Acetaminophen kinetics in acutely poisoned patients

A kinetic model of acetaminophen elimination over a wide dose range has been developed on the basis of (1) kinetic data from normal adults who received a usual dose (up to 2 gm) of the drug and (2) the composition of urinary metabolites of acetaminophen excreted within 24 hr by 29 patients who had ingested up to 26 gm of acetaminophen in suicide attempts (including 2 that were fatal and 5 with evidence of severe intoxication). The model consists of the following parallel pathways: conjugation with glucuronide by Michaelis-Menten kinetics, conjugation with sulfate by Michaelis-Menten kinetics, renal excretion of acetaminophen by apparent first-order kinetics, and formation of an oxidative metabolite (which is responsible for the hepatotoxicity of acetaminophen) by apparent first-order kinetics. There is good agreement between the model-predicted and actual urinary excretion of individual acetaminophen metabolites for doses of 0.8 to 26 gm and between model-predicted and actual plasma acetaminophen concentrations in both the low (normal subjects) and high (intoxicated subjects) concentration ranges. Computer simulations indicate that unsaturation of acetaminophen sulfate formation, previously shown to be feasible in vivo, should decrease the formation of the hepatotoxic metabolite. This prediction is consistent with experimental data obtained in preliminary studies on mice.

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Acetaminophen is a widely used nonnarcotic analgesic and antipyretic drug with an excellent record of safety when taken in usually recommended doses for limited periods of time. However, accidental or intentional ingestion of large amounts of the drug can cause serious, often irreversible and fatal hepatotoxicity, as well as necrosis of other vital organs.[9] Due to the popularity of this useful nonprescription drug, the incidence of acetaminophen intoxications has been substantial and appears to be increasing.[2, 27]

Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates.[1a, 2, 13, 22, 24] Other quantitatively less important pathways include renal excretion of unmetabolized drug and formation of *N*-hydroxyacetaminophen. The latter appears to be converted to a reactive metabolite, acetimidoquinone,[4] which is metabolized primarily to a glutathione conjugate (with subsequent conversions to cysteine and mercapturic acid conjugates of acetaminophen) but which can bind covalently to tissue macromolecules,[7, 21] causing necrosis of hepatic and other tissues. Studies in animals have revealed a limited availabil-

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ity of glutathione, resulting in more extensive covalent binding of the reactive metabolite upon depletion of glutathione after administration of large doses of acetaminophen.[20, 21]

Specific treatment of acetaminophen intoxication is based largely on the results of biochemical studies in animals and is directed to the prevention of glutathione depletion or the inhibition of the oxidative biotransformation of acetaminophen.[6, 21] Little or no attention has been given to the feasibility and utility of reducing the fraction of an acetaminophen dose converted to the oxidative metabolite by enhancing one of the parallel and therefore competing processes of acetaminophen elimination. Consideration of these possibilities and a better understanding of the events associated with acetaminophen intoxication should be facilitated by the availability of a kinetic model of acetaminophen elimination that encompasses not only the elimination kinetics of usual therapeutic doses but also of doses large enough to cause severe intoxication and death.

Man has a limited capacity to conjugate phenolic drugs with sulfate. Results of earlier studies in this laboratory suggested that acetaminophen sulfate formation may become capacity-limited (saturable) upon administration of a 2-gm dose to adults.[15] Concomitant administration of salicylamide[15] or ascorbic acid,[5] both of which are partly converted to sulfate metabolites, causes inhibition of acetaminophen sulfate formation in man. This inhibition can be prevented by oral administration of a sulfate donor[15] or of inorganic sulfate,[5] showing that the availability of sulfate, rather than its subsequent activation or transfer to the phenolic substrate, is rate-limiting in the formation of phenolic sulfate.

Man also has a limited capacity to form certain phenolic glucuronides, including those of salicylamide[12] and salicylic acid.[14] It has not been feasible to obtain direct evidence of this saturability in the case of acetaminophen because of potential hazards of administering sufficiently large doses to human subjects. There is, however, some indirect evidence. Concomitant administration of acetaminophen and salicylamide causes a transient decrease of acetaminophen glucuronide formation.[15] Inhibition of acetaminophen sulfate formation by concomitant administration of ascorbic acid causes an increase in the fraction of acetaminophen excreted as such and as the glucuronide, but the relative increase of the latter is not as large as that of the former.[5] Were renal excretion and glucuronide formation linear processes, the increase in their urine fractions should be equal upon inhibition of sulfate formation.

Several groups of investigators [1, 1a, 13, 22, 24] have characterized the kinetics of acetaminophen in the usual therapeutic dose range (single doses up to 2 gm) where the overall elimination kinetics are apparently linear. These investigations cannot be extended to larger doses except by studying patients who have, on their own, taken overdoses. A conventional assessment of acetaminophen elimination kinetics in severely overdosed patients may be compromised by liver damage which may ensue before all drug and metabolites have been eliminated from the body. We will describe here the development of a pharmacokinetic model based on (1) pharmacokinetic data previously obtained in this and other laboratories from studies on adult subjects who had taken usual doses of the drug and (2) metabolic data obtained by Davis and coworkers,[2] who determined the composition of urinary metabolites of acetaminophen during the first 24 hr and the total urinary recovery of these metabolites in patients, some of whom had taken very large doses in suicide attempts.* Urinary excretion and plasma concentration data predicted by computer simulations based on the pharmacokinetic model have been compared to actual data over a wide dose range, and the potential utility of "unsaturating" acetaminophen sulfate formation to reduce the formation of the reactive metabolite of acetaminophen has been examined.

