT

Papaverine hexametaphosphate and papaverine polymetaphosphate salts were prepared and isolated. Experiments were conducted in mongrel dogs to compare the bioavailability of papaverine hydrochloride, papaverine hexametaphosphate and papaverine polymetaphosphate. The metaphosphates resulted in greater area under the curve compared to the hydrochloride salt, however, there was no difference observed in the lag time, apparent absorption rate constant, time of peak or maximum plasma concentrations obtained by any of the three salts. Intravenous doses of papaverine hydrochloride were given to all dogs to determine the absolute bioavailability. The pharmacokinetic parameters and first order transfer constants for drug disposition were calculated from the intravenous data; whereas, the apparent absorption rate constant was estimated from percent unabsorbed versus time plots. The pharmacokinetic analysis confirm a three compartment model for the drug in the mongrel dog.

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INTRODUCTION

Papverine has been used as a peripheral vasodilator for many years. It is a benzylisoquinoline compound, present to the extent of about 1% in crude opium, but differing from the morphine group of alkaloids both chemically and pharmacologically and contributing very little to the overall pharmacology of opium. Papaverine is neither a narcotic nor is it addictive.

Papaverine is available for oral administration and for injection. The average dose is 100 to 150 mg two or three times daily. The low therapeutic blood levels obtained after administration of high oral doses of this drug to human volunteers[1, 2] suggests that the drug either distributes to tissues extensively or may be absorbed too slowly or incompletly.

Polyphosphates have been known to interact with various cationic drugs to form complexes[3, 4]. In 1957, Kaplan[5] prepared a tetracycline hexametaphosphate complex and reported later that the tetracycline-hexametaphosphate complex was absorbed faster and gave higher blood levels than compared to tetracycline[6]. The complex was found to be stable and non-toxic. These observations were later confirmed separately by Pulaski[7] and Welch[8].

This investigation was undertaken to determine if such complex formations could enhance the bioavailability of papaverine. Some of the pharmacokinetic aspects of papaverine in the dog were also studied.

EXPERIMENTAL

Preparation of Papavereine Metaphosphates

Papaverine metaphosphates were prepared by an acid-base interaction[9]. Papaverine hydrochloride was dissolved in distilled water. An aqueous solution of sodium hexmaetaphosphate or potassium polymetaphosphate was slowly added to the drug solution while stirring. The mixture was then stirred in a covered, light-protected beaker for 12 hours. The precipitate was retained in a Buchner funnel, washed with water, acetone, and dried *in vacuo* for 24 hours. at 40°C. The dried residue was comminuted in a mortar and passed through a 80/100 mesh sieve.

Animals

Four healthy male mongrel dogs ranging from 17.5 to 27.0 kg in weight were housed in stainless steel cages under controlled temperature, food ingestion and lighting.

Protocol

The dogs were fasted a minimum of 24 hours before and 18 hours after administration of the drug, with water allowed at all times. Each dog was given papaverine hydrochloride (PHCl), papaverine hexametaphosphate (PHMP) or papaverine polymetaphosphates (PPMP) equivalent to 10 mg of papaverine base per kg body weight in accordance with the following randomized block design.

Dog		Week		
Name	Weight (kg)	1	2	3
A	27.0	PHCl	PHMP	PPMP
B	22.0	PHMP	PPMP	PHCl
C	17.4	PPMP	PHCl	PHMP
D	27.0	PHCl	PHMP	PPMP

The experiments were repeated three more times using the above schedule in which the last dose was 5 mg/kg body weight. A period of at least one week was allowed between doses. The drug (80/100 mesh, 163 microns) was administered orally in loosely packed gelatin capsules.

Blood samples were taken by venipuncture of the jugular vein and collected in 7 ml vacutainers (Benton-Dickinson, EDTA). A sample was obtained just prior to dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours thereafter.

Intravenous doses equivalent to 10 mg of papaverine base per kg body weight were also given to all dogs. The drug was administered by intravenous injection into the leg vein over a period of two to three minutes. Blood samples were taken at 0, 5, 10, 15, 20, 25, 30, 40, 60, 90, 120, 180, 240, 300 and 480 minutes after administration.

