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Single dose bioavailability of acetaminophen following oral administration

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Summary

Saliva acetaminophen concentrations were determined in 15 subjects after administration of 5 different doses of commercial acetaminophen tablets (325 mg, 500 mg, 1000 mg, 1500 mg and 2000 mg acetaminophen). Drug concentration–time profiles were best described by either a one- or two-compartment pharmacokinetic model, depending on the treatment and subject. Statistically significant ($P < 0.05$) differences in elimination rate and dose-corrected area under the curve were found among treatments (doses) suggestive of dose-dependent pharmacokinetics.

Introduction

Acetaminophen has been widely used as an analgesic and antipyretic agent. The drug is eliminated in the urine primarily as glucuronide and sulfate conjugates with only 2–5% of a therapeutic dose being excreted unchanged (Cummings et al., 1967). Acetaminophen is also partly metabolized during absorption. A systemic availability study conducted by Rawlins et al. (1977) suggested that saturation of presystemic biotransformation occurs at doses greater than 500 mg since the apparent bioavailability was significantly less after 500 mg than after 1000 mg or 2000 mg orally. Reduced bioavailability at an oral dose of 625 mg was also reported by Ameer et al. (1983). In Rawlins' study with 6 subjects and 3 oral doses, no difference in half-life was observed between doses. However, plasma acetaminophen concentrations were monitored for only 6 h postdosing. The possibility of reduced bioavailability at lower doses is important when considering development of acetaminophen sustained action formulations. If oral bioavailability decreases with lower doses due to presystemic biotransformation, then sustained action products (which give continuous but slow drug input) may not give complete bioavailability compared to the same total dose administered as an immediately available oral preparation.

The present study was conducted with 15 subjects, each of whom received 5 different oral doses

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of acetaminophen. Saliva samples were collected for 16 h postdosing for determination of acetaminophen bioavailability parameters. Mean saliva acetaminophen levels have been reported to be proportional and virtually equivalent to serum levels (Glynn and Bastain, 1973; Ahmed and Enever, 1981; Adithan and Thangam, 1982). An HPLC method for measuring acetaminophen concentration in saliva was developed which was a modification of an assay used by Gwilt (personal communication).

Materials and Methods

Bioavailability study

Fifteen healthy male and female volunteers participated in this study after giving informed written consent. Vital statistics are provided in Table 1. The study was approved by the University Protection of Human Subjects Committee. All participants were taking no other medications during or one week prior to study initiation and had no history of chronic disease. In addition, no alcohol was allowed on treatment days. Each volunteer received 5 different doses of commercial acetaminophen tablets as the following treatments: (A) one 325 mg tablet Tylenol (lot SF0099S, McNeil, Fort Washington, PA); (B) one Tylenol Extra-Strength 500 mg tablet (lot SSF187, McNeil, Fort Washington, PA); (C) two Tylenol Extra-Strength 500 mg tablets (1000 mg dose); (D) three Tylenol Extra-Strength 500 mg tablets (1500 mg dose); (E) four Tylenol Extra-Strength 500 mg tablets (2000 mg dose). Treatments were administered on 5 separate occasions separated by at least 3 days according to a randomized block design (Snedecor and Cochran, 1980). Subjects fasted for at least 12 h prior to dosing and for an additional 2 h post dosing. Tablet(s) were swallowed with 180 ml of water, immediately followed by a rinse with 20 ml mouthwash in an attempt to remove any drug that may have adsorbed to the buccal mucosa. Saliva samples were collected by chewing on Parafilm (American Can Co., Greenwich, CT) squares (2.5 × 2.5 cm) for 1 min with simultaneous spitting into 12 ml centrifuge tubes. Samples were collected by each subject at 0, 10, 20, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 16 h. Saliva was centrifuged at 3000 rpm for 25 min to remove mucous and particulate matter. Salivary supernatant was transferred to a polypropylene container with a lock cap and frozen at −20 °C until analyzed.

TABLE 1

Vital statistics of subjects participating in bioavailability study

Subject	Sex	Age (years)	Weight (kg)
1	F	25	50.8
2	F	34	50.8
3	M	44	77.1
4	M	24	77.1
5	F	23	56.7
6	F	29	43.1
7	M	26	60.8
8	F	30	68.0
9	M	27	68.0
10	M	27	63.5
11	M	45	81.6
12	M	35	73.5
13	M	28	77.1
14	F	28	53.1
15	M	29	72.6
Mean		30.3	64.9
S.D.		6.6	11.9
Range		23–45	43.1–81.6