Theoretical considerations

Based on the available evidence suggestive of capacity-limited formation of acetaminophen glucuronide and acetaminophen sulfate, it was assumed that the elimination of acetaminophen

*We thank Dr. M. Davis and colleagues of the Liver Unit, King's College Hospital and Medical School, Denmark Hill, London, United Kingdom, for making the individual data from their published report available to us.[2]

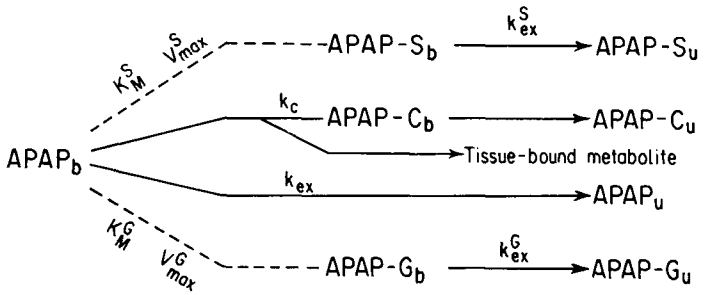

Fig. 1. Kinetic model of acetaminophen (APAP) elimination in man. Conjugates are identified as: *S*, sulfate; *G*, glucuronide; *C*, cysteine and mercapturic acid. The subscripts *b* and *u* refer to drug or conjugate in the body and urine, respectively. K_M is the in vivo Michaelis-Menten constant. V_{max} is the maximum velocity for formation of the conjugate or other proximate metabolite. Abbreviations are further defined in Tables I and II.

from the body can be described by the kinetic model in Fig. 1. The model consists of four parallel elimination processes: formation of acetaminophen glucuronide and acetaminophen sulfate by Michaelis-Menten kinetics, urinary excretion of unmetabolized acetaminophen by apparent first-order kinetics, and oxidative biotransformation of acetaminophen by apparent first-order kinetics (designated by rate constant k_c) to a metabolite that is eventually transformed to (and excreted as) cysteine and mercapturic acid conjugates of acetaminophen. These conjugates therefore serve as a measure of the amount of metabolite formed by oxidative biotransformation of acetaminophen. Even if some of the reactive metabolite of acetaminophen is covalently bound to tissue macromolecules, the available evidence[7] indicates that this would be quantitatively negligible relative to the amount of acetaminophen ingested or converted to cysteine and mercapturic acid conjugates.

It is assumed that the urinary excretion of the various conjugates of acetaminophen is describable by apparent first-order kinetics, although this assumption, as well as the assigned values for the excretion rate constants, is not essential for the intended data analysis (acetaminophen metabolite composition as a function of dose) with the possible exception of doses so large that excretion of metabolites is not substantially completed during the first 24 hr.

The apparent in vivo Michaelis-Menton parameters in the model designate the kinetic characteristics of the rate-limiting step in the sequence of processes that result in the formation of a proximate metabolite of acetaminophen. In the case of acetaminophen sulfate formation, the rate-limiting process appears to be the mobilization or supply of sulfate for activation to 3′-phosphoadenosine-5′-phosphosulfate (PAPS) rather than the activation itself or the transfer of activated sulfate to the drug substrate.[5, 14] It is also assumed and implied in the model that the kinetics of acetaminophen disposition are not time-dependent and that the rate-limiting processes for formation of proximate metabolites do not change as a function of drug concentration.

Studies in animals have shown that glutathione can be depleted by large doses of acetaminophen.[20, 21] Time-dependent and probably capacity-limited formation of the glutathione conjugate of acetaminophen may therefore occur in man. This is immaterial for the intended data analysis because the glutathione conjugate is not a proximate metabolite of acetaminophen and because competing pathways for elimination of its precursor appear to be quantitatively negligible.[16]

In our analysis, no consideration has been given to the rate of absorption of the ingested acetaminophen.[1] There is some indication that even very large doses of the drug are absorbed quite rapidly.[26] It will be shown subsequently that substantial differences in absorption rate should have a very small effect on the 24-hr composition of urinary metabolites of acetaminophen.

Table I. *Source of kinetic constants used in simulations*

Source	Number of subjects	Apparent first-order rate constants,*† hr^{-1}					
		k_f^S	k_f^G	k_{ex}^S	k_{ex}^G	k_{ex}	K
Cummings et al.[1a]	4	0.070-0.090	0.13-0.16	1.25-1.50	0.47-1.01	0.010-0.014	0.27-0.35
Levy and Regårdh[13]	5	0.059-0.093	0.12-0.26			0.004-0.012	0.25-0.43
Nelson and Morioka[22]	5						0.24-0.43
Prescott et al.[24]	8						0.23-0.46

*k, First-order rate constant; f, formation; S, sulfate conjugate; G, glucuronide conjugate; ex, urinary excretion (no superscript refers to unchanged drug); K, overall elimination rate constant of drug = 0.693/t½.