RESULTS AND DISCUSSION

Figure 1 shows a typical plasma levels-time profile after oral administration of papaverine formulations to individual dogs. Marked intersubject variation was observed in the profiles; however, intrasubject variation was much less (see Tables 1-3). Dog A showed the highest blood concentrations (C_{max}) and Dog C the lowest. The extent of absorption of oral formulations in comparison to intravenous administration of the drug and the relative extent of absorption of metaphosphates in comparison to the hydrochloride salts were calculated using equations 1 and 2.

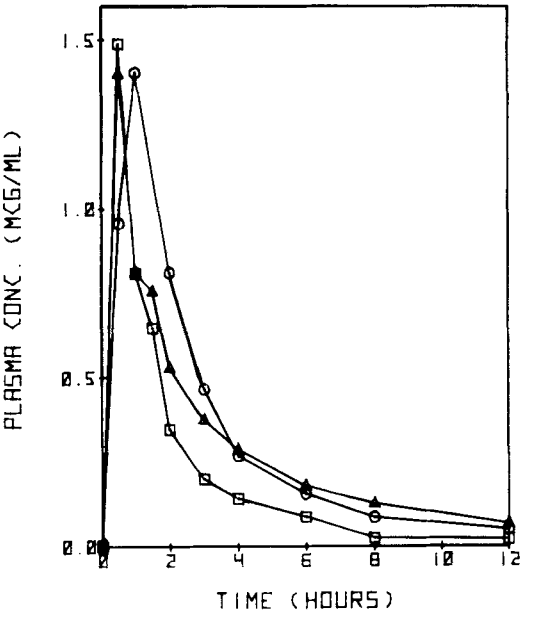


Figure 1. A plasma concentration versus time plot following the oral administration of 10 mg/kg of papaverine to Dog A as: □ PHCL, △ PHMP and ○ PPMP.

$$\text{Absolute Bioavailability} = \frac{\text{Area}_{\text{p.o.}}}{\text{Area}_{\text{i.v.}}} \quad (1)$$

$$\text{Relative Bioavailability} = \frac{\text{Area}_{\text{p.o.}}\ \text{(Test Formulation)}}{\text{Area}_{\text{p.o.}}\ \text{(Standard Formulation)}} \quad (2)$$

These areas (0-infinity) are listed in Table 2. The average values of absolute and relative bioavailabilities of orally administered PHMP and PPMP were greater compared to the PHCl formulation in all dogs except Dog D where the average for PHMP was lower than PHCl.

The bioavailability parameters derived from plasma levels following oral doses are summarized in Table 2. It can be seen

TABLE 1

Absolute and Relative Bioavailabilities Following Oral Administration of Papavereine Salts to Dogs

Dog	HCL	HMP	PMP
Absolute Bioavailability			
A	55.65% (14.5)	62.60% (14.4)	65.36% (9.2)
B	29.56% (3.9)	30.75% (2.4)	33.44% (5.0)
C	25.74% (0.9)	28.79% (1.0)	34.57% (7.0)
D	57.04% (12.4)	54.84% (14.9)	77.73% (17.4)
Relative Bioavailability			
A	100%	112.5% (13.4)	117.4% (26.3)
B	100%	104.0% (26.8)	101.0% (33.7)
C	100%	110.0% (3.5)	134.7% (23.3)
D	100%	96.1% (19.0)	136.3% (2.0)

from the data that higher area values were observed for PPMP compared to PHMP. These values were statistically significant at a level of $p < .1$. The maximum concentration (C_{max}) showed no difference for the oral preparations. The mean observed time of peak concentration (t_p) showed an increased trend in the order of PHCl (1.27 hours), PHMP (1.30 hours) and PMP (1.65 hours) but was not statistically significant. Since t_p is a function of elimination and distribution as well as absorption, it was decided to compare the apparent absorption rate constant (k_a) which is independent of these factors.