Determination of acetaminophen in saliva

Concentrations of acetaminophen in saliva were determined by a modified HPLC method of Gwilt (personal communication). Stock solutions containing 20, 50, 100, 200, 300, 400, 500, 600, 1000 and 1500 μg/ml of acetaminophen (USP reference standard, USP, Inc., Rockville, MD) were prepared in distilled, deionized water. An 80 μg/ml solution of 2-acetamidophenol (Aldrich Chemical Co., Inc., Milwaukee, WI) in water was used as the internal standard. Standards were prepared by spiking 500 μl of blank saliva with 25 μl of the above stock solutions. 50 μl of standard or unknown was combined with 50 μl of internal standard solution in a 250-μl polyethylene centrifuge tube and vortexed thoroughly. All samples were analyzed in duplicate on two different days. Acetaminophen concentration was determined by HPLC analysis using a delivery pump (M-6000A,

Waters Associates, Milford, MA), automatic sample injector (WISP 710B, Waters), 30-cm reverse phase C18 column (μBondapak, Waters), 10-cm guard column packed with reverse phase C18, UV detector (Model 440, Waters) set at 254 nm and dual pen recorder (Soltec Co., Encino, CA). The mobile phase consisted of methanol in distilled water (25 : 75) at a flow rate of 1.5 ml/min with a chart speed of 10 cm/h. Injections (10 μl) were made at 0.02 AUFS sensitivity for concentrations under 20 μg/ml. For higher concentrations the sensitivity was adjusted to 0.05 AUFS. Retention times for acetaminophen and 2-acetamidophenol were 4 and 6 min, respectively. Peak height ratios versus standard concentrations were fit to a line via linear regression. Standard curves were prepared daily and had correlation coefficients, $r \geq 0.996$. The coefficient of variation varied from 2.0 to 10.4% over the range 0.95 to 50 μg/ml of acetaminophen. The sensitivity of the assay was approximately 1 μg/ml.

Compartmental analysis

Data were analyzed by AUTOAN2 (Sedman and Wagner, 1972). Saliva acetaminophen concentrations were fitted to a linear sum of two or three exponential terms in the form of a one- or two-compartment open model with first order absorption. The model providing the best fit was selected by AUTOAN2. Coefficients and exponents from fitted functions were used to calculate the area under the saliva concentration–time curve (AUC) and the mean residence time (MRT) which involves a composite of drug release, absorption, and disposition processes (Yamaoka et al., 1978; Riegelman and Collier, 1980).

Non-compartmental analysis

Bioavailability parameters were also obtained from saliva acetaminophen concentration–time data by model-independent calculations. Terminal elimination rate constants (k) were estimated by least squares regression of concentration–time data points lying in the terminal log-linear region of the curves. The area under the drug concentration vs time curve from time zero to infinity (AUC) and area under the first moment curve from time zero to infinity (AUMC) were calculated using the linear trapezoidal rule (Gibaldi and Perrier, 1982). Mean residence time (MRT) was calculated as the ratio of AUMC to AUC (Riegelman and Collier, 1980). The peak plasma concentration (C_{max}) and time of peak concentration (T_{max}) were obtained directly from individual concentration–time data.

Statistical analysis

Statistical analysis of selected bioavailability parameters and dose-corrected parameters was performed using analysis of variance (ANOVA) and Least Significant Difference (LSD) for multiple comparisons (Snedecor and Cochran, 1980).

Results and Discussion

The mean saliva acetaminophen concentrations obtained after 325 mg, 500 mg, 1000 mg, 1500 mg, and 2000 mg doses are shown in Fig. 1. The data were not well fit by a pharmacokinetic model with Michaelis–Menten elimination, which has been used to describe capacity-limited acetaminophen sulfate formation in rats (Watari et al., 1983). However, saliva acetaminophen concentration–time data were well computer-fitted with either a one- or two-compartment open pharmacokinetic model with rapid first order absorption and first order elimination. Mean pharmacokinetic parameters for acetaminophen following oral administration are given in Table 2 for data best described by a two-compartment open model and Table 3 for data fitted to a one-compartment open model. The data for Subject 6 for the 325 mg dose and Subject 12 for the 500 mg dose were fitted to a two-compartment open model with instantaneous input because they could not be described by a model with first order absorption as there were no detectable saliva drug concentrations prior to the peak concentration. This procedure provided estimates of distribution and elimination rate constants. However, AUC for these subjects was calculated with the linear trapezoidal rule since use of the equation based on instantaneous input would result in an overestimate of AUC between time zero and time to peak concentration (time of the first detectable drug concentration). Data for Subjects 8 and 12 for the 325 mg dose, Subject 5