†Range of values reported in the cited studies.

Methods

Apparent first-order rate constants for renal excretion of acetaminophen (k_{ex}) and for formation of acetaminophen glucuronide (k_f^G) and acetaminophen sulfate (k_f^S) were obtained from two studies[1a, 13] on a total of 9 normal adults. The apparent first-order rate constant for elimination of acetaminophen (K) was obtained from four studies[1a, 12, 21, 22] on a total of 22 normal adults. The apparent first-order rate constants for renal excretion of acetaminophen glucuronide (k_{ex}^G) and acetaminophen sulfate (k_{ex}^S) are based on data from 4 subjects studied by Cummings, King, and Martin.[1a] The ranges of reported values for all these constants are shown in Table I. The individual values for each of the constants were averaged to obtain first estimates for the model.

A first estimate of the apparent first-order rate constant for oxidation of acetaminophen (k_c) was made by subtracting the sum of k_{ex}, k_f^G, and k_f^S from K. This yielded a value of 0.065 hr^{-1}, which is relatively high compared to the K value of 0.35 hr^{-1}. It was recognized that this may be an overestimate due to the possible presence of other minor metabolic routes or incomplete urinary recovery of acetaminophen and metabolites in the urine. Mitchell and coworkers[21] recovered about 4% of 0.9 to 1.8 gm doses of acetaminophen as acetaminophen mercapturic acid from 10 subjects. They also detected but did not quantify a small amount of the cysteine conjugate of acetaminophen. Based on this information and on the results of initial simulations which overpredicted the amounts of cysteine and mercapturic acid conjugates excreted by the subjects in the study of Davis and co-workers,[2] k_c was reduced to 0.0325 hr^{-1} and k_{ex}, k_f^S, and k_f^G were increased proportionately so that the sum of these four constants remained 0.35 hr^{-1}.

Table II. *Value of constants for the kinetic model of acetaminophen elimination in man*

Kinetic constant*	Value
K_M^S, mmole (gm)	7.14 (1.08)†
K_M^G, mmole (gm)	13.4 (2.02)
V_{max}^S, mmole/hr (gm/hr)	0.650 (0.0982)
V_{max}^G, mmole/hr (gm/hr)	2.80 (0.423)
k_{ex}^S, hr^{-1}	1.26
k_{ex}^G, hr^{-1}	0.624
k_c, hr^{-1}	0.039
k_{ex}, hr^{-1}	0.012

*K_M, In vivo Michaelis constant; V_{max}, maximum rate of formation; k_c, apparent first-order rate constant for formation of *N*-hydroxyacetaminophen; other definitions as in Table I.

†All values in parentheses expressed in terms of acetaminophen.

Estimates of the maximum formation rates (apparent in vivo V_{max}) of acetaminophen glucuronide and acetaminophen sulfate were made on the basis of the individual data from the study of Davis and co-workers.[2] Examination of the amounts of acetaminophen glucuronide and sulfate excreted in 24 hr as a function of dose revealed a curvilinear relationship. The patient who took the largest dose (50 gm) is a special case that will be considered separately. The 24-hr excretion data from the patient who took the next-to-largest amount of acetaminophen (26 gm) were consistent with data from the remainder of the group and served as estimates of V_{max} values for formation of acetaminophen glucuronide and sulfate. The amount of acetam-

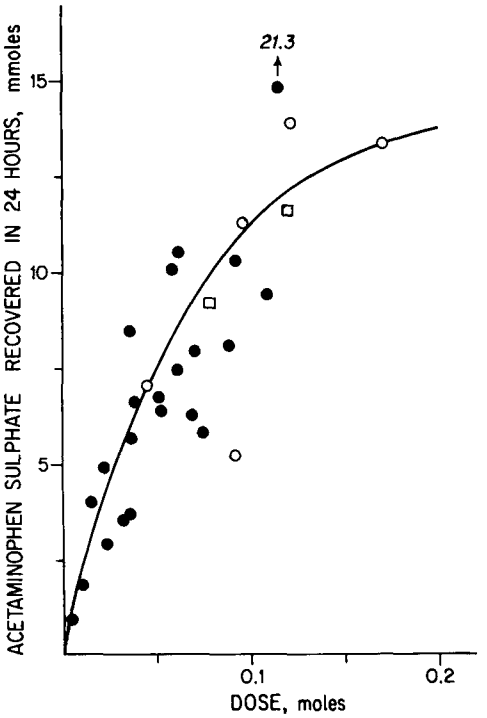

Fig. 2. Theoretically predicted *(solid line)* and reported amounts of acetaminophen sulfate recovered in the urine of 29 patients in 24 hr as a function of acetaminophen dose. *Solid circles,* Patients with symptoms of minimal, mild, and moderate intoxication; *open circles,* patients with symptoms of severe intoxication who recovered; *open squares,* patients with symptoms of severe intoxication who expired subsequently. Actual urinary excretion data in this and subsequent figures from a study by Davis and co-workers.[2] Correlation between predicted and actual amounts: $r = 0.786$ ($p < 0.001$); without the data point with arrow, $r = 0.841$ ($p < 0.001$). One-tenth mole of acetaminophen equals 15.1 gm.

