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The effect of pH and concentration on α-methyldopa absorption in man

A. E. MERFELD*, A. R. MLODOZENIEC, M. A. CORTESE, J. B. RHODES†, J. B. DRESSMAN‡ AND G. L. ADMIDON‡

INTERx, Merck Sharp & Dohme Research Laboratories, 2201 West 21st Street, Lawrence, KS 66046, †Division of Gastroenterology, Kansas University School of Medicine, Kansas City, KS 66103 and ‡College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109-1065, USA

An open crossover study of the absorption of α-methyldopa has been conducted in normal healthy adult male volunteers in whom a triple lumen perfusion tube had been placed. Three volunteers were perfused on separate occasions with 0·1 mM α-methyldopa at pH 4·5, 6·0 and 7·4. Three other volunteers were perfused on separate occasions with 0·1, 1·0 and 10 mM α-methyldopa at pH 6·0. Two additional subjects were perfused with 0·1 mM α-methyldopa at pH 6·0. Absorption was not a linear function of concentration above 1 mM α-methyldopa. There was also a weak trend toward greater absorption near pH 6·0. At higher concentrations of drug in the perfusion solution (10 vs 1 mM), the free fraction of α-methyldopa in plasma samples was increased significantly. Thus, although absorption of α-methyldopa is more efficient at lower concentrations, bioavailability may not be substantially enhanced due to increased sulphation in the gut wall. Comparison of permeabilities with previous results from our laboratories suggests the rat is a good model for predicting the behaviour of α-methyldopa after its oral administration to man.

Although α-methyldopa is widely used in the treatment of hypertension, it is incompletely absorbed from the gastrointestinal tract. The fraction of the dose available to the systemic circulation as free α-methyldopa averages 25% after an oral solution (Kwan et al 1976) and 27% when given as tablets (Dobrinska et al 1982). Oral bioavailability in man also varies greatly. Kwan et al (1976) found the oral absorption ranged from 8 to 62% of the dose, while Stenbaek et al (1982) found that the percentage absorbed varied by a factor of at least 3. Furthermore, in a replicate dose study, the intra-subject variability was nearly as high as inter-subject variability in bioavailability (Schrogie et al 1979). Although the incomplete bioavailability of α-methyldopa can be attributed to poor absorption and to first-pass metabolism in the gut wall (Stenbaek et al 1977; Saavedra et al 1975), the underlying causes for its limited bioavailability have not been fully established.

The purpose of the present study was to test the hypothesis that the oral absorption of α-methyldopa is pH- and/or concentration-dependent. If this hypothesis is correct, manipulation of the pH microenvironment and/or release rate of the drug from the dosage form would provide a strategy for improving α-methyldopa bioavailability. α-Methyldopa is structurally similar to the neutral amino acids which are absorbed from the intestine by concentration-dependent saturable mechanisms (Munck 1981). There is also evidence that the transport of certain amino acids and dipeptides is pH-dependent (Adibi et al 1972; Fogel & Adibi 1972; Burston et al 1982). Furthermore, previous studies in our laboratories (Amidon et al 1986) found that the intestinal absorption of α-methyldopa from perfused segments of rat intestine depended on both pH and concentration but was not a function of the intestinal region. An open crossover study in which a triple lumen perfusion tube was used was done to determine whether these trends occur in man. Normal adult male volunteers were perfused with buffered solutions of α-methyldopa at three pH values and three concentrations.

* Correspondence.

MATERIALS AND METHODS

Materials

α-Methyldopa sesquihydrate and α-methyldopa were supplied by Merck Sharp & Dohme. [1,2-^{14}C]-Polyethylene glycol ([^{14}C]PEG 4000) was purchased from New England Nuclear. Ascorbic acid (Mallinckrodt), sodium phosphate monobasic (City Chemical), sodium phosphate dibasic anhydrous (Fisher), polyethylene glycol (PEG 4000) (Fisher), citric acid (Humco Lab), sodium citrate (Mallinckrodt) and phenol red (Fisher) were supplied by the Department of Pharmacy, the University of Kansas Medical Center College of Health Sciences and Hospital. All materials used were USP grade.