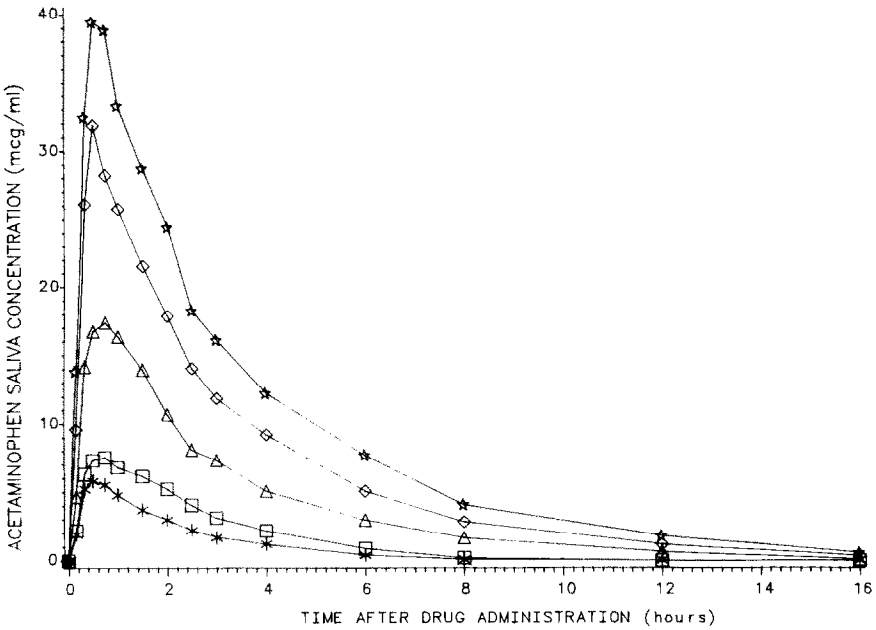

Fig. 1. Mean saliva concentrations of acetaminophen following administration of single oral doses of acetaminophen tablets to 15 subjects. 325 mg (A), *———*; 500 mg (B), □———□; 1000 mg (C), △———△; 1500 mg (D), ◇———◇; 2000 mg (E), ☆———☆.

TABLE 2

Pharmacokinetic parameters for two-compartment open model following oral administration of acetaminophen tablets

Dose (mg)		α (h^{-1})	β (h^{-1})	K_a (h^{-1})	K_{el} (h^{-1})	K_{12} (h^{-1})	K_{21} (h^{-1})	t_l [a] (h)	$t_{1/2}$ [b] (h)
325	Mean [c]	2.35	0.257	9.74	0.522	0.697	1.22	0.12	2.70
	S.D.	1.24	0.080	3.08	0.135	0.390	0.845	0.05	
	C.V. (%)	52.65	31.01	31.57	25.82	55.93	69.38	41.63	
	Range	1.02–4.22	0.165–0.367	5.70–14.40	0.342–0.676	0.331–1.72	0.482–2.810	0.00–0.15	
500	Mean [d]	2.11	0.275	9.26	0.614	0.766	1.00	0.06	2.52
	S.D.	1.16	0.118	4.55	0.232	0.523	0.770	0.08	
	C.V. (%)	55.00	42.93	49.12	37.73	68.31	76.91	124.7	
	Range	0.935–4.25	0.171–0.521	2.49–13.58	0.337–0.993	0.175–1.44	0.360–2.65	0.00–0.15	
1000	Mean [e]	1.90	0.201	5.75	0.491	0.788	0.826	0.13	3.45
	S.D.	1.61	0.100	3.22	0.158	0.825	0.804	0.10	
	C.V. (%)	84.51	49.57	55.93	32.10	104.7	97.36	77.35	
	Range	0.587–4.92	0.073–0.380	1.59–11.85	0.293–0.828	0.144–2.68	0.136–2.63	0.00–0.30	
1500	Mean [f]	1.72	0.210	11.15	0.457	0.746	1.40	0.14	3.30
	S.D.	2.20	0.092	11.47	0.215	1.27	2.08	0.07	
	C.V. (%)	128.4	43.67	102.8	46.99	170.3	149.1	53.97	
	Range	0.529–7.12	0.100–0.362	2.56–38.59	0.337–0.982	0.117–3.88	0.159–6.16	0.00–0.26	
2000	Mean [g]	1.28	0.222	10.11	0.430	0.399	0.674	0.14	3.12
	S.D.	0.680	0.075	6.54	0.129	0.329	0.368	0.08	
	C.V. (%)	53.10	33.73	64.65	30.07	82.61	54.55	59.21	
	Range	0.477–2.67	0.100–0.356	2.20–22.41	0.184–0.699	0.078–1.18	0.191–1.26	0.00–0.31	

[a] Lag time.
[b] $0.693/\beta$.
[c] $n = 8$.
[d] $n = 7$.
[e] $n = 10$.
[f] $n = 9$.
[g] $n = 12$.

