J Clin Pharmacol. 1981; **21**:284-287.

The Effect of Obesity on Acetaminophen Pharmacokinetics in Man

WINSTON H. LEE,* Pharm. D., WILLIAM G. KRAMER, Ph.D., and GEORGE E. GRANVILLE, M.D. Houston, Tex.

Abstract: This study examined the absorption and disposition of orally administered acetaminophen in morbidly obese patients as compared to subjects of normal weight, and possible changes in disposition as the patients underwent weight reduction through dietary modification. The overall disposition of acetaminophen was not affected by a weight loss of 8 to 30 kg; elimination half-life, time to reach the peak, and peak plasma concentration varied within each subject but not in a systematic way. The half-life was the same in the obese patients (2.6 ± 0.85 hours) and normal subjects (2.6 ± 0.12 hours). However, maximum plasma concentrations were reached at a significantly later time and were significantly lower in the obese patients as compared to the normals, implying an apparently lower absorption rate. The area under the plasma concentration-time curve for the obese patients when normalized to ideal body weight was more consistent with that in the normal subjects than when normalized to total body weight. Administration of a normal dose of acetaminophen to an obese patient should yield plasma levels in the same range as persons of normal weight. As total weight may exceed 200 per cent of the ideal weight in this patient group, dosing according to total rather than ideal weight could lead to toxic or lethal effects when using the 10 mg/kg dosing recommendation.

ACETAMINOPHEN is a widely used analgesic and antipyretic. When taken at the normally recommended oral dose of 650 mg every 4 hours (approximately 4 Gm/day), it is a relatively safe drug. Peterson and Rumack[1] consider 10 mg/kg every 4 hours to be free of adverse effects in an adult; 140 mg/kg in a single dose is likely to produce toxic effects.[2] The question arises as to the most appropriate weight (either total or ideal body weight) to use in dosage calculations of acetaminophen for an obese patient. A morbidly obese patient is one whose weight is greater than 120 per cent of ideal body weight and may exceed 200 per cent of ideal body weight with cardivascular, pulmonary, or endocrinologic disorders. One could administer either normal or toxic doses of certain agents when dosing is based upon the ideal or total body weight; the result depends upon the disposition of the drug.

Discussions with obese patients have shown that they tend to take two or three times the "normal" dose of this drug in a self-medicating situation, on the premise that their two- or threefold excess body weight requires a similar increase in dose. The purpose of the study reported here was to examine the absorption and disposition of acetaminophen in the morbidly obese patient as compared to individuals of normal weight to determine the most appropriate regimen. In addition, possible changes in drug disposition as the patients underwent reduction were also examined.

From the College of Pharmacy, University of Houston, Texas Medical Center; and the Veterans Administration Medical Center, Houston, Tex.

* Present address: Drug Information Services, Alta Bates Hospital, Berkeley, Calif.

Methods

Subjects

The population of morbidly obese individuals consisted of four male patients hospitalized on the Endocrinology Ward of the Veterans Administration Medical Center, Houston, Tex., for the purpose of weight reduction through dietary modification. Each patient was maintained on a diet of less than 1200 calories per day and a constant number of calories and percentage of carbohydrates, protein, and fat for at least three days. None of the patients studied was in any phase of acute or rapid weight loss. The control subjects were three volunteer males of normal body weight. All patients and subjects gave signed informed consent and had no evidence of hepatic or renal disorder.

Drug Administration and Sample Collection

For either group, acetaminophen was administered orally as two 325-mg tablets (Philips Roxane brand of acetaminophen) with 8 oz. of water after an overnight (8-hour) fast. Blood samples were collected before and at 0.25, 0.50, 0.75, 1, 1.5, 2, 4, 6, 8, and 12 hours after drug ingestion. The plasma was separated by centrifugation and frozen until assayed. Plasma acetaminophen concentrations were determined using a high-pressure liquid chromatographic method.

