Eur J Clin Pharmacol (1986) 30: 273–278

European Journal of Clinical Pharmacology

The Effect of Acetaminophen Administration on its Disposition and Body Stores of Sulphate

S. Hendrix-Treacy[1], S. M. Wallace[1], K. W. Hindmarsh[1], G. M. Wyant[2], and A. Danilkewich[3]

[1] College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan, [2] Pain Management Service and [3] Department of Family Medicine, University Hospital, Saskatoon, Saskatchewan, Canada

Summary. This investigation was designed to investigate the effects of ingestion of multiple therapeutic doses of acetaminophen on the disposition of the drug and on the cosubstrate, sulfate. Nine healthy volunteers and nine outpatients receiving acetaminophen for chronic pain were involved in the study. Volunteers were given a single 650 mg oral dose of acetaminophen. One week later they were given 650 mg of acetaminophen every six hours for five doses. Patients were maintained on their normal treatment and dosage schedules (600 mg every 3 to 8 h) for the study.

In healthy volunteers the half-life of acetaminophen after single and multiple dosing was not significantly different. However, the fraction of acetaminophen recovered in the urine as the sulfate conjugate was less and the glucuronde conjugate greater after multiple dosing than after a single of the drug. There was no difference in the percentage recovered as the parent compound between single and multiple dosing.

Serum sulfate levels fluctuated over the 6-h period following administration of single and multiple doses of acetaminophen to volunteers. The mean serum sulfate concentration was less after administration of five sequential 650 mg doses of acetaminophen than after a single dose. The renal clearance of inorganic sulfate showed a corresponding decrease. Unexpectedly, patients on chronic acetaminophen therapy exhibited elevated serum sulfate levels (levels higher than the maximum sulfate concentration seen in volunteers).

Key words: acetaminophen; chronic therapy, disposition, sulfate stores, serum sulfate

Acetaminophen is a common non-prescription drug used as an analgesic for relief of mild to moderate pain and as an antipyretic. In therapeutic doses, it is well tolerated with allergic reactions and drug fever occurring rarely [1].

In therapeutic doses, acetaminophen is metabolized primarily by conjugation with sulfate and glucuronic acid. Some microsomal oxidation leading to production of cysteine and mercapturate conjugates also occurs [1]. The amount of drug conjugated via a specific pathway is controlled by the capacity of the pathway and the supply of cosubstrate [2.]. While the disposition of acetaminophen is affected by the body's supply of cosubstrates, acetaminophen can, in turn, alter the body stores of these cosubstrates. For example, a single dose of 1.5 g of acetaminophen can cause partial depletion of body stores of sulfate in man [3].

Although the most common indication for acetaminophen is the relief of acute symptoms, patients with chronic pain have been prescribed acetaminophen for prolonged periods. There is, however, very little information on the disposition of the drug and its effects on important cosubstrates such as sulfate after administration of multiple doses to humans. Two studies have reported no accumulation of acetaminophen [4, 5] and no significant change in elimination half-life [5] after administration of multiple doses of acetaminophen to patients. However, neither study compared the metabolite excretion pattern of the effect of acetaminophen on sulfate levels in the body after single and multiple doses of the drug. The effect of continued dosing with acetaminophen on levels of inorganic sulfate has really only been studied in animals. Based on studies in rats, Galinsky and Levy [6] estimate that administration of 12 g of acetaminophen in divided doses over a 24-h period could lead to almost complete depletion of free sulfate levels. This in turn may affect the disposition of other drugs and endogenous substances also eliminated by sulfate conjugation [7].

The objectives of this study were to determine if the rate of acetaminophen elimination