Dose-dependent pharmacokinetics of acetaminophen: Evidence of glutathione depletion in humans

The time course of excretion of acetaminophen and its metabolites in urine was determined in eight healthy adults (seven men and one woman) who ingested 1 gm of the drug and collected timed urine samples for 24 hours. The mean time of peak excretion rate was 1.3 to 3.7 hours for acetaminophen, its glucuronide, sulfate, cysteine, mercapturate, and methoxy metabolites but 13.5 hours for methylthioacetaminophen. The mean half-life of acetaminophen was 3.1 hours and the mean half-life of the metabolites other than methylthioacetaminophen ranged from 4.1 to 5.7 hours. The half-life of methylthiometabolite could not be determined because of its very late peak time. In a second study the effect of dose on the clearance of acetaminophen was determined in nine healthy adult subjects (eight men and one woman) who received doses of 0.5 and 3 gm acetaminophen on separate occasions, separated by 4 to 10 days. The renal clearance of acetaminophen and the formation clearances of the sulfate, glutathione, and catechol metabolites were lower (by 38%, 41%, 35%, and 46%, respectively) at the higher dose. The renal clearance of acetaminophen sulfate and glucuronide conjugates were not different between doses. In a third study (10 men), 10 gm *N*-acetylcysteine was found to increase the formation clearance of the sulfate conjugate by 27% and that of the glutathione conjugate by 10%. The data suggest that the hepatic supply of reduced glutathione and 3′-phosphoadenosine 5′-phosphosulfate begins to be depleted over the range of 0.5 to 3 gm acetaminophen and that the depletion is overcome by the administration of *N*-acetylcysteine. (CLIN PHARMACOL THER 1987;41:413-8.)

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The hepatotoxicity caused by the ingestion of large doses of acetaminophen, a popular analgesic and antipyretic drug, arises as a consequence of the oxidative metabolism of the drug to the putative reactive intermediate, *N*-acetyl-*p*-benzoquinoneimine (NAPQI).[1-6] Under normal circumstances, NAPQI is eliminated through conjugation with glutathione, eventually resulting in cysteine, mercapturic acid, and methylthiometabolites that are found in urine.[5-7] Evidence obtained from experimental animals suggests that when acetaminophen is administered in large doses, hepatic stores of glutathione become depleted resulting in the covalent binding of NAPQI to hepatic macromolecules and cellular necrosis.[5,8] The evidence of the mechanism of toxicity of acetaminophen obtained in experimental animals forms the basis for the administration of *N*-acetylcysteine, a precursor of glutathione, in cases of acetaminophen overdose.[9-14]

Although *N*-acetylcysteine has proved to be a very effective antidote to acetaminophen intoxication in humans, no direct evidence that acetaminophen ingestion might result in the depletion of hepatic stores of glutathione has been obtained. In experimental animals the depletion of glutathione is reflected in the diminished recovery of glutathione-derived acetaminophen conjugates in urine as acetaminophen dose increases.[3,15] Dose dependence of nontoxic routes of acetaminophen elimination (i.e., formation of glucuronide and sulfate conjugates) has been established in humans.[16] Saturation of sulfation occurs at relatively low doses of the drug, could contribute to toxicity, and is reversed by the administration of *N*-acetylcysteine.[9,17,18]

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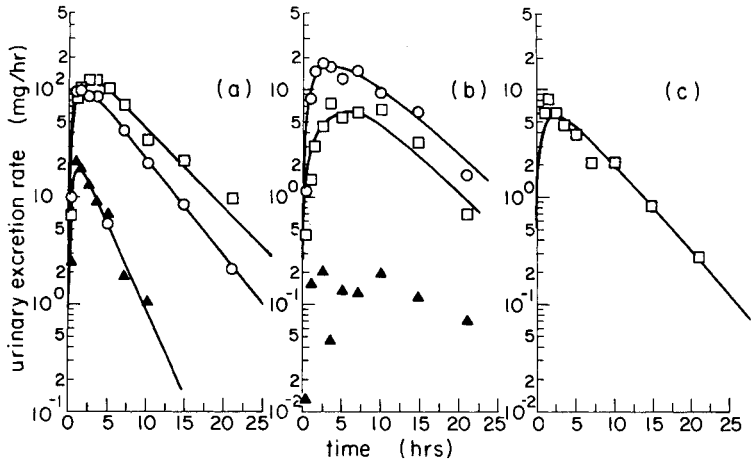