TABLE 3

Pharmacokinetic parameters for one-compartment open model following oral administration of acetaminophen tablets

Dose (mg)		K_a (h^{-1})	K_{el} (h^{-1})	t_1 [a] (h)	$t_{1/2}$ [b] (h)
325	Mean [c]	5.52	0.631	0.27	1.10
	S.D.	3.49	0.266	0.25	
	C.V. (%)	63.34	42.11	91.45	
	Range	2.22 –11.47	0.368–1.02	0.00–0.47	
500	Mean [d]	3.53	0.465	0.29	1.49
	S.D.	2.23	0.151	0.18	
	C.V. (%)	63.15	32.52	61.87	
	Range	1.56 – 7.54	0.308–0.775	0.13–0.67	
1000	Mean [e]	5.57	0.405	0.27	1.71
	S.D.	4.28	0.092	0.16	
	C.V. (%)	76.80	22.82	61.23	
	Range	0.914–10.50	0.269–0.465	0.11–0.45	
1500	Mean [f]	8.20	0.324	0.15	2.14
	S.D.	8.46	0.077	0.06	
	C.V. (%)	103.2	23.69	41.53	
	Range	2.51 –25.04	0.203–0.384	0.10–0.27	
2000	Mean [g]	7.85	0.271	0.15	2.56
	S.D.	3.57	0.025	0.15	
	C.V. (%)	45.41	9.26	97.90	
	Range	4.40 –11.52	0.253–0.299	0.00–0.30	

[a] Lag time.
[b] $0.693/K_{el}$.
[c] $n = 5$.
[d] $n = 7$.
[e] $n = 4$.
[f] $n = 6$.
[g] $n = 3$.

for the 500 mg dose, and Subject 13 for the 1000 mg dose were not included in the compartmental analysis because the saliva acetaminophen concentrations fluctuated radically over time, resulting in illogical profiles which could not be fit to a smooth curve for estimation of pharmacokinetic parameters. Such fluctuations may be due to intrasubject variability in distribution of drug in the saliva (Danhof and Breimer, 1978). The concentration–time curve for Subject 12 for the 1500 mg dose was best fitted by a linear sum of 4 exponential terms (a three-compartment open model). Since a specific 3-compartment model is indeterminate with the data collected, the only pharmacokinetic parameter calculated for these data was the elimination rate constant (slope of the terminal phase), which was obtained from NONLIN (Metzler et al., 1974). AUC was calculated with the linear trapezoidal rule.

The distribution phase was fairly rapid for data that were best fitted by a triexponential equation, and the distribution half-life tended to increase with dose (mean $t_{1/2\alpha} = 0.29$ h for the 325 mg dose and 0.54 h for the 2000 mg dose). However, values for α were quite variable among subjects (C.V. ranged between 53% and 128%). The mean elimination half-life was shorter for data fit to a one-compartment model than to a two-compartment model, as expected, and tended to increase with dose. However, as the dose increased, the difference between mean elimination half-life for the one- and two-compartment models became smaller ($t_{1/2\text{kel}} = 1.10$ h and $t_{1/2\beta} = 2.70$ h for 325 mg dose; $t_{1/2\text{kel}} = 2.56$ h and $t_{1/2\beta} = 3.12$ h for 2000 mg dose).

Values for the absorption rate constant were extremely variable, as reflected by the high coefficient of variation associated with the estimated values (C.V. ranged between 32% and 103%). Estimates of K_a were probably not reliable because there were not enough data points prior to the peak concentration to characterize the absorption phase. Mean drug absorption was quite rapid at all doses, but somewhat slower in subjects whose data were best described by a one-compartment model. However, rate of absorption appeared to be independent of dose. For many of the concentration–time curves there was a lag time between administration of the drug and onset of absorption. Mean lag time was longer for data better described by a one-compartment than by a two-compartment model.

At lower oral doses (325 mg and 500 mg), acetaminophen exhibited either one-compartment or two-compartment behavior about equally while at higher doses (1000–2000 mg) more of the concentration–time profiles were better described by the two-compartment model. This is consistent with a previous pharmacokinetic study comparing two different oral dosage forms of acetaminophen (650 mg) in which plasma concentration–time data were well described by a two-compartment open model with first order absorption and a lag time (Albert et al., 1974a and b). Acetaminophen is also known to display two-compartment char-

TABLE 4

Selected mean compartmental pharmacokinetic parameters [a] following administration of commercial acetaminophen tablets to 15 subjects

Parameter	Dose (mg)					ANOVA [b] (among treatments)	Pairwise comparisons [c]
	325 (A)	500 (B)	1 000 (C)	1 500 (D)	2 000 (E)		
Elimination rate constant (K) (h^{-1}) [d]	0.401 ± 0.251	0.370 ± 0.164	0.259 ± 0.134	0.255 ± 0.101	0.232 ± 0.070	0.02	A B C D E
Half-life (h) [e]	1.73	1.87	2.67	2.71	2.99	–	
MRT (h)	3.08 ± 1.18	3.07 ± 0.89	4.23 ± 1.69	3.91 ± 1.07	4.09 ± 1.33	0.04	A B D C E
AUC ($\mu g \times h/ml$)	17.3 ± 7.4	25.2 ± 8.2	63.0 ± 20.8	104.8 ± 37.6	142.0 ± 39.0	< 0.01	A B C D E