TABLE 2

Average Bioavailability Parameters Obtained Following Oral Administration of Papavereine Salts to Dogs

Dog	HCl	HMP	PMP
Parameter: Area			
A	4.095 (1.07)	4.606 (1.06)	4.809 (0.68)
B	2.306 (0.31)	2.399 (0.19)	2.609 (0.39)
C	1.470 (0.05)	1.644 (0.06)	1.974 (0.40)
D	2.257 (0.49)	2.170 (0.59)	3.076 (0.69)
Parameters: C_{max}			
A	1.246 (0.291)	1.450 (0.071)	1.375 (0.141)
B	0.956 (0.215)	0.640 (0.075)	0.780 (0.322)
C	0.485 (0.052)	0.635 (0.158)	0.675 (0.380)
D	0.822 (0.648)	1.016 (0.671)	0.866 (0.163)
Parameter: t_p			
A	0.900 (0.652)	1.000 (0.500)	1.125 (0.630)
B	1.000 (0.000)	1.375 (0.479)	1.800 (0.837)
C	1.250 (0.289)	1.625 (0.479)	1.300 (0.274)
D	1.833 (1.041)	1.667 (0.289)	2.167 (0.764)
Parameter: ka			
A	0.661 (0.079)	0.692 (0.199)	1.130 (0.011)
B	1.172 (0.238)	0.821 (0.069)	0.850 (0.161)
C	0.944 (0.177)	1.070 (0.623)	2.500 (1.330)
D	1.081 (0.274)	0.996 (0.561)	0.754 (0.244)

Note: The number in paranthesis represent 1 standard deviation.

To obtain the apparent absorption rate constants, it was necessary to calculate the values of the fraction of drug remaining to be absorbed with time. Values of k_a can be obtained by plotting the percent of drug unabsorbed versus time on a semilog seale. The

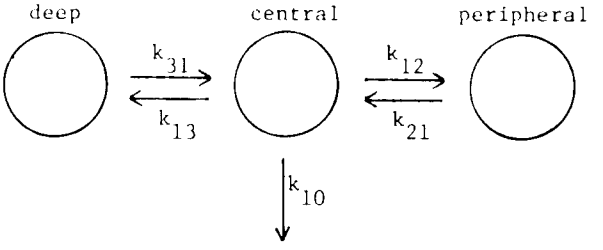
TABLE 3

Pharmacokinetic Parameters Following I.V. Administration of Papavereine to Dogs

Parameter	Dog A	Dog B	Dog C	Dog D
Dose, mg.	270.00	220.00	174.00	230.00
Animal wt. (kg)	27.00	22.00	17.40	23.00
A, mcg/ml	4.89	4.56	2.46	2.82
B, mcg/ml	1.14	1.60	0.73	0.12
P, mcg/ml	2.64	5.57	5.78	-
α (1/hr.)	1.49	1.42	1.12	1.45
β (1/hr.)	0.26	0.32	0.25	0.24
π (1/hr.)	10.95	7.73	4.56	-
$t_{\frac{1}{2}}$ (hrs.)	2.64	2.15	2.75	2.88
k_{12}	1.81	2.28	1.27	0.44
k_{21}	6.19	4.64	2.26	0.29
k_{13}	0.68	0.65	0.59	-
k_{31}	0.52	0.58	0.40	-
k_{10}	1.05	1.32	1.40	1.21
Vc, liters	31.34	18.75	19.34	78.31
C_o, mcg/ml	8.66	11.73	8.97	2.94

percent of drug unabsorbed was calculated using the mass balance equations for a three compartment model[10]. The equations were used without the Taylor series approximation. The absorption rate constant obtained by such a method can be overestimated when lag

times, incomplete absorption, g-i drug degradation or simulatenous zero order absorptions[11, 12] are occurring; nevertheless, these values are useful for bioavailability comparisons. The mass balance equations employ the first order rate constants for the transfer of a drug from one compartment to another. These constants were calculated in accordance with Scheme I by the pharmacokinetic analysis of the intravenous data.



Scheme I: Distribution of a Drug in a Three Compartment Open System.