To determine the effect of weight loss on acetaminophen disposition, each obese patient was restudied after an average weight reduction of 14 kg (range 13 to 30 kg); two of the patients were studied twice and the other two patients after three periods of weight loss (Table I).

Pharmacokinetic Analysis

For each set of data, the elimination of half-life ($t_{1/2}$) was calculated from the slope of a semilogarithmic plot of the terminal plasma concentrations versus time; all slopes were determined using linear regression. The maximum plasma concentration (C_{max}) and time to reach maximum concentration (t_p) were determined directly from the data. The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal method from time zero until the final sampling time and by extrapolation from the final sampling time to infinity using the elimination constant determined above.

TABLE I

Weight Loss Observed in Obese Patients

Patient no.	Study no.*	Elapsed time (days)	Weight loss (kg)	Weight (kg)	
				Total	Ideal
1	1	0	—	133	84
	2	91	13	120	
2	1	0	—	161	84
	2	44	11	150	
	3	98	19	131	
3	1	0	—	189	84
	2	35	13	176	
	3	71	14	162	
4	1	0	—	135	79
	2	91	8	127	

* Patients were restudied after weight losses averaging 13 kg. See Methods.

Results

Figure 1 contains plots of plasma acetaminophen concentration versus time for the three treatments for a representative obese patient. For clarity in presentation and to aid in the comparison among treatments, curves predicted by the nonlinear fitting of a polyexponential equation (i.e., $C = \Sigma A_i e^{-\lambda_i t}$) are shown without the data. However, all fitted curves agreed well with the experimental data, as shown in Fig. 2 for an obese patient and a normal subject.

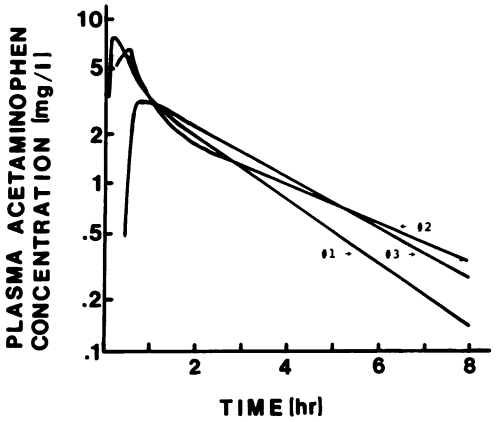

Fig. 1. Semilogarithmic plot of plasma acetaminophen concentration-time curves predicted by fitting polyexponential equations to the data obtained from the three treatments for one obese patient.

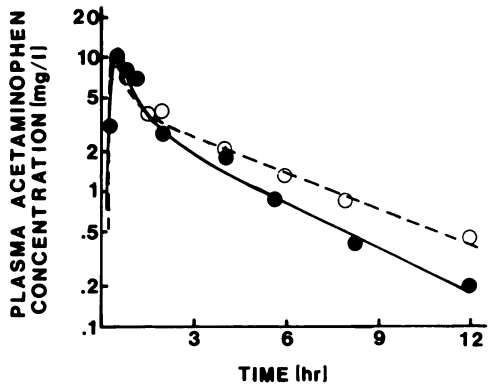

Fig. 2. Semilogarithmic plots of plasma acetaminophen concentration vs. time for an obese patient (o) (patient 4, treatment 2) and a normal subject (•). The solid and dashed lines were obtained by computer fitting of a polyexponential equation.

TABLE II

Acetaminophen Absorption and Disposition Parameters in the Obese Patients

Patient No.	Study No.*	$t_{1/2}$ (hr)	t_p (hr)	C_{max} (μg/ml)	AUC (μg/ml · hr)
1	1	3.4	0.5	9.8	26
	2	2.9	1.1	3.0	25
2	1	1.6	0.3	7.6	12
	2	2.6	0.5	6.5	12
	3	2.0	1.1	4.4	10
3	1	3.7	1.1	6.6	22
	2	2.3	2.1	3.7	18
	3	2.5	0.6	6.1	20
4	1	2.1	0.8	6.0	19
	2	1.6	0.5	10.0	26

* See Table I.