Fig. 1. Time course of the appearance of acetaminophen and its metabolites in the urine of a single subject. This subject is generally representative for compounds other than 3-methylthioacetaminophen. *Panel a,* acetaminophen and direct conjugates: acetaminophen, ▲; acetaminophen glucuronide, □; acetaminophen sulfate, ○. *Panel b,* glutathione-derived conjugates: 3-methylthioacetaminophen, ▲; 3-cysteineacetaminophen, □; 3-mercapturate acetaminophen, ○. *Panel c,* catechol derived: 3-methoxyacetaminophen, □.

Studies of the pattern of metabolites recovered in the urine of patients who had ingested overdoses of acetaminophen clearly indicate the saturation of the sulfation pathway.[12,16,19,20] The data regarding the glutathione pathway are not clear, however. Patients who have ingested large doses of acetaminophen and who have received only supportive treatment exhibit greater recoveries of glutathione-derived conjugates as their degree of liver impairment or dose increased.[12,16,20] This finding may reflect a greater oxidative capability among such individuals rather than a lack of depletion of glutathione[15]; thus data in patients do not support or refute depletion of glutathione. One study in healthy volunteers has reported the recovery of acetaminophen mercapturate at doses of 0.9 to 1.8 gm acetaminophen.[5] The fraction of dose recovered as the mercapturate conjugate (possibly representing the cysteine as well) remained constant over this two-fold range of dose; the fraction recovered as other metabolites was not determined. If this result were obtained in the presence of a saturated parallel pathway (e.g., sulfation), it would be consistent with capacity-limited formation of the glutathione conjugate. There are no data in humans that establish that the formation of the glutathione conjugate is capacity limited.

The purpose of the present study was to more completely characterize in humans the dose dependence of acetaminophen disposition over a range of dose at which saturation of sulfation has previously been observed but in which toxicity does not occur. Since the time course of the excretion of the glutathione-derived conjugates of acetaminophen in humans has not been reported, a preliminary study of the urinary kinetics of acetaminophen and its metabolites was carried out before addressing the question of dose-dependent elimination.

MATERIAL AND METHODS

Time course of metabolite excretion in urine. Eight healthy adults (seven men and one woman) received a 1.0 gm dose of acetaminophen (Tylenol, McNeil Laboratories, Inc., Fort Washington, Pa.). Urine was collected just before the dose was ingested and at 0.75, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hours after ingestion. Volume of urine was determined and an aliquot was frozen before analysis for acetaminophen and its metabolites (performed on the following day). The assay was calibrated with authentic standards each day. Half-life ($t_{1/2}$) and peak rate of appearance in urine were determined from excretion rate plots according to standard methods.

Dose dependence of acetaminophen elimination. Nine healthy adults (eight men and one woman; weight 71.9 ± 7.4 kg, mean ± SD) received 0.5 and 3.0 gm doses of Tylenol on separate occasions at least 4 days and no more than 10 days apart in a balanced crossover design. The subjects fasted for 12 hours before ingesting the drug and were allowed a light breakfast 2 hours

thereafter. A heparin lock was placed in a forearm vein for blood sampling. Blood samples (5.0 ml over Na EDTA) were withdrawn immediately before and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours after ingestion.

Samples were centrifuged and the plasma was refrigerated until analyzed (within 72 hours); degradation of acetaminophen and its sulfate and glucuronide conjugates is not detectable under these conditions during a period of 5 days (data not shown). Before ingesting the drug, subjects emptied their bladders and collected a blank urine sample over ascorbic acid. Urine was then collected for the following 24 hours over 3.0 g of ascorbic acid and was maintained at 0-5° C during that period. After the final collection, the total urine volume was measured and a 100 ml aliquot withdrawn and stored at −70° C until analyzed by HPLC.

Effect of N-acetylcysteine administration. A separate panel of 10 healthy male adults (weight 74.7 ± 7.2 kg) fasted for 12 hours before drug administration and for 2 hours after. In balanced crossover design, the subjects received either 240 ml of cola beverage followed by 3.0 gm acetaminophen or 10.0 gm *N*-acetylcysteine as a 20% solution (Mucomyst, Mead Johnson & Co., Evansville, Ill.) followed by 240 ml of cola beverage and 3.0 gm acetaminophen. Urine and blood were collected as in the study of dose dependence.