Experimental procedure

Normal adult male volunteers, aged 25 to 48 years, were perfused with buffered solutions of α-methyldopa. Two clear polyvinyl tubes (2·5 mm o.d.) and one radiopaque tube (2·5 mm o.d.) were used to construct a triple lumen perfusion tube (Fordtran et al 1962; Cooper et al 1966). A latex bag containing 1 ml of mercury was attached to the distal end of the tube to facilitate rapid tube placement. The drug solution was infused through infusion port A (stainless steel, cylindrically shaped, 9 × 4 mm, 6-1 mm drilled holes) spliced into one of the tubes (Fig. 1). Similar devices (ports B and C) were inserted into the other tubes to aspirate fluid 15 cm (12 × 4 mm, 13-1 mm holes) and 45 cm (17 × 6 mm, 25-1 mm holes) distal to the infusion port. Therefore, the length of the mixing segment (the segment between port A and port B) was 15 cm and the length of the test segment (the segment between port B and port C) was 30 cm.

The subjects were intubated on the evening before the perfusion period and fasted until the tube was removed. The tube was positioned in the upper jejunum with the infusion port beyond the ligament of Treitz. Tube placement was determined before and after perfusion by image intensification fluoroscopy.

The drug solution was delivered at a rate of 7 ml min^{-1} by a Harvard infusion pump to each subject for 60–90 min. Steady state infusion conditions (Soergel 1971) and adequate volume collections from sampling port C (Fig. 1) were obtained.

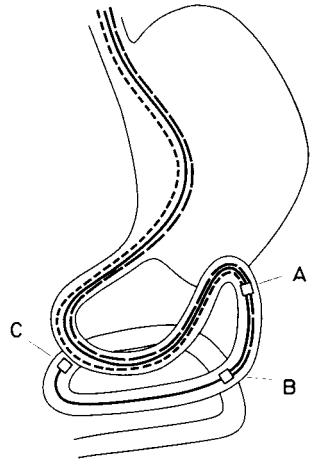

FIG. 1. Diagram of triple lumen perfusion tube. - - - - Constant infusion port A, — — — — Aspiration port B, ——— Aspiration port C.

Perfusate was collected over 10 min intervals. A 5 ml sample was collected from aspiration port B (the tube was flushed with air every 2–3 min to ensure a representative sample due to the 4 ml dead space of the tube). As much fluid as possible was collected from aspiration port C by gentle syringe suction. The pH and volume of each perfusate sample was measured, then the sample was acidified immediately with 1 M HCl, divided, and duplicates stored at −80 °C until analysed.

Venous blood samples were withdrawn from the median vein of the left forearm via an indwelling catheter with a heparin lock into heparinized vacutainers at 0, 0·5, 1, 2, 3 and 4 h. The blood was allowed to stand for 10 min at room temperature (20 °C), was centrifuged (3500 rev min^{-1}, 10 min) and the plasma separated. Duplicate plasma samples were stored at −80 °C until analysed. Pulse and blood pressure measurements were taken at 0, 1, 4, 8 and 12 h.

The perfusion method (Fordtran et al 1962; Cooper et al 1966) was employed to allow precise pH control, to ensure a specific region of the intestine was studied and to maintain a regular flow pattern independent of gastric emptying. Furthermore, this method permitted transport rates to be determined at low α-methyldopa concentrations where the amount absorbed results in plasma levels below detectable limits. The study protocol was approved by the Human Subjects Committee of the University of Kansas Medical Center College of Health Sciences and Hospital and informed consent obtained from each subject.

Solutions

Buffered, iso-osmotic solutions of α-methyldopa were prepared at several pH values and concentrations. A 0·067 M phosphate buffer was used at pH 6 and a 0·134 M phosphate buffer at pH 7·4. Citric acid (2·2%) and sodium citrate (3%) were used to prepare a pH 4·5 buffer. Osmolality was adjusted to 295–300 mmol kg^{-1} with sodium chloride. [^{14}C]PEG 4000 (10 μCi $litre^{-1}$) was included as a non-absorbable volume marker with 0·01% PEG 4000 which prevented labelled marker from binding to the perfusion tubing. To retard oxidation of α-methyldopa the following measures were taken: (i) solutions were made up immediately before use, (ii) ascorbic acid (0·02%) was included in all perfusion solutions, (iii) nitrogen was bubbled through the solutions for 10 min before use, at a rate of 50 ml min^{-1} and (iv) the drug solution and pump syringes were covered with aluminum foil to exclude

light. Control samples of the drug reservoir solution were taken before and after the perfusion period. No degradation of α-methyldopa was detected.