PHARMACOKINETICS

Intravenous administration:

Semilogarithmic plots of the experimental plasma concentrations obtained following intravenous administrations and the corresponding computer-simulated curves are shown in Figures 2-3. Computer curve fitting[13] resolved the plasma concentration-time curve into three exponential terms for Dogs A-C.

$$C_p = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t} \quad (3)$$

where

$$P = \frac{(k_{31} - \pi)(k_{21} - \pi)D}{(\alpha - \pi)(\beta - \pi)V_c} \quad (4)$$

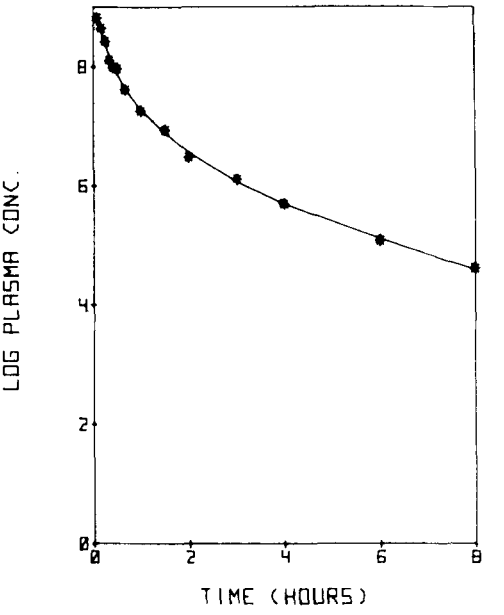


Figure 2. A semilogarithmic plot of plasma concentration versus time following the I.V. administration of 10 mg/kg of papaverine (as the hydrochloride) to Dog C.

Key: The solid line is the theoretically generated curve in accordance with a three compartment model for a bolus I.V. injection. The (*) are experimentally observed data.

$$A = \frac{(k_{31} - \alpha)(k_{21} - \alpha)D}{(\pi - \alpha)(\beta - \alpha)V_c} \quad (5)$$

$$B = \frac{(k_{31} - \beta)(k_{21} - \beta)D}{(\pi - \beta)(\alpha - \beta)V_c} \quad (6)$$

D represents dose administered, V_c represents the volume of the actual compartment, β represents the terminal log linear phase and $\pi > \alpha > \beta$. The k_{ij}'s are defined in Scheme I.

Figure 3 shows a biphasic curve for Dog D which followed a two

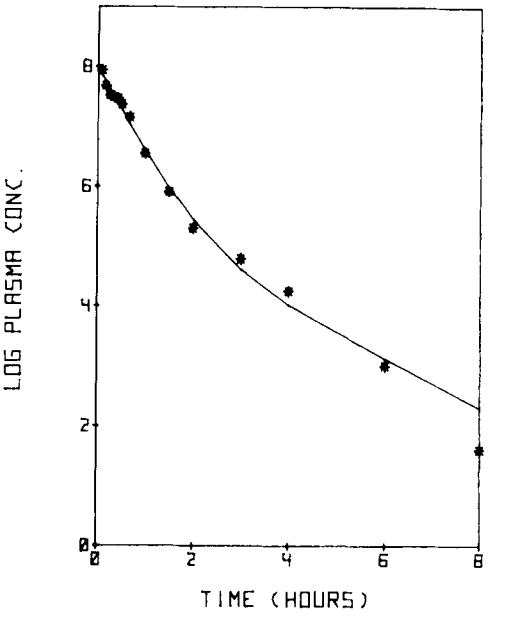


Figure 3. A semilogarithmic plot of plasma concentration versus time following the intravenous administration of 10 mg/kg dose of papaverine to Dog D.

Key: The solid line represents a computer fitting of a two compartment model for bolus injection (weighted data). The (*) are experimentally observed data.

compartment model and was therefore described by a two exponential equation.

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \quad (7)$$

where

$$A = \frac{(a - k_{21})D}{(\alpha - \beta)V_c} \quad (8)$$

and

$$B = \frac{(k_{21} - \beta)D}{(\alpha - \beta)V_c} \quad (9)$$

For this particular dog a good biexponential fit for 5 and 10 mg/kg could be obtained only by weighting each plasma concentration by its reciprocal. The eight hour plasma concentration in Figure 3 represents the lower limit of assay sensitivity; however, removal of the point did not alter the fact that a better fit could be obtained with a weighted biexponential equation.