Analytic methods. Acetaminophen and metabolites in urine were assayed by an HPLC method.[21] Plasma (0.7 ml) was added to a 1.5 ml microcentrifuge tube containing 0.7 ml 1.0 mol/L $HClO_4$. The tube was vortexed for 2 minutes and centrifuged at 12,000 g for 4 minutes, after which 0.8 ml of the supernatant was transferred to a second microcentrifuge tube and 0.4 ml 1.0 mol/L K_2HPO_4 was added. The tube was shaken for 30 seconds and centrifuged at 12,000 g for 2.0 minutes. Five microliters of the supernatant was injected into the HPLC.

Acetaminophen total plasma clearance (CL) was calculated from the AUC. Formation clearance of the various metabolites and the renal clearance (CL_R) of acetaminophen was calculated as the product of the fraction of the dose found in the urine as the respective compound and the CL. CL_R of acetaminophen sulfate and glucuronide was calculated as the ratio of the amount of that conjugate found in urine to the AUC of the respective conjugate. The amount of the glutathione conjugate found (i.e., formed) was calculated as the sum of the 3-cysteine, 3-mercapturate, and 3-methylthioconjugates and the catechol metabolite as the sum of 3-hydroxy- and 3-methoxy-acetaminophen. Peak time was taken as the time the highest concentration was observed. Half-life ($t_{1/2}$) was calculated from the slope (determined by linear regression) of the decline of log excretion rate, plotted as a function of time.

Table I. Pharmacokinetic parameters of acetaminophen and metabolites in humans after a 1 gm dose*

	Time to peak (hr)	*$t_{1/2}$ (hr)*
Acetaminophen	1.3 (0.34)	3.1 (0.78)
Acetaminophen glucuronide	2.9 (0.73)	4.1 (1.03)
Acetaminophen sulfate	1.7 (0.41)	4.1 (0.57)
3-Cysteine acetaminophen	3.8 (1.61)	5.7 (1.63)
Acetaminophen 3-mercapturate	3.7 (1.41)	5.6 (1.32)
3-Methylthioacetaminophen	13.5 (3.87)	ND
3-Hydroxyacetaminophen	ND	ND
3-Methoxyacetaminophen	2.0 (0.83)	5.2 (1.02)

ND, not determined; 3-hydroxyacetaminophen was not detected in most subjects.
*Mean (SE) of eight subjects.

RESULTS

Excretion rate profiles of acetaminophen and its metabolites after a 1gm oral dose in a representative subject are shown in Fig. 1. After the peak, the rate of excretion declined in an apparently log-linear fashion for all compounds. The $t_{1/2}$ of appearance and time of peak excretion rate of each compound are given in Table I. When all subjects are considered, the time of peak excretion rate of acetaminophen and the sulfate conjugate were similar (about 1 to 2 hours). The peak excretion rate for the methoxy, glucuronide, cysteine, and mercapturate metabolites occurred somewhat later (about 3 to 4 hours), but the excretion rate of the methylthiometabolite peaked very late (13.5 ± 3.87 hours). The mean value of the $t_{1/2}$ of acetaminophen was 3.1 hours, whereas the $t_{1/2}$s of the sulfate, glucuronide, cysteine, mercapturate, and methoxy metabolites were slightly longer (from 4.1 to 5.7 hours). Because of the relatively few samples collected after the peak, the $t_{1/2}$ of the methylthiometabolite could not be determined.

The effect of acetaminophen dose on formation clearances of its metabolites and its own CL_R and CL is given in Table II. The CL of acetaminophen was 22% lower after the higher dose, primarily because of the 41% lower formation clearance of the sulfate conjugate at the higher dose. The formation clearance of the glutathione conjugate was 35% lower at the higher dose. CL_R of acetaminophen was 38% lower at the higher dose, but the formation clearance of the glucuronide conjugate was unchanged. The dose of acetaminophen

Table II. Effect of acetaminophen dose on formation clearance of metabolites, acetaminophen CL_R, and CL

	CL (L/hr)	
	0.5 gm	*3.0 gm*
Renal	1.09 ± 0.429*	0.675 ± 0.199†
Glucuronide	11.5 ± 2.65	10.3 ± 2.51
Sulfate	6.83 ± 2.51	4.06 ± 1.07†
Glutathione	1.79 ± 0.351	1.17 ± 0.415†
Catechol‡	2.20 ± 1.04	1.19 ± 0.283†
Total	22.3 ± 2.45	17.3 ± 3.53†

*Mean ± SD; n = 9.
†Significantly different, paired t test; $P < 0.05$.
‡n = 6.

was completely accounted for by the urinary products assayed. The amount recovered was 101% ± 4.1% (mean ± SD) after the low dose and 99.5% ± 3.2% after the high dose.