Study design

Three volunteers were perfused on separate occasions with 0·1 mM α-methyldopa at pH 4·5, 6·0 and 7·4. Three other volunteers were perfused on separate occasions with 0·1, 1·0 and 10 mM α-methyldopa at pH 6·0. Two additional subjects were perfused with 0·1 mM α-methyldopa at pH 6·0. Perfusion periods for each subject were at least six days apart. The amount of α-methyldopa perfused ranged from 10 to 1200 mg. The usual daily dosage of α-methyldopa to effect blood pressure control varies between individuals and ranges from 500 mg to 2·0 g (Physicians' Desk Reference 1986).

α-Methyldopa stability in human perfusate

The test procedure was validated before the drug study began. Subject 1 was intubated with the triple lumen tube as described and perfused at a rate of 7 ml min^{-1} with the pH 6 buffer containing ascorbic acid and PEG 4000. Approximately 250 ml of perfusate (pH 6·6) was collected from both sampling ports and frozen at −80 °C. The pH of the perfusate was adjusted to 7·4 with concentrated sodium hydroxide since degradation would be fastest at the highest pH and samples were spiked with 0·1 mM α-methyldopa. The samples were covered to exclude light and incubated at 37 °C for 90 min. No degradation of α-methyldopa in the luminal perfusate was detected.

Transit time study

The transit time within the 30 cm test segment was determined by injecting a 1 ml saturated phenol red solution into aspiration port B (Fig. 1), while the subject was being infused with a buffered solution from port A at 7 ml min^{-1}, thus mimicking the flow conditions within the drug study period. Fluid was collected from aspiration port C over 5 min intervals. The volume of each perfusate sample was measured and duplicates were stored at −80 °C until analysed. Phenol red concentration was determined by diluting the samples with 1 M sodium hydroxide and measuring the absorbance at 558 nm. Five of the volunteers participated in this study which was done immediately after the α-methyldopa perfusion.

Ten minutes after the phenol red bolus was given at port B, 66 ± 18% (mean ± s.d.) of the dye was recovered at port C. After 15 min, 90 ± 7% (mean ± s.d.) of the dye was recovered. Whalen et al (1966) reported a mean transit time of 13·6 min for a 30 cm segment. Thus, when loss of α-methyldopa from the test segment was determined, comparisons were staggered such that a distal perfusate sample was compared with a proximal perfusate sample of the previous 10 min. Staggered collections give more reliable results since changes in intestinal motility and fluctuations in fluid secretion can be more closely monitored as the solution passes each collection port (Whalen et al 1966; Soergel 1971).

Analysis

A previously published (Saari et al 1984) HPLC assay was used with modifications. The basic system utilized a mobile phase of acetonitrile (5% v/w) in aqueous phosphoric acid (0·1%), and a Brownlee column, RP-18 Spheri-5 (4·6 × 100 mm). Mobile phase flow rate was 1·0 ml min^{-1}. An ESA 5100 A Coulochem detector was set at an oxidation potential of 0·10 V. The Wisp Model 710B was used for automatic sample injection. Data acquisition and peak integration were accomplished by the Waters Data Module, Model 710B. α-Ethyldopa was incorporated into the samples as an internal standard. Standard solutions of α-methyldopa in human perfusate (collected from subject 1) were run in parallel with the samples. Results were linear over the range of interest.

Plasma samples were assayed for both free and acid-labile conjugated α-methyldopa. Conjugates of α-methyldopa were hydrolysed in concentrated HCl and $HClO_4$ at 99 °C for 15 min (Saari et al 1984). Plasma reference standards were also run and found to be linear. The limit of detection of α-methyldopa in plasma was 25 ng ml^{-1}.

The concentration of [^{14}C]PEG 4000 in the perfusate samples was determined by liquid scintillation counting. A 500 μl sample of perfusate was mixed with 10 ml Scinti-Vers I scintillation cocktail (Fisher) and counted in a liquid scintillation spectrometer (Beckman LS 6800). There were no corrections necessary for bile quenching due to the dilution.