The parameters of the general equations for the plasma level as a function of time were initially estimated by the computer program CSTRIP[14] and later refined by a non-linear regression computer program BMDP3R[13]. These parameters showed no significant dose dependency for doses of 5 and 10 mg/kg given to Dogs A-D. The pharmacokinetic constants are listed in Table 3.

Single Oral Doses

Following oral administration a semi-logarithmic plot of plasma concentration against time can be represented by Scheme I but including an oral absorption step. Theoretically, the oral curve can be represented by a four exponential equation.

$$C_p = A_1 e^{-kat} + A_2 e^{-\pi t} + A_3 e^{-\alpha t} + A_4 e^{-\beta t} \quad (10)$$

where

$$A_1 = \frac{k_a FD}{V_e} \cdot \frac{(k_{21} - \alpha)(k_{31} - \alpha)}{(\beta - \alpha)(\pi - \alpha)(k_a - \alpha)} \quad (11)$$

$$A_2 = \frac{k_a FD}{V_c} \cdot \frac{(k_{21} - \beta)(k_{31} - \beta)}{(\alpha - \beta)(\pi - \beta)(k_a - \beta)} \quad (12)$$

$$A_3 = \frac{k_a FD}{V_c} \cdot \frac{(k_{21} - \pi)(k_{31} - \pi)}{(\alpha - \pi)(\beta - \pi)(k_a - \pi)} \quad (13)$$

$$A_4 = \frac{k_a FD}{V_c} \cdot \frac{(k_{21} - k_a)(k_{31} - k_a)}{(\alpha - k_a)(\beta - k_a)(\pi - k_a)} \quad (14)$$

and F represents the fraction of the administered dose absorbed; other terms are as previously described.

The apparent absorption rate constant for each oral dose was calculated from percent unabsorbed versus time plots (Figure 4). The transfer rate constants, other than absorption, were obtained from the intravenous data and the values substituted into equation 10 along with k_a to obtain theoretical values of plasma concentration versus time. From the log percent unabsorbed versus time plots, it was observed that a significant lag time was present before absorption occured (0.52 ± 2.8 hrs, N = 48). The lag time was calculated from the slope intercept of the line of best fit according to equation 15.

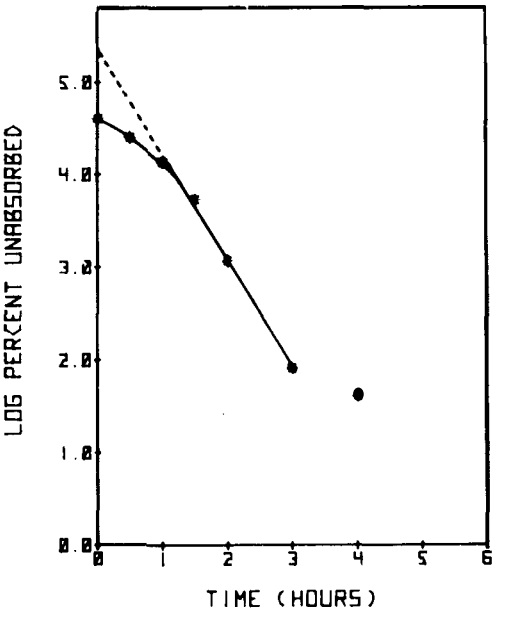


Figure 4. Semilogarithmic plot of percent of drug unabsorbed versus time following the oral administration of 10 mg/kg of papaverine polymetaphosphate to Dog A.

$$\text{Lag time } (t_1) = \frac{(\log \text{intercept} - \log 100)}{\text{apparent } k_a} \quad (15)$$

Allowing for the lag time equation 15 becomes

$$C_p = A_1 e^{-k_a(t-t_1)} + A_2 e^{-\pi(t-t_1)} + A_3 e^{-\alpha(t-t_1)} + A_4 e^{-\beta(t-t_1)} \quad (16)$$