[a] Average values ± S.D. K, MRT and AUC are calculated using pharmacokinetic parameters from fitted model.
[b] Analysis of Variance for completely randomized design, significance level of difference.
[c] LSD comparisons at $P = 0.05$; differences between treatments sharing an overhead bar are not statistically significant.
[d] Slope of the terminal portion of the saliva acetaminophen concentration-time curve from AUTOAN2. One-compartment (K_{el}) and two-compartment (β) values were averaged together.
[e] $0.693/K$.

acteristics after i.v. injection (Clements and Prescott, 1976; Rawlins et al., 1977; Ameer et al., 1983). The distributive phase may not be observed following oral administration, which results in drug concentration–time curves which appear to be biexponential (one-compartment) rather than multiexponential (Gibaldi and Perrier, 1982). Also, limitations imposed by the sensitivity of the assay did not allow for concentrations to be followed beyond a certain time at lower doses, while at higher doses, detectable saliva drug levels were observed for as long as 16 h postdosing. There may be an exponential phase at later times which cannot be detected following administration of low doses. Therefore, estimates of half-life for data best described by a one-compartment model are expected to be shorter than for data following two-compartment behavior and may be underestimates of the true half-life. Alternatively, higher plasma concentrations may correlate with longer

TABLE 5

Selected mean non-compartmental pharmacokinetic parameters [a] following administration of commercial acetaminophen tablets to 15 subjects

Parameter	Dose (mg)					ANOVA [b] (among treatments)	Pairwise comparisons [c]
	325 (A)	500 (B)	1 000 (C)	1 500 (D)	2 000 (E)		
Elimination rate constant (K) (h^{-1}) [d]	0.361 ± 0.169	0.386 ± 0.264	0.267 ± 0.111	0.271 ± 0.106	0.243 ± 0.067	0.06	B A D C E
Half-life (h) [e]	1.92	1.80	2.60	2.55	2.85	–	
MRT (h)	3.30 ± 1.10	3.58 ± 1.39	4.11 ± 1.37	3.85 ± 1.04	4.10 ± 1.29	0.37	
AUC ($\mu g \times h/ml$)	17.6 ± 6.9	26.8 ± 8.4	64.3 ± 19.8	106.0 ± 36.4	146.0 ± 40.5	< 0.01	A B C D E
C_{max} ($\mu g/ml$)	6.97 ± 2.25	9.98 ± 2.68	21.0 ± 6.0	36.0 ± 11.7	44.7 ± 11.6	< 0.01	A B C D E
T_{max} (h)	0.55 ± 0.25	0.74 ± 0.49	0.82 ± 0.57	0.70 ± 0.39	0.53 ± 0.18	0.25	

[a] Average values ± S.D.
[b] Analysis of Variance for completely randomized design, significance level of difference.
[c] LSD comparisons at $P = 0.05$; differences between treatments sharing an overhead bar are not statistically significant.
[d] Slope of the terminal log-linear region of the saliva acetaminophen concentration–time curve calculated by least squares regression.
[e] $0.693/K$.

half-lives if the kinetics are dose-dependent. In this case the apparent half-life for lower doses would also be less than the apparent half-life for higher doses.

Selected mean pharmacokinetic parameters obtained by compartmental fitting of the concentration-time data are given in Table 4. Although the study was designed as a randomized block experiment, pharmacokinetic parameters were compared according to a one-way ANOVA (completely randomized design) because of missing data in 4 of the blocks (subjects). It was recognized that analyzing the data in such a manner would result in decreased precision. However, the estimated efficiency of a randomized block relative to a completely randomized design for this set of data was only 1.3, meaning that analysis with blocking would have resulted in only a slight increase in precision.

Statistically significant differences in the compartmental MRT and elimination rate constants were found among treatments (Table 4). The corresponding noncompartmental average K and MRT values (Table 5) were similar to those obtained by compartmental analysis. However, statistical comparison of non-compartmental MRT values revealed no significant differences among treatments, while differences among non-compartmental elimination rate constants were marginally significant ($P = 0.06$).

Elimination appears to be dose-dependent since the half-life is statistically significantly increasing with dose, although the increase is relatively small and gradual. Pairwise comparisons of compartmental elimination rate constants revealed that the elimination rate constant after 2000 mg was significantly less than after 325 mg or 500 mg orally ($P < 0.05$). The elimination rate constant after 1000 mg or 1500 mg was also significantly less than after 325 mg. The same differences were observed for non-compartmental elimination rates, with an additional statistically significant difference found between the 500 mg and 1500 mg treatments. Thus, the apparent half-life of acetaminophen in saliva is prolonged at higher doses. This is contrary to what Rawlins et al. (1977) observed after oral administration of 500 mg, 1000 mg, and 2000 mg doses. However, drug concentrations were monitored for only 6 h postdosing in this earlier study. Therefore, for the higher doses, the calculated elimination rate constant for these data would have been a hybrid constant obtained during the distributive phase and the first part of the postdistributive phase of drug decline, and would be greater than the elimination rate constant measured solely in the postdistributive phase.