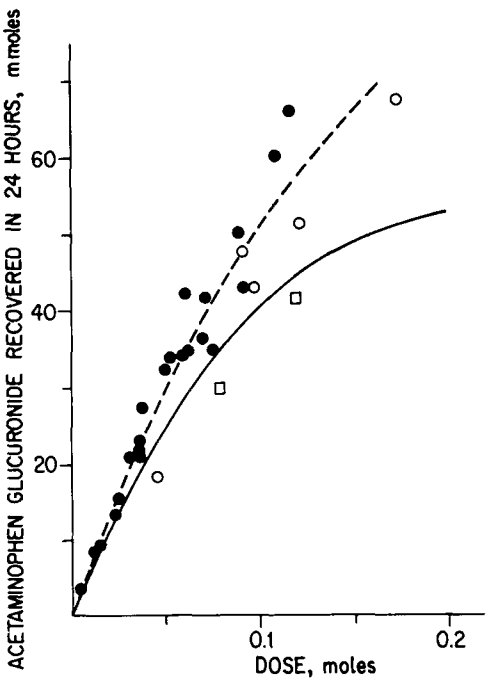

Fig. 3. Theoretically predicted *(solid line)* and reported amounts of acetaminophen glucuronide recovered in the urine of 29 patients in 24 hr as a function of acetaminophen dose. *Stippled line,* Predicted sum of acetaminophen glucuronide and acetaminophen excreted in 24 hr as a function of acetaminophen dose. All symbols as in Fig. 2. Correlation: *Solid line,* $r = 0.639$ ($p < 0.001$); *stippled line,* $r = 0.944$ ($p < 0.001$).

inophen in the body of the latter patient at 24 hr was about 4 times the estimated apparent in vivo Michaelis constant (K_M) for acetaminophen sulfate and about twice the estimated K_M for acetaminophen glucuronide. The K_M values were calculated on the basis of the relationships

$$K_M^G = V_{max}^G/k_f^G \text{ and } K_M^S = V_{max}^S/k_f^S \quad (1)$$

using the adjusted averaged values of k_f^G and k_f^S.

Digital computer simulations were carried out with a CYBER 173 computer using the program MIMIC[18] and the kinetic model and constants in Fig. 1 and Table II, respectively.

The time-course of the amount of acetaminophen in the body ($APAP_b$) was determined on the basis of the following equation which relates the rate of change of $APAP_b$ to the four parallel elimination processes

$$\frac{dAPAP_b}{dt} = -(k_c + k_{ex})(APAP_b) - \frac{V_{max}^S\, APAP_b}{K_M^S + APAP_b} - \frac{V_{max}^G\, APAP_b}{K_M^G + APAP_b} \quad (2)$$

The urinary excretion of acetaminophen sulfate was determined on the basis of the equation

$$\frac{dAPAP\text{-}S_b}{dt} = \frac{V_{max}^S\, APAP_b}{K_M^S + APAP_b} - k_{ex}^S\,(APAP\text{-}S_b) \quad (3)$$

which describes the rate of change of acetaminophen sulfate in the body ($APAP\text{-}S_b$) and the equation

$$\frac{d\text{APAP-S}_u}{dt} = k_{ex}^{S}\ (\text{APAP-S}_b) \qquad (4)$$

which characterizes the excretion process. Analogous equations were used for acetaminophen glucuronide. An equation analogous to Equation 4 characterizes the urinary excretion of acetaminophen itself. The rate of oxidation of acetaminophen is equal to k_c ($APAP_b$). Since rate constants for the subsequent processes leading to the formation of the cysteine and mercapturic acid conjugates of acetaminophen and their urinary excretion were not available, excretion was assumed to be rate-limited by formation. The fraction of the dose converted to these conjugates was taken to be equal to the fraction converted to the oxidized metabolite.

Results

The theoretically predicted and the observed amounts of acetaminophen sulfate recovered in the urine of 29 patients in 24 hr as a function of dose are shown in Fig. 2. There is a very good correlation between the predicted and observed excretion of acetaminophen sulfate over a wide (0.8 to 26 gm) dose range. There was no apparent separation of data obtained from patients with minimal to moderate intoxication on one hand and patients with severe intoxication on the other.

The theoretical estimates of acetaminophen glucuronide output were somewhat lower than the reported values, particularly at high doses (Fig. 3). On the other hand, there is a strong correlation between the reported data and the predicted output of acetaminophen glucuronide and free acetaminophen combined. Patients with severe intoxication tended to excrete somewhat less acetaminophen glucuronide than moderately intoxicated patients who had taken comparable amounts of the drug.