Calculations

The amount of α-methyldopa 'lost' from the perfusate was assumed to have been absorbed and this was expressed as a percentage of that entering the 30 cm test segment. Comparisons were staggered by 10 min as previously discussed. The first 20 to 60 min of each perfusion were allowed for equilibration, with 30 min being adequate in most cases. The amount of drug absorbed was then based on the average of the subsequent 10 min collection periods

which appeared to be at steady state. A minimum of three collection periods was used in each case. Any changes in fluid volume were determined by changes in the [^{14}C]PEG 4000 concentration. Thus for a given 10 min collection period:

$$\% \text{ absorbed} = \left[1 - \frac{[\alpha MD]_C}{[\alpha MD]_B} \cdot \frac{[[^{14}C]PEG\ 4000]_B}{[[^{14}C]PEG\ 4000]_C}\right] \times 100\%$$

where $[\alpha MD]_{B,C}$ = α-methyldopa concentration at aspiration ports B and C (Fig. 1), respectively, and $[[^{14}C]PEG\ 4000]_{B,C}$ = [^{14}C]PEG 4000 concentration at aspiration ports B and C, respectively.

The effective dimensionless permeability for α-methyldopa was calculated for each pH/concentration condition using the method of Elliott et al (1980) which normalizes the results with respect to the perfusion hydrodynamics as well as the segment length used. The calculated permeability can then be directly compared with results obtained for other drugs under different experimental conditions.

To summarize:

$$P^*_{eff} = \frac{\ln [(C_m/C_0)]_{exp}}{-4G_z} = P_{eff} \cdot \frac{R}{D}$$

where:

$$\frac{C_m}{C_o} = \frac{[\alpha MD]_C}{[\alpha MD]_B} \cdot \frac{[[^{14}C]PEG\ 4000]_B}{[[^{14}C]PEG\ 4000]_C}$$

$G_z = \pi DL/2Q$, D = solute diffusivity in the perfusing fluid, L = length of perfused segment of intestine, Q = volumetric flow rate of perfusate = $\pi R^2\langle v\rangle$, R = radius of perfused intestine, $\langle v\rangle$ = mean flow velocity, P^*_{eff} = dimensionless effective permeability, P_{eff} = effective permeability (cm s^{-1}).

RESULTS

[^{14}C]PEG 4000 recovery

As much perfusate as possible was recovered from sampling port C (Fig. 1) since any drug not collected could be absorbed further down the gastrointestinal tract where the pH and flow rate could not be monitored or controlled. A mean of 43 ± 12% (s.d.; range 21 to 62%) of the total amount of [^{14}C]PEG 4000 perfused was recovered from sampling ports B and C. Recovery of [^{14}C]PEG 4000 was much less than the phenol red recovery in the transit time study. The transit time studies were done at the end of the drug perfusion period when steady state conditions were operating. The recovery of [^{14}C]PEG 4000 included the initial part of the perfusion before flow conditions were equilibrated and when test solution reflux was probably significant (Gustke et al 1970). Thus, the measured blood concentrations are a composite of α-methyldopa absorbed from the test and mixing segment plus drug absorbed from the unrecovered solution.

Water flux

The fluid volume within the lumen increased substantially during the perfusion period as evidenced by a dilution in the concentration of [^{14}C]PEG 4000 in the perfusate samples. This dilution was a result of gastric juices, bile, pancreatic juices and water secreted from the jejunum. The perfusate samples were yellow indicating the presence of bile. In addition, the mean osmolality of perfusate samples collected from port C (Fig. 1) was 282 mmol kg^{-1} while that of the infused solution was 300 mmol kg^{-1}. The fluid volume increased by 24 ± 8% (mean ± s.d.) within the 15 cm mixing segment during the 20 perfusions conducted. The percentage change in fluid volume within the 30-cm test segment was 11·1 ± 5·5% (mean ± s.d.). However, in 5 of the 20 perfusions there was net absorption of fluid within the latter segment. The initial α-methyldopa concentration in the perfusion solution did not affect the volume of fluid secreted in either segment. Furthermore, there was no correlation between the fluid movement and the amount of drug absorbed.