An increase in acetaminophen half-life with increasing dose would also be consistent with a reduced first-pass hepatic effect which results in greater amounts of unchanged drug in the body (Forrest et al., 1979). Acetaminophen metabolism is altered following overdosage (Prescott, 1980) when the overdose is large enough to produce liver damage, and prolongation of half-life is related to the severity of hepatic injury (Gazzard et al., 1977; Prescott and Wright, 1973; Prescott et al., 1971). Although 2000 mg is well below a toxic dose for healthy subjects, saturation of metabolism (sulfate and glucuronide conjugation) in some subjects could account for slower elimination. Thus, nonlinearity in metabolism of drug in the body may be occurring at higher doses of acetaminophen. Within a given subject, acetaminophen half-life in saliva varied considerably but was usually longer at higher doses.

The mean non-compartmental MRT values were higher than the corresponding compartmental values at doses of 325 mg and 500 mg. Compartmental fitting of the data resulted in underestimation of AUC and AUMC for some individuals in which the observed concentrations deviated above the fitted curve during the elimination phase. However, there was still a trend for MRT to increase with dose between the 500 mg and 1000 mg doses, as did the half-life. Above 1000 mg acetaminophen, MRT values remained constant. Significant differences in compartmental MRT estimates were found between 2000 mg and 325 mg or 500 mg doses, respectively, and between 1000 mg and 325 or 500 mg doses, respectively ($P < 0.05$). MRT has been interpreted as "the mean time for intact drug molecules to transit through the body" (Riegelman and Collier, 1980), and because elimination is slower at higher doses, transit of drug molecules will be slower as reflected in the magnitude of MRT. It has been

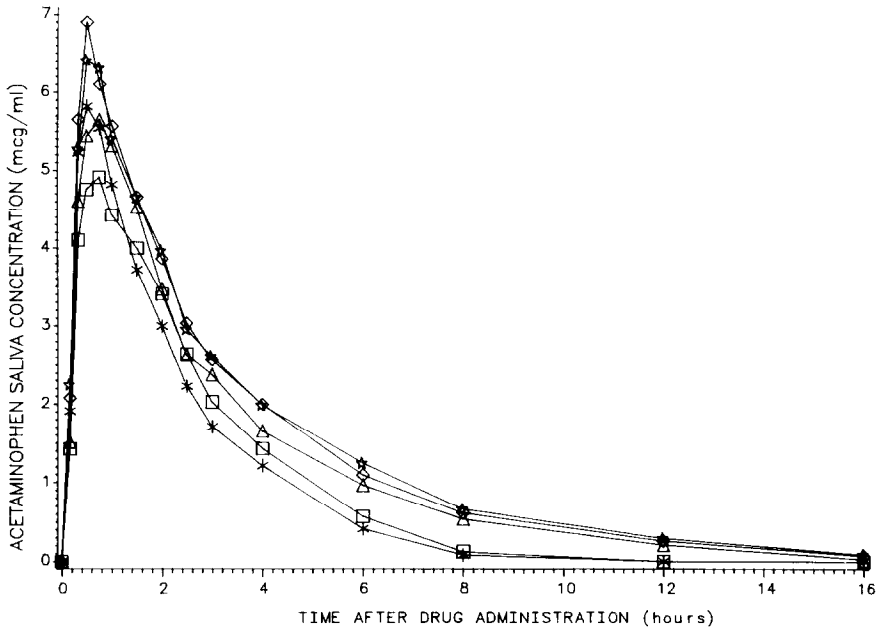

Fig. 2. Mean saliva concentrations of acetaminophen following administration of single oral doses of acetaminophen tablets to 15 subjects. Data normalized to the 325 mg dose. 325 mg (A), * ——— *; 500 mg (B), □———□; 1000 mg (C), △———△; 1500 mg (D), ◇———◇; 2000 mg (E), ☆———☆.

reported that differences in MRT of drug concentration–time curves with dose may suggest saturation of drug metabolism (i.e., non-linearity) (Yamaoka et al., 1978).

Other non-compartmental bioavailability parameters (Table 5), such as AUC and C_{max}, were significantly different among treatments, as expected with increasing doses. T_{max} values were not significantly different, which indicates similar drug absorption rates as the acetaminophen dose is increased. This is in agreement with the lack of dose-dependency for K_a estimates. Thus, observed differences in MRT, which is a composite of in vivo absorption and disposition processes, are most likely due to differences in elimination and not absorption. Individual concentration–time data, C_{max} and AUC were dose-corrected by normalizing all values to a 325 mg dose. If linear pharmacokinetics hold for acetaminophen, the curves should be superimposable. Average dose-corrected concentration–time curves are given in Fig. 2. Analysis of mean dose-corrected concentrations at

TABLE 6

Dose-corrected mean non-compartmental AUC and C_{max} following administration of commercial acetaminophen tablets to 15 subjects [a]

Parameter	Dose (mg)					ANOVA [b] (among treatments)	Pairwise comparisons [c]
	325 (A)	500 (B)	1 000 (C)	1 500 (D)	2 000 (E)		
AUC (μg × h/ml)	17.6 ± 6.9	17.4 ± 5.5	20.9 ± 6.5	23.0 ± 7.9	23.7 ± 6.6	0.04	A B C D E
C_{max} (μg/ml)	6.97 ± 2.25	6.49 ± 1.74	6.82 ± 1.95	7.79 ± 2.53	7.26 ± 1.88	0.53	
AUC/D (kg × h/l)	3.32 ± 0.99	3.43 ± 1.04	4.03 ± 0.98	4.40 ± 1.09	4.59 ± 1.19	< 0.01	A B C D E

[a] Average values ± S.D.