Fig. 4 is a plot of the theoretically predicted and the observed 24-hr excretion of cysteine and mercapturic acid conjugates of acetaminophen as a function of dose. Both the predicted and actual amounts increase more than proportionately with increasing dose. In contrast, the excreted amounts of acetaminophen glucuronide and sulfate increase less than proportionately with increasing dose. Severely intoxicated patients excreted relatively more of

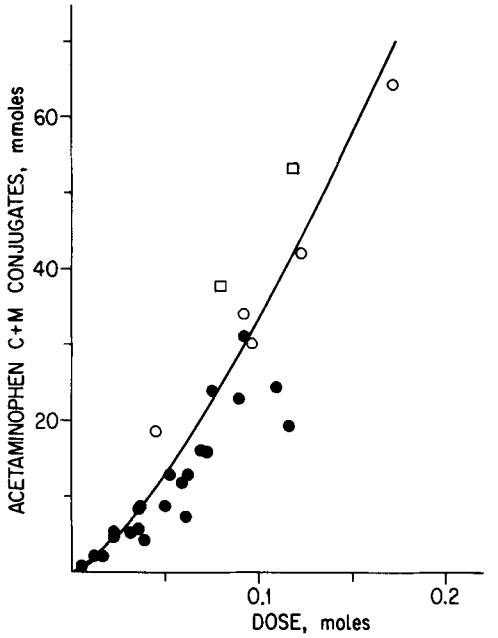

Fig. 4. Theoretically predicted *(solid line)* and reported amounts of cysteine and mercapturic acid conjugates of acetaminophen (derived from the oxidative metabolite of acetaminophen) recovered in the urine of 29 patients in 24 hr as a function of acetaminophen dose. All symbols as in Fig. 2. Correlation: $r = 0.915$ ($p < 0.001$).

the cysteine and mercapturic acid conjugates (and, by inference, formed more of the reactive metabolite of acetaminophen) than the minimally to moderately intoxicated patients who had taken comparable amounts of the drug.

The computer simulations predict a pronounced dose dependence of acetaminophen elimination (Fig. 5). While the predicted elimination kinetics are not exponential, experimental data could easily be mistaken for such. Biologic half-life ($t_{1/2}$) values determined on that premise are about 3 hr, 6.5 hr, and 15 hr for the 1, 10, and 100 gm dose, respectively.

The metabolic fate of acetaminophen, as predicted by the computer simulations and as evident in the data of Davis and co-workers,[2] is dose-dependent. The results of the computer simulations over a dose range of 1 to 32 gm of acetaminophen show that the fractions of the dose excreted as acetaminophen and as the cysteine and mercapturic acid conjugates of acetaminophen increase more than threefold, the

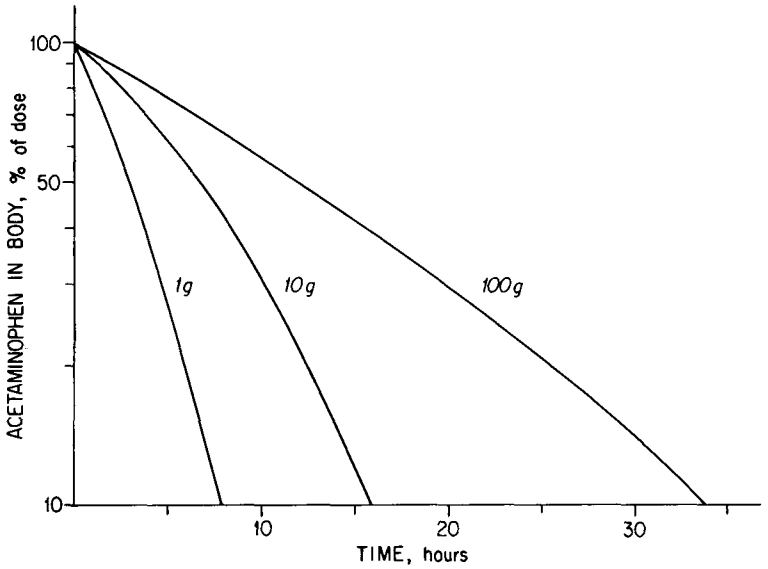

Fig. 5. Predicted relative time-course of acetaminophen elimination from the body as a function of dose, based on the kinetic model in Fig. 1 and the constants in Table II. It is assumed that hepatotoxicity, which usually becomes clinically apparent several days after drug ingestion, does not affect the elimination kinetics during the time periods of the simulations.

Table III. *Predicted relationship between dose and metabolic fate of acetaminophen in adults**

	Composition of urinary excretion products, percent of dose			
Dose (gm)	*Acetaminophen (A)*	*A glucuronide*	*A sulfate*	*C and M conjugates† of A*
1	4.27	59.4	22.5	13.9
2	5.01	58.3	20.4	16.3
4	6.26	55.6	17.8	20.4
6	7.32	52.8	16.1	23.8
8	8.21	50.2	14.9	26.7
10	8.99	47.9	13.9	29.2
12	9.68	45.8	13.0	31.5
16	10.8	42.2	11.7	35.2
32	13.8	32.7	8.66	44.8

*Based on the pharmacokinetic model shown in Fig. 1 and the constants listed in Table II.