Loss of α-methyldopa from perfusate

The percentage of α-methyldopa absorbed from the 30 cm test segment as a function of concentration at pH 6·0 is shown in Table 1. The percentage absorption tended to decrease as the α-methyldopa concentration in the perfusion solution increased. Fig. 2 shows the mean effective permeability at pH 6·0 plotted against α-methyldopa concentration. The calculated permeability is constant if absorption is a linear function of concentration. A decreasing permeability suggests a saturable transport mechanism is involved. A paired *t*-test was used to compare the

Table 1. The effect of concentration on α-methyldopa absorption at pH 6.

Concn (mM)	Percentage absorbed in a 30-cm test segment Subject 2	3	6
0·1	5·9	12·0	2·6
1·0	4·1	6·0	5·9
10·0	1·8	3·3	0·9

Table 2. Results of statistical analysis of the effect of pH and α-methyldopa concentration on the effective permeability in human intestinal perfusions.

pH	Concn (mM)	t (paired or unpaired)	t	Significance	Degrees of freedom
6·0	0·1 vs 1·0	paired	0·580	$0{\cdot}35 > P > 0{\cdot}30$	2
6·0	0·1 vs 10	paired	2.27	$0{\cdot}10 > P > 0{\cdot}05$	2
6·0	1·0 vs 10	paired	3·99	$0{\cdot}05 > P > 0{\cdot}025$*	2
4·5 vs 6·0	0·1	unpaired	0·901	$0{\cdot}25 > P > 0{\cdot}20$	6
6·0 vs 7·4	0·1	unpaired	1·35	$0{\cdot}15 > P > 0{\cdot}10$	6
4·5 vs 7·4	0·1	paired	1·55	$0{\cdot}15 > P > 0{\cdot}10$	2

* Significant at a 5% level.

data (see Table 2). The effective permeabilities were statistically different between the 1·0 and 10 mM data. However, the means from the 0·1 and 10 mM data did not demonstrate any differences.

Table 3 shows the percentage of α-methyldopa absorbed from the test segment as a function of pH at 0·1 mM α-methyldopa. Although there was scatter within each pH group, the percentage of drug absorbed was greater at pH 6 and pH 4·5 for two of the three subjects. The data for subject 7 at pH 6·0 was omitted from the permeability calculations because a negative percentage absorbed suggested steady state conditions were not achieved. Thus, a one-tailed t-test was used to compare the pH data using the other five subjects at the 0·1 mM α-methyldopa pH 6 conditions. Fig. 3 shows the effect of pH on the effective permeability at 0·1 mM α-methyldopa. The mean effective permeability was highest near pH 6.0. Although there were weak trends toward differences between the pH groups, variability in the pH 6·0 data precluded the demonstration of any statistically significant differences (Table 2). In spite of the use of high capacity buffers while still retaining isotonicity, the pH of the collected samples tended to move toward pH 6·0 regardless of the initial pH of the perfusion solution. The mean pH of samples from distal collection port C (Fig. 1) and the ranges were 5·3 (5·2–5·3), 6·0 (5·7–6·7) and 6·9 (6·8–7·0) for the pH 4·5, 6·0 and 7·4 perfusion solutions, respectively.

Table 3. The effect of pH on α-methyldopa absorption at 0·1 mM.

	Percentage absorbed in a 30-cm test segment Subject							
pH	1	2	3	4	5	6	7	8
4·5	—	—	—	—	3·2	—	1·0	5·1
6·0	3·0	5·9	12·0	3·3	2·8	2·6	−2·2	4·9
7·4	—	—	—	—	2·0	—	1·2	3·1

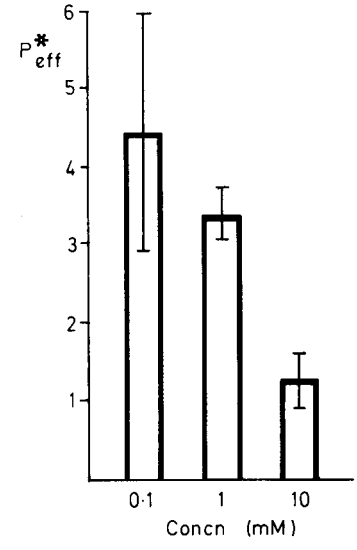

FIG. 2. Effect of α-methyldopa concentration on effective permeability at pH 6·0 in human intestinal perfusions. Bars represent mean value ± s.e.m. (n = 3).