[b] Analysis of Variance for completely randomized design, significance level of difference.

[c] LSD comparisons at $P = 0.05$; differences between treatments sharing an overhead bar are not statistically significant.

individual sampling times revealed statistically significant differences ($P < 0.05$) among treatments at all times greater than or equal to 3 h. Mean dose-corrected C_{max} and AUC values appear in Table 6. C_{max} values were not significantly different among treatments. However, AUC increased more than proportionately with dose. Dose-corrected AUC at 1500 mg and 2000 mg acetaminophen were significantly higher than at 325 mg or 500 mg, respectively. This trend was also observed in the ratios of AUC to dose (mg/kg b. wt.) which are given in Table 6. Mean AUC/D values for 1500 mg and 2000 mg were significantly greater than for the 325 mg or 500 mg doses, respectively.

The observation that AUC increases more than proportionately with dose is indicative of differences in apparent bioavailability (F) with dose which have been reported by Rawlins et al. (1977) for acetaminophen. However, Rawlins reported no difference in half-life but in the present study, elimination appears to be dose-dependent, which results in non-proportional changes in AUC with dose. In this case, if F is calculated from AUC without correcting for differences in elimination rate, then one would conclude that apparent bioavailability increases with an increase in dose. If a correction for changing elimination rate is made, AUC vs dose is non-linear and suggests non-linear pharmacokinetics. Also, since volume of distribution is directly correlated with AUC, differences in AUC with dose, which would be reflected in apparent bioavailability, could occur if the apparent volume of distribution was changing with dose. In Rawlins' study, bioavailability decreased from 0.90 at 1000 mg and 2000 mg oral doses to 0.63 for a 500 mg oral dose. Such incomplete systemic availability for low doses could be explained by increased presystemic biotransformation due to either first-pass hepatic extraction or metabolism in the epithelium and/or lumen of the GI tract, or by a combination of these processes (George, 1981; Ameer et al., 1983). Although differences between the dose-corrected AUC for 1000 mg and 500 mg or 325 mg doses, respectively, in this study were not statistically significant, they may be important in relative bioavailability studies because the average dose-corrected AUC increased by 20% in going from 500 mg to 1000 mg orally.

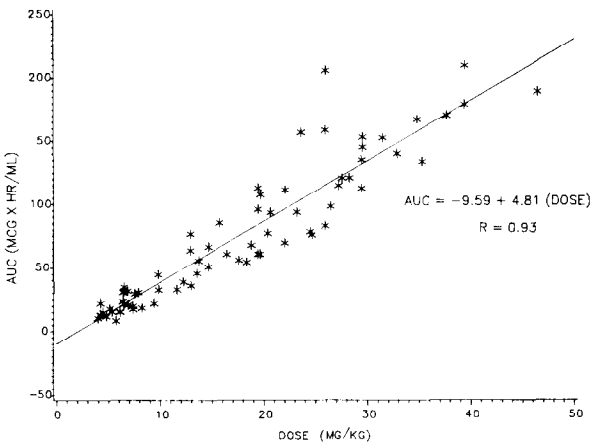

Fig. 3. Relationship between area under the curve (0–∞) and dose (mg acetaminophen/kg b. wt.).

Fig. 3 depicts the relationship between non-compartmental AUC and dose (adjusted for subject weight). The data were well described by a line having a statistically significant ($P < 0.05$) non-zero intercept and a correlation coefficient r of 0.93. The non-zero intercept suggests non-linear kinetics. However, the coefficient of a quadratic term (dose squared) was not statistically significant ($P = 0.12$) even though the data appear to exhibit slightly concave curvature. The mean AUC vs dose data (Table 5) were well fitted to a parabola ($r = 0.999$), which is also suggestive of non-linear kinetics.