†Cysteine and mercapturic acid conjugates of acetaminophen.

fraction excreted as acetaminophen glucuronide decreases by 45%, and that excreted as acetaminophen sulfate decreases by 61% over that dose range (Table III). It is apparent that there is only a modest change in the composition of urinary excretion products at doses up to 4 gm, so that it will be relatively difficult if not impossible to demonstrate the dose dependence in normal volunteers.

Prescott and co-workers[26] have determined plasma concentrations of acetaminophen at two points in time, 8 hr apart, in groups of patients who developed liver damage, patients who did not develop liver damage, and normal subjects, respectively. These concentrations, which are in the high, intermediate, and low range, have been converted to amounts of drug in the body on the basis of an apparent volume of distribution of 850 ml/kg[25] and a body weight of 70 kg. The much slower elimination of acetaminophen

Table IV. *Urinary recovery of acetaminophen metabolites from one patient who took 331 mmoles (50 gm) of acetaminophen**

Acetaminophen metabolite	*Amount recovered in 24 hr (mmoles)*	
	Reported	*Theoretical†*
Sulfate	23.8	14.3
Glucuronide	175	57.1 (104)‡
Cysteine and mercapturic acid conjugates	95.3	154

*Dose based on total urinary recovery. Patient developed moderate liver damage and survived. Data supplied by Dr. M. Davis, from a published study.[2]

†Based on kinetic model depicted in Fig. 1.

‡Sum of glucuronide and free acetaminophen in parentheses.

by the intoxicated patients than by the normal subjects is in good agreement with the computer simulations (Fig. 6).

Since it is feasible under certain circumstances to "unsaturate" the process of acetaminophen sulfate formation by administration of inorganic sulfate or sulfate precursors, the effect of such unsaturation on the elimination kinetics of acetaminophen has been explored by substituting $(APAP_b)\ V^S_{max}/K^S_M$ for $V^S_{max}(APAP_b)/(K^S_M + APAP_b)$ in Equation 2. The results of these simulations (Fig. 6) indicate pronounced enhancement of acetaminophen elimination at doses of 10 gm or more. Associated with this effect is a corresponding decrease in the fraction of acetaminophen converted to the oxidative metabolite. For example, the predicted dose of acetaminophen necessary to produce 25 mmoles of reactive metabolite (which appears to be the amount above which most adult patients become severely intoxicated; see Fig. 4) is increased from about 12 gm to about 20 gm if sulfate formation is changed from capacity-limited to apparent first-order kinetics.

One patient in the group studied by Davis and co-workers[2] had taken 50 gm of acetaminophen (based on urinary recovery), substantially more than any other patient in the group, but developed only moderate liver damage. The composition of acetaminophen metabolites recovered in the urine of that patient differs markedly from theoretical predictions (Table IV). He formed

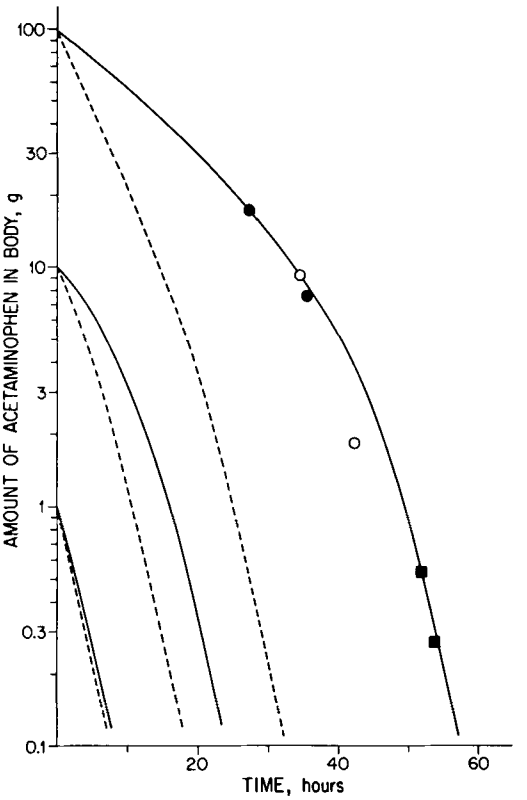

Fig. 6. Predicted absolute time-course of acetaminophen elimination from the body as a function of dose, based on the kinetic model in Fig. 1 and the constants in Table II *(solid lines)*. Also shown is the predicted time-course assuming "unsaturation" of the sulfate conjugation process as explained in the text *(stippled lines)*. *Symbols*, Amounts of acetaminophen in the body calculated from plasma concentrations reported by Prescott and co-workers[26] and assuming an apparent volume of distribution of 850 ml/kg.[25] The first of each pair of data points was placed on the kinetic model–derived curve and the second point was plotted 8 hr later (the time interval between the drug concentration data reported by Prescott and co-workers). *Solid circles*, Data from 17 patients who developed liver damage; *open circles*, data from 13 patients who did not develop liver damage; *solid squares*, data from 17 normal subjects.