The parameters describing acetaminophen absorption and disposition in the obese patients are shown in Table II and are compared to those in the normal subject in Table III.

Discussion

It is evident from Fig. 1 and the parameters shown in Table II that the overall disposition of acetaminophen was not affected

TABLE III

Comparison of Acetaminophen Absorption and Disposition Parameters in Obese Patients and Normal Subjects*

Parameter	Obese patients	Normal subjects
$t_{1/2}$ (hr)	2.5 ± 0.71	2.6 ± 0.12
t_p (hr)	0.84 ± 0.053	0.51 ± 0.025
C_{max} (μg/ml)	6.4 ± 2.4	10.8 ± 0.51
AUC (μg/ml · hr)		
per kg total body weight	0.13 ± 0.053	0.38 ± 0.10
per kg ideal body weight	0.23 ± 0.072	

* Values reported as mean ± standard deviation for ten studies in four obese patients and three studies in normal subjects.

by weight reductions ranging from 8 to 30 kilograms. Values for half-life, time to reach the peak (t_p), and maximum plasma concentration (C_{max}) varied within each subject but not in a systematic manner. The same is true for the plasma concentration-time curve; although variable within a subject among treatments (Fig. 1), the degree should not be sufficient to alter the therapeutic outcome. The variability in the parameters among the obese patients, however, was greater than that seen in normal subjects.

The elimination half-life was essentially the same in the obese patients (2.5 ± 0.71 hours) and normal subjects (2.6 ± 0.12 hours) (Table III) and was consistent with values reported by others.[3–5] However, maximum plasma concentrations were reached at a significantly later time ($P < 0.01$) and were significantly lower ($P < 0.05$) in the obese patients as compared to the normals. Consequently, the apparent rate of absorption of acetaminophen may be slower in the obese patients. There was an apparent absorption lag time for each group, in both cases averaging 10 minutes.

The area under the plasma concentration-time curve (*AUC*), a measure of the extent of absorption, was significantly less in the obese patients than those of normal weight when expressed per kg of total body weight ($P < 0.01$). It was also significantly less when expressed per kg of ideal body weight ($0.05 < P < 0.01$), although the significance was somewhat borderline. Consequently, it appears that the *AUC*, and thus the observed plasma concentrations, may be more closely related to ideal than total body weight. This is also apparent upon examination of Fig. 2; the levels obtained for a single dose do not appear to differ between the obese patient and normal volunteer.

It would appear that obesity does not affect the extent to which acetaminophen is absorbed or its rate of elimination. The rate of absorption, however, does appear to be slower in the obese patient. Administration of a normal dose will yield plasma concentrations in the same range as those found in persons of normal weight and should, in theory, produce the same degree of effect. The dose of acetaminophen should be based on ideal, not total, body weight in the obese patient to avoid the possibility of high levels and hepatotoxic effects when using the 10 to 20 mg/kg recommendation.

References

1. Peterson RG, Rumack BH. Pharmacokinetics of acetaminophen in children. *Pediatrics*. 1978; **62 (Suppl.)**: 877-879.
2. Peterson RG, Rumack BH. Toxicity of acetaminophen overdose. *J Am Coll Emer Phys*. 1978; **7**:202-205.
3. Albert KS, Sedman AJ, Wagner JG. Pharmacokinetics of orally administered acetaminophen in man. *J Pharmacokinet Biopharm*. 1974; **2**: 381-393.
4. Clements JA, Prescott LF. Data point weighting in pharmacokinetic analysis: intravenous paracetamol in man. *J Pharm Pharmacol*. **28**:707-709.
5. Perucca E, Richens A. Paracetamol disposition in normal subjects and in patients treated with antiepileptic drugs. *Br J Clin Pharmacol*. 1979; **7**:201-206.

Reprint request to: Dr. W. G. Kramer, Department of Pharmaceutics, University of Houston, Texas Medical Center, 1441 Moursund St., Houston, Tex. 77030.