The line in Fig. 3 represents an "average" relationship since it includes data for all subjects. Representative individual AUC vs dose plots are shown in Fig. 4. Inspection of individual curves indicated that drug bioavailability (AUC) was linear with dose in some subjects (Fig. 4A) and non-linear in other subjects with AUC increasing disproportionately at doses > 20 mg/kg (Fig. 4B), but occasionally not changing with dose at the higher doses (Fig. 4C). Although non-linear increases in AUC as the dose is increased can be explained by saturable metabolism as discussed previously, the less frequently observed decrease in AUC with dose may be due to intraindividual variability in drug absorption at higher doses related to slower dissolution. Separate studies have

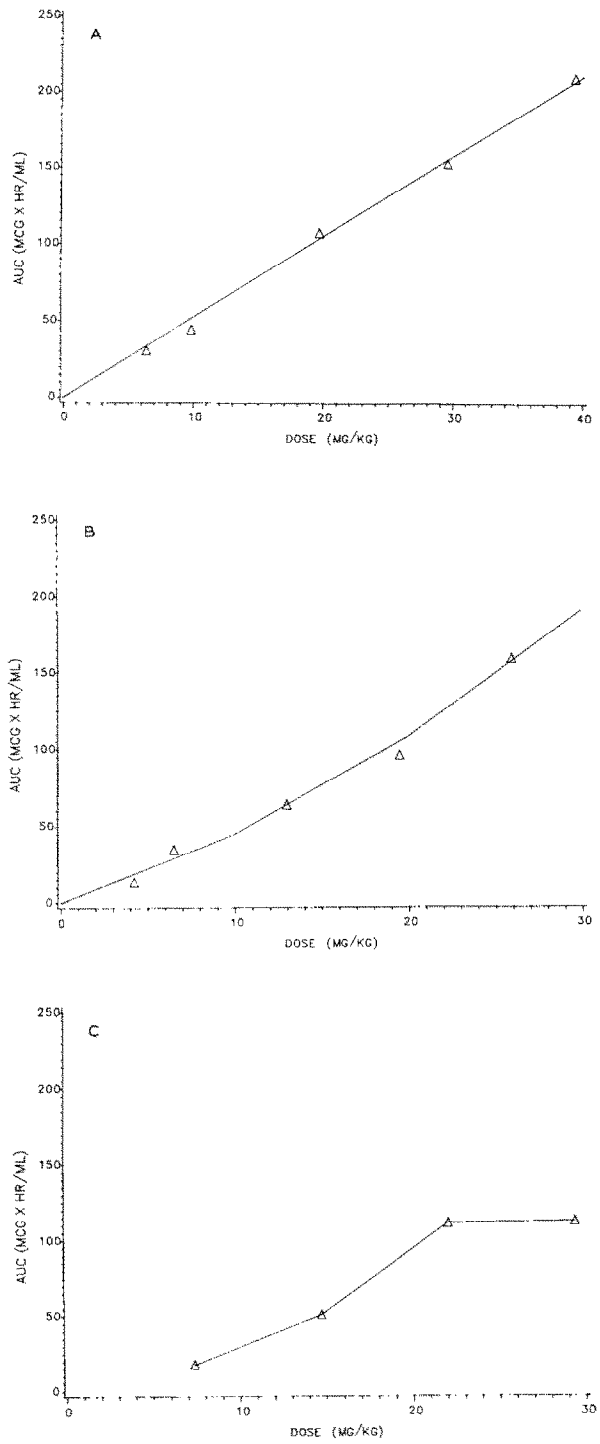

Fig. 4. A: area under the curve vs dose (mg acetaminophen/kg b. wt.) for Subject 2. B: area under the curve vs dose (mg acetaminophen/kg b. wt.) for Subject 3. C: area under the curve vs dose (mg acetaminophen/kg b. wt.) for Subject 8.

shown that the rate of acetaminophen dissolution in vitro is slower for four 500 mg tablets than for one 500 mg tablet. Approximately half the subjects exhibited a linear AUC–dose relationship, while the remaining individual curves were non-linear, mostly concave.

The lack of Michaelis–Menten characteristics in individual and pooled subject concentration–time data suggests that a slight non-linearity observed in AUC with dose may not be due to saturation of elimination processes. However, this observation has also been reported for theophylline using computer simulations (Wagner, 1985). This suggests the possible operation of Michaelis–Menten kinetics with acetaminophen even though the concentration–time profiles do not have Michaelis–Menten characteristics. Michaelis–Menten kinetics are most easily recognized from steady-state studies, and thus, the single dose data presented in this report do not allow for an unambiguous interpretation of non-linear drug metabolism.

Conclusion

The relative apparent bioavailability of acetaminophen, on average, was found to be dose-dependent based on statistically significant differences in elimination half-life and dose-corrected AUC among treatments (doses). The AUC–dose relationship was substantially non-linear for some subjects and approximately linear for others. Reasons for this finding cannot be differentiated based on the data collected. Mean compartmental and non-compartmental bioavailability parameters were similar, except for MRT values at 325 mg and 500 mg which were higher when calculated from non-compartmental AUC and AUMC estimates. Despite evidence of non-linearity in drug disposition with dose, concentration–time curves were well described by one- or two-compartment models with first order absorption and elimination. Further work is needed with multiple dose administration of variable acetaminophen doses to evaluate potential non-linear drug accumulation at steady state.

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