much more of the glucuronide and sulfate conjugates and much less of the reactive metabolite-derived cysteine and mercapturic acid conjugates than predicted. Nevertheless, the amount of cysteine and mercapturic acid (i.e., reactive metabolite-derived) conjugates was considerably larger than that excreted by other

Table V. *Predicted effect of acetaminophen infusion rate on the urinary excretion of acetaminophen and its metabolites in man (15-gm dose*)*

Infusion		Amount recovered (mmole)							
		Acetaminophen (A)		A glucuronide		A sulfate		C and M conjugates† of A	
Rate (gm/hr)	Duration (hr)	24 hr	100 hr	24 hr	100 hr	24 hr	100 hr	24 hr	100 hr
Rapid injection		10.5	10.6	40.6	43.1	11.2	12.0	34.1	34.4
7.5	2	10.1	10.2	40.8	43.7	11.3	12.2	32.8	33.2
3.0	5	9.60	9.77	41.2	45.1	11.5	12.7	31.2	31.8
1.5	10	8.75	9.06	41.1	47.3	11.6	13.5	28.4	29.4

*99.3 mmoles.

†Cysteine and mercapturic acid conjugates.

patients who became severely intoxicated. Perhaps elimination of the reactive metabolite was also unusually rapid in this patient, thereby minimizing hepatotoxicity.

Discussion

Rational management of acetaminophen intoxication is likely to be facilitated by an understanding of the kinetics of acetaminophen elimination after very large doses. Rigorous quantitative characterization, by conventional methods, of the kinetics of acetaminophen elimination by severely intoxicated patients is almost impossible due to the presently employed therapeutic interventions, the hepatic damage which may cause a time-dependent change in the pharmacokinetics by affecting the terminal phase of drug elimination, and other practical difficulties. It was therefore necessary to use a different approach to develop a suitable pharmacokinetic model. Data from numerous investigations were combined to construct a quantitative model which was used to provide information that could be verified on the basis of available clinical data.* Specifically, the model was used to predict the composition of urinary metabolites of acetaminophen following ingestion of a wide range of doses of the drug. These predictions were found to be in very good agreement with actual clinical data.

The kinetic model consists of two saturable biotransformation pathways, conjugation of acetaminophen with glucuronic acid and with sulfate, as well as two apparent first-order processes, renal excretion of acetaminophen and oxidation of the drug to *N*-hydroxyacetaminophen, which in turn is converted to a reactive metabolite thought to be responsible for hepatic and other tissue injury. The limited capacity of the direct conjugation pathways causes a greater than proportional increase in the formation of the *N*-hydroxy compound with increasing dose. Provided that the subsequent conversion of this compound to the reactive metabolite is not capacity-limited and in parallel with a competing apparent first-order process (and there is no published evidence of either capacity-limited kinetics or a quantitatively significant competing pathway), the amount of reactive metabolite will also increase more than proportionately with increasing dose of acetaminophen. This prediction is consistent with the observations by Davis and co-workers[2] of proportionately increased urinary excretion of cysteine and mercapturic acid conjugates of acetaminophen with increasing dose.

The metabolic fate of drugs that are eliminated by parallel linear and nonlinear processes is affected by the rate of absorption.[10] The kinetic model developed in this investigation does not include an absorption step so that the simulations based on the model imply the assumption of instantaneous absorption. The possible error introduced by this assumption was examined by determining, by simulation, the quantitative metabolic fate of a 15-gm and a 50-gm dose of acetaminophen following rapid injection and constant rate infusion over 2, 5, and 10

*The model applies only to adults since the kinetics of acetaminophen elimination by adults and infants or children differ quantitatively.[11, 17]

Table VI. *Predicted effect of acetaminophen infusion rate on the urinary excretion of acetaminophen and its metabolites in man (50-gm dose*)*

Infusion		Amount recovered (mmole)							
		Acetaminophen (A)		A glucuronide		A sulfate		C and M conjugates† of A	
Rate (gm/hr)	Duration (hr)	24 hr	100 hr	24 hr	100 hr	24 hr	100 hr	24 hr	100 hr
Rapid injection		47.3	51.8	57.1	88.0	14.3	22.8	154	168
25	2	46.1	51.3	56.9	89.8	14.3	23.3	150	167
10	5	44.3	50.4	56.5	92.6	14.2	24.0	144	164
5	10	40.7	49.0	55.6	97.4	14.1	25.3	132	159

*330.9 mmoles.

†Cysteine and mercapturic acid conjugates.

hr (Tables V and VI). The different input rates had practically no effect on the amounts of acetaminophen glucuronide and acetaminophen sulfate excreted in 24 hr. This is a consequence of the limited capacity of these processes. On the other hand, protracted absorption will affect the urinary excretion of acetaminophen and the cysteine and mercapturic acid conjugates of acetaminophen. For example, constant rate input over 5 hr will reduce the amounts of these products excreted over 24 hr by almost 10%. In fact, the data in Fig. 4 are consistent with these considerations, i.e., the values for many of the patients are somewhat lower than the theoretical predictions.