Plasma levels of α-methyldopa

α-Methyldopa was not detected in the plasma in any of the subjects when the 0·1 mM α-methyldopa solution was perfused, regardless of the pH of the solution used. Plasma concentrations of free and total α-methyldopa for the 1 and 10 mM perfusion solutions are shown in Table 4. The peak plasma value of α-methyldopa always occurred at 2 h even though the perfusions were stopped after 60 or 90 min. This is not surprising since the unrecovered α-methyldopa solution could still be absorbed after the infusion stops. A comparison of the concentrations of total α-methyldopa at 1 h gives an indication of the relative absorption of the 2 doses at steady state conditions. In the three subjects studied, the amount of total α-methyldopa was only 4·2 times higher for the 10 vs 1 mM perfusion solution, indicating a non-linear transport process is involved.

Table 4. Plasma concentrations (μg ml^{-1}) of free and total[a] α-methyldopa after perfusion with 1 and 10 mM solutions at pH 6·0.

Time (h)	Subject 2				Subject 3				Subject 6			
	1 mM		10 mM		1 mM		10 mM		1 mM		10 mM	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
0·5	ND	0·122	0·283	0·439	0·043	0·104	0·164	0·268	ND	0·092	0·207	0·328
1·0	0·082	0·506	1·48	2·08	0·139	0·341	0·979	1·41	0·045	0·205	0·464	0·893
2·0	0·158	0·563	2·75	3·77	0·224	0·730	2·60	4·34	0·060	0·339	0·545	1·62
3·0	0·103	0·498	1·78	2·85	0·095	0·644	1·45	3·56	0·044	0·185	0·339	1·40
4·0	0·072	0·334	0·804	1·93	0·061	0·444	0·669	2·72	0·092	ND	0·124	0·854

ND = not detectable.
[a] Total α-methyldopa includes free α-methyldopa and acid-labile conjugates.

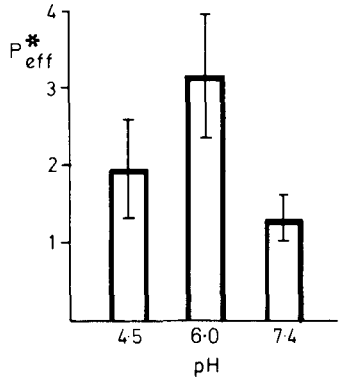

FIG. 3. Effect of pH on effective permeability of α-methyldopa in human intestinal perfusions. Concentration of α-methyldopa was 0·1 mM. Bars represent mean values ± s.e.m. (n = 3 for pH 4·5 and 7·4; n = 7 for pH 6).

In addition, the greater fraction of free α-methyldopa at 1 h for the 10 mM perfusion solution suggests that the first-pass metabolism of α-methyldopa is a saturable process since a significantly higher percentage of α-methyldopa is conjugated at the lower concentration.

Estimated α-methyldopa absorption in entire small intestine

The validity of the test procedure is supported by an estimate of the percentage of α-methyldopa that would be absorbed in the entire 500 cm of the small intestine (Gray's Anatomy 1980). We assumed that the first 100 cm behaved as the pH 6·0 data, while the remaining 400 cm of small intestine behaved as the pH 7·4 data. This predicted that 44% (one standard deviation range, 23–64%) of the dose given would have been absorbed. In normal, healthy subjects or in hypertensive patients, following oral doses of ^{14}C-labelled α-methyldopa, 40% of the radioactivity is recovered in the urine (Au et al 1972; Stenbaek et al 1977), a value consistent with that predicted from the present study.

DISCUSSION

The data from this study and other evidence from the literature suggest that α-methyldopa is absorbed via a non-passive transport process. In the three subjects studied the mean effective permeability at pH 6·0 decreased by a factor of 2·7 when the α-methyldopa concentration in the perfusion solution increased from 1 to 10 mM. This mimics our earlier findings (Amidon et al 1986) where the calculated wall permeability in rat perfused intestine also decreased as the α-methyldopa concentration in the perfusion solution increased from 0·01 to 10 mM. In fact, at 0·1 mM α-methyldopa at pH 6·0, the permeability values are nearly identical ($P^*_{eff} = P_{eff} \cdot R/D = 0{\cdot}33$ and 3·2) for rat and human subjects if the radius of the human intestine is assumed to be 10 times the radius of the rat intestine. A decreasing wall permeability indicates that the transport rate of a drug is not increasing linearly with concentration, suggesting a saturable transport mechanism is involved. The ratios of total plasma concentrations of α-methyldopa at 10 and 1 mM at each time point were always smaller than the concentration ratio indicating that measurement of absorbed drug also supported this concept.