Using the lag times and k_a values obtained from the percent unabsorbed time plots along with the pharmacokinetic parameters calculated from the i.v. data, the theoretical values of plasma concentrations versus time for the oral doses were calculated using equation 16 and plotted. Figure 5 shows such a plot on a semilogarithmic

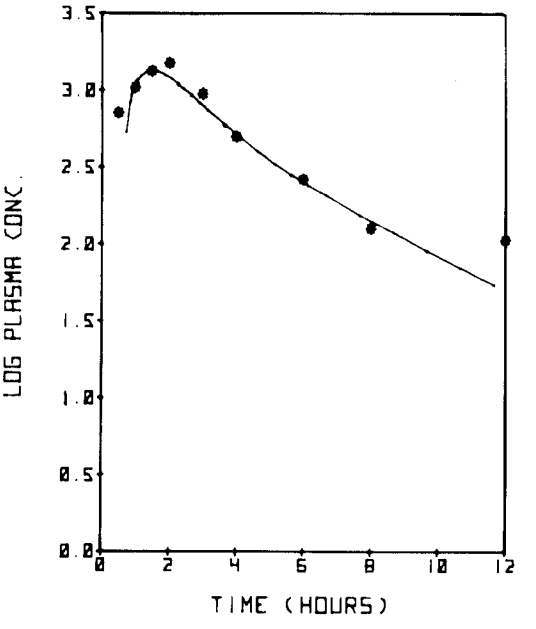


Figure 5. A semilogarithmic plot of plasma concentration versus time following the oral administration of 10 mg/kg of papaverine polymetaphosphate to Dog A.

Key: The solid line is the theoretically generated curve in accordance with a three compartment model including an oral absorption step. The (*) are experimentally observed data.

scale. A reasonably good fit was obtained between the theoretically generated curve (solid line) and the experimentally observed data points lending credence to the three compartment model proposed for the dog in Scheme I.

CONCLUSION

The comparative bioavailability of papaverine hydrochloride, papaverine hexametaphosphate and papaverine polymetaphophate was studied. It was observed that there was a considerable degree of intersubject variation but much less intrasubject variation in papaverine bioavailability for the three formulations. The peak plasma concentration ranged from 1.499 to 0.485 mcg/ml and the half-lives from 1.155 to 3.26 hours. Overall PHMP showed an 8.0% increase and PPMP a 26% increase in area under the curve compared to PHCl. The two factor analysis of variance data are shown in Table 4. The results show a statistically significant difference in area under the curve of metaphosphates at a p level of < 0.1. Since the number of subjects were limited, further studies in larger populations are necessary in order to detect statistical significance at a lower p value.

The pharmacokinetic analysis suggests a three compartment model for papaverine in the mongrel dog. The model was confirmed by comparing the experimentally observed plasma levels for single oral dose data to the theoretically generated curve using transfer rate constants obtained from the i.v. data. A lag time was needed to describe the oral data. The intravenous data showed a closer fit between the predicted and experimentally observed curve than the fit obtained to the oral data.

TABLE 4

Analysis of Variance Data

Source	Degrees of Freedom	Sum of Squares	F Ratio[1]
Dependent Variable (AUC)			
Formulation	2	0.8769	
Dog	3	31.8760	4.250
Formulation*Dog	6	0.617	
Dependent Variable (C_{max})			
Formulation	2	0.009	
Dog	3	2.255	0.208
Formulation*Dog	6	0.130	
Dependent Variable (t_p)			
Formulation	2	0.929	
Dog	3	3.696	1.492
Formulation*Dog	6	1.867	
Dependent Variable (ka)			
Formulation	2	0.933	
Dog	3	0.693	1.773
Formulation*Dog	6	1.040	
Dependent Variable ($t_{\frac{1}{2}}$)			
Formulation	2	0.513	
Dog	3	0.486	1.12
Formulation*Dog	6	0.726	

1. The F Ratio is obtained by: $\frac{\text{S.S. Formulation/df}}{\text{S.S. (Formulation*Dog)/df}}$

For statistical significance, the F Ratio should be higher than:

3.46 at an α level of 0.10
5.14 at an α level of 0.05

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