The CL_R of the sulfate and glucuronide conjugates was not different between the two doses (Table III).

Table IV shows the effect of the oral administration of 10 gm *N*-acetylcysteine on the formation clearances of acetaminophen metabolites and the CL_R of the drug. The formation clearance of the sulfate conjugate was increased 27% by *N*-acetylcysteine administration, and that of the glutathione conjugate was increased 10%. The CL_R of acetaminophen and the formation clearances of other metabolites were not changed.

DISCUSSION

The results of the excretion rate studies (Fig. 1; Table I) are consistent with those reported by others for acetaminophen and its glucuronide and sulfate conjugates.[22,23] The urinary kinetics of the glutathione-derived conjugates are similar to those of the glucuronide (and to a lesser extent the sulfate) conjugate in that their appearance in the urine is rate limited by the excretion rather than the formation step. The very late peak of the methylthioconjugate is consistent with observations in the hamster.[15] Studies in the hamster suggest that the methylthioconjugate is formed after biliary excretion of the glutathione conjugate into the intestine.

The formation clearance results indicate dose dependence in the generation of all metabolites other than the glucuronide. CL_R of acetaminophen, but not that of its sulfate and glucuronide conjugates, also decreases with dose. Previous studies of the dose dependence of acetaminophen disposition in humans have shown that sulfation and have suggested that glucuronidation are

Table III. Effect of acetaminophen dose on CL_R of sulfate and glucuronide conjugates

Acetaminophen conjugate	*CL_R (L/hr)*	
	0.5 gm	*3.0 gm*
Sulfate*	11.2 ± 2.86	10.2 ± 1.5
Glucuronide	9.09 ± 2.13	8.89 ± 2.17

*n = 7 for sulfate; n = 9 for glucuronide (mean ± SD). Differences not significant between doses by paired t test.

saturable processes.[16] The saturation of sulfation is caused by the limited availability of inorganic sulfate, which is a precursor to 3′-phosphoadenosine 5′-phosphosulfate (PAPS), the cofactor required for the formation of sulfoconjugates.[24-26] In another group of 14 subjects, we have observed that the 24-hour urinary excretion of inorganic sulfate is approximately 30% less after a 3 gm dose of acetaminophen than after 0.5 gm.[27] The saturation of sulfoconjugation can be overcome by the administration of inorganic sulfate or of a thiol-containing amino acid (this effect was observed after the administration of *N*-acetylcysteine in this study), but the kinetics become enzyme limited at higher concentrations.[28,29] In a separate group of four subjects, 10 gm *N*-acetylcysteine increased the amount of inorganic sulfate excreted in urine over 24 hours after 3 gm acetaminophen by four-fold.[27] On the other hand, the formation clearance of acetaminophen glucuronide was not different between doses. Saturation of glucuronidation can be described by simple Michaelis-Menten kinetics and apparently occurs at doses higher than those that saturate sulfoconjugation or those used in this study.[22,23]

Data regarding the effect of dose on the formation of the glutathione-derived conjugates of acetaminophen in humans are available from studies of patients who have ingested overdoses of the drug. Although such patients generally receive *N*-acetylcysteine, some data are available from patients who have received supportive treatment only. In 1976 Davis et al.[19] published a study of metabolite recovery in 30 patients who had ingested doses of up to 26 gm acetaminophen. These data allowed the construction of a pharmacokinetic model of elimination of acetaminophen in humans that encompassed toxic doses.[16] The data and model suggested that the formation of the glutathione conjugate was consistent with linear kinetics and that the recovery of the glutathione-derived conjugates of acetaminophen would increase more than proportionately with dose, a result that seemed to contradict the depletion of glu-

tathione expected to occur based on studies in experimental animals.[8]

Prescott[12] and Forrest et al.[20] have also studied the recovery of acetaminophen metabolites in the urine of patients who have taken an overdose and received supportive treatment only. The studies included three groups of individuals: healthy subjects who took a 20 mg/kg dose, patients who ingested an overdose but did not develop hepatotoxicity, and patients who ingested an overdose but developed severe hepatotoxicity. Recovery of the glutathione-derived conjugates in the urine of patients who had taken an overdose who did not develop liver damage was slightly (16%) less than that of the healthy volunteers. The amount of acetaminophen-derived material in the urine (an index of dose) of the overdosed but nonintoxicated patients was approximately eight times that recovered from the healthy subjects. In patients who developed severe liver damage (and from whom the amount of acetaminophen-derived material recovered in urine was similar to that recovered from patients who did not develop liver toxicity), the fraction recovered as glutathione-derived conjugates was approximately twice that of the nonhepatotoxic patients and healthy subjects. A possible explanation is that patients who develop hepatotoxicity at a given dose of acetaminophen may have a greater propensity to form the toxic intermediate than those patients who do not develop toxicity, for genetic or environmental reasons. The possibility that the results are confounded because the individuals comprising the groups differ in oxidative capability prevents conclusions regarding the effect of dose on the recovery of glutathione-derived conjugates from studies of patients.

Finally, Mitchell et al.[8] have studied the recovery of acetaminophen mercapturate over a two-fold range of acetaminophen dose (0.9 to 1.8 gm) in a group of 12 healthy adults and found that the fraction of dose recovered as the mercapturate conjugate did not change over this dose range. However, inasmuch as the formation of acetaminophen sulfate becomes saturated at these doses, the constant fraction recovered as the mercapturate conjugate may indicate a capacity limitation of the glutathione pathway.

The crossover design, six-fold range of dose, and determination of the formation clearance of several metabolites were included in the present study to overcome the difficulties encountered in the previous studies. The lower formation clearance of glutathione conjugates at the 3 gm dose in our study is consistent with results of urinary excretion studies in mice[3] and hamsters.[3,15] In rats the recovery of the mercapturate conjugate has been reported to remain constant over a dose range of 50 to 1200 mg/kg[3] but has also been reported to increase about 50% over a dose range of 20 to 600 mg/kg.[30] In the former report the constant fraction recovered as acetaminophen mercapturate occurred in spite of an increased fraction recovered as acetaminophen glucuronide and free acetaminophen (by about 50% and 100%, respectively) and saturation of the formation of acetaminophen sulfate (fraction decreased three-fold). In the latter report the increase in the recovery of the mercapturate was much less than the increases in the recovery of acetaminophen glucuronide and free acetaminophen (both about four-fold) but also occurred in the presence of a decline in the fraction recovered as acetaminophen sulfate (about three-fold). Thus the studies in rats suggest that the formation clearance of the glutathione-derived conjugates declines as dose increases, as suggested in mice and hamsters and as shown for humans in this study.

Table IV. Effect of 10 gm *N*-acetylcysteine on acetaminophen CL_R and metabolite formation clearances*

	Clearance (L/hr)	
	Control	*NAC*
Renal	0.621 ± 0.159	0.649 ± 0.180
Glucuronide	11.8 ± 2.74	11.6 ± 2.59
Sulfate	4.35 ± 1.15	5.53 ± 1.40†
Glutathione	1.20 ± 0.249	1.32 ± 0.300‡
Catechol	1.23 ± 0.730	1.20 ± 0.312
Total	19.3 ± 3.00	20.3 ± 2.59†

NAC, *N*-acetylcysteine.
*3.0 gm acetaminophen; n = 10, mean ± SD.
†$P < 0.005$, paired t test.
‡$P < 0.05$, paired t test.

It is noteworthy that the mechanism of the dose-dependent decrease in the formation clearance of the glutathione conjugate apparently differs from that of the catechol metabolite, because only the former is reversed by *N*-acetylcysteine administration. The data suggest that the form of cytochrome P-450 involved in the formation of the catechol metabolite may become saturated as acetaminophen dose is increased. The mechanism for the decrease in formation clearance of the glutathione conjugate of acetaminophen is not completely clear, but its reversal by the administration of *N*-acetylcysteine suggests the involvement of glutathione depletion. Depletion of glutathione could compromise the conjugation of NAPQI or promote the destruction of the form of cytochrome P-450 involved in the formation of NAPQI.

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