Several groups of investigators[1a, 13, 22, 24] have recovered from about 2% to about 4% of usual doses (1 to 2 gm) of acetaminophen in unmetabolized form in the urine. Davis and co-workers[2] did not report the 24-hr output of unmetabolized acetaminophen in their patients but stated that the quantities were an insignificant fraction of the dose. Our predictions of the 24-hr output of acetaminophen glucuronide in the urine of these patients were lower than the actual data. On the other hand, very good agreement was obtained when it was assumed that the acetaminophen glucuronide assay used by Davis and co-workers[2] served also to determine acetaminophen itself. It is also possible that the small amounts of acetaminophen reported by previous investigators are due to partial hydrolysis or degradation of one or more of the acetaminophen conjugates.

It is interesting that the metabolic fate of acetaminophen in severely intoxicated patients does not differ strikingly from that in minimally to moderately intoxicated subjects. The most pronounced difference between these populations is in the amount of cysteine and mercapturic acid metabolites excreted; the severely intoxicated subjects tended to excrete relatively larger amounts of these conjugates which are derived from the hepatotoxic metabolite of acetaminophen. The cause-effect aspects of this apparent difference are not determinable from the available data. It is known that enzyme induction increases the hepatotoxicity of acetaminophen due to enhanced formation of reactive metabolite.[19] One may speculate that the severely intoxicated patients may have been exposed to enzyme inducers.

The longer apparent biologic t½ of acetaminophen in severely intoxicated patients has generally been attributed to hepatotoxicity. The results of our study suggest that an apparently prolonged biologic t½ of acetaminophen during the first day after ingestion of a large dose is a reflection of the capacity-limited pharmacokinetics of the drug. This does not exclude the possibility that subsequent hepatotoxicity could affect the later phases of elimination of the drug; in fact, plasma-acetaminophen concentration data reported by Prescott and co-workers[26] seem to reflect such an effect of liver damage. On the other hand, there is some evidence that acetaminophen concentrations in plasma of humans[23, 25, 26] and mice[20, 28] decline exponentially with time even after ingestion or administration of large doses, but with an increasing biologic half-life with increasing dose. However, the urinary metabolites excretion data

obtained in humans[2] and in rodents,[8] and acetaminophen conjugates concentration data in plasma of humans who have ingested large doses of the drug,[25] provide strong evidence for saturation of glucuronide and sulfate conjugate formation. These observations appear to be internally inconsistent. More intensive monitoring of plasma acetaminophen concentrations in the initial time period after administration or ingestion of large doses, determination of the plasma protein binding and distribution of acetaminophen in the body as a function of concentration and time, and other more detailed investigations will be required to resolve this question.

Pharmacokinetic analysis of the data by Davis and co-workers[2] does not definitively establish that, as is the case in mice and hamsters,[8] conjugation of the reactive metabolite of acetaminophen with glutathione was capacity-limited and time-dependent due to glutathione depletion in patients who had taken large doses. It appears, however, that such depletion of glutathione may not be substantial in man since otherwise the amount of the cysteine and mercapturic acid conjugates excreted by patients who took very large doses of the drug would have been less than predicted (Fig. 4). It must be cautioned, however, that this conclusion is based primarily on the urinary excretion data from the one subject who had taken 26 gm of acetaminophen and who should therefore have had significant amounts of the drug in the body even 24 hr after ingestion.

Exploration of the consequences of "unsaturating" the process of acetaminophen sulfate formation (Fig. 6) was based on the assumption that such a change can be simulated by assigning to the process an apparent first-order formation rate constant equal to V^S_{max}/K^S_M. Implied in this simulation is the assumption that the consequent possible change in the rate-limiting step of acetaminophen sulfate formation does not involve a new rate-limiting process which itself becomes capacity-limited at higher drug concentrations. In general, assigning a value of V^S_{max}/K^S_M to the first-order rate constant for acetaminophen sulfate formation to predict the effect of unsaturation would seem to be conservative. Formation of acetaminophen sulfate is the result of successive processes including mobilization of sulfate, conversion of sulfate to 3′-phosphoadenosine-5′-phosphosulfate, and transfer of the activated sulfate to acetaminophen, with mobilization of sulfate being the rate-limiting step.[5, 15] If the mobilization of sulfate were no longer rate-limiting, then another step in the sequence should become rate-limiting and should, by definition, have a rate constant larger than V^S_{max}/K^S_M. It may be possible to verify this experimentally in man and we are presently attempting to do so.

In the interim, preliminary studies have been carried out on mice to determine the effect of inorganic sulfate administration on the lethality of large doses of acetaminophen. Without having attempted to optimize the dosage regimen and route of administration, it was found that sodium sulfate given intraperitoneally significantly increased the median lethal dose of intraperitoneally injected acetaminophen in these animals.[29]

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