Other studies supporting a facilitated transport mechanism for α-methyldopa can be found in the literature. Young & Edwards (1966) have shown in rats that the (−)-form of α-methyldopa is absorbed to a much greater extent than the (+)-form and also competes for uptake with other amino acids. In

addition, α-methyldopa uptake appeared to be saturable above 9·5 mM and temperature dependent in intestinal rings (Porter et al 1985). Au et al (1972) demonstrated in man that bioavailability of the (+)-form of α-methyldopa is less than half that of the (−)-form. However, Stenbaek et al (1982) found no statistical differences in area under the curves for total radioactivity when ^{14}C-labelled α-methyldopa was given alone or with a mixture of amino acids. When α-methyldopa was given with a protein meal in this latter study the amount of free drug in plasma was significantly reduced, although the area under the curve for total radioactivity was the same. These results suggest increased metabolism rather than competition between α-methyldopa and amino acids in specific transport systems is responsible for the lowered bioavailability. While this is plausible, there was considerable intersubject variability and in three of the five subjects studied there was a decrease in total plasma radioactivity when ^{14}C-labelled α-methyldopa was given with amino acids or roast beef.

Sulphate conjugation has been shown to be an important pathway in the biotransformation of orally administrated α-methyldopa. Evidence indicates that this process occurs in the intestinal mucosa during absorption (Kwan et al 1976; Saavedra et al 1975). The free fraction of α-methyldopa in the plasma at 1 h was 1·7 to 4·5 times higher for three subjects when the α-methyldopa concentration in the perfusion solution was 10 vs 1 mM. Kochak (1982) found similar trends when two oral doses were given to dogs. It appears that α-methyldopa exhibits saturable first-pass sulphate transformation. Thus, while it may be possible to maximize drug absorption by delivering α-methyldopa at low concentrations, bioavailability is compromised and may not be substantially enhanced due to increased sulphation in the gut wall. Sulphate conjugation might also explain the variability in α-methyldopa bioavailability after oral dosing. Saavedra et al (1975) found that 4 h after oral dosing of 1 g of α-methyldopa the ratio of free to sulphate conjugated α-methyldopa varied from 0·83 to 3·73 in seven subjects. It appears that both the absorption and first-pass metabolism of α-methyldopa are concentration-dependent above 1 mM while being quite variable amongst subjects.

While the trends toward a pH effect on α-methyldopa absorption were similar to those observed in rats (Amidon et al 1986), no statistical differences in the effective permeabilities were seen in the present study. This is possibly due to the small sample size and variability in the pH 6·0 data. In addition, because of the difficulty in maintaining the luminal pH at a desired value, the effective pH range studied was between 5·3 and 7·0 while in the rat study the range was pH 4·5 to 7·4. This larger range may explain why the earlier study (Amidon et al 1986) was able to demonstrate statistically maximum absorption of α-methyldopa near pH 6·0 in rats. Thompson et al (1970) also demonstrated in rats that several neutral amino acids had their transfer significantly increased by low pH (6·3) when compared with control transfers at pH 7·3.

The rat appears to be a good model for predicting the behaviour of α-methyldopa after oral administration in man. Although intersubject variability coupled with a small sample size make predictions from this study more tentative, the data are consistent with a saturable transport mechanism for α-methyldopa. There appears to be a concentration effect above 1 mM α-methyldopa in man and greater absorption near pH 6·0. These two effects, along with variations in intestinal transit time and sulphate conjugation, may explain the variations in α-methyldopa plasma concentrations after a regular oral dose is given. These conclusions probably also apply to hypertensive patients since the bioavailability of α-methyldopa after oral administration is the same as in healthy volunteers (Prescott et al 1966; Au et al 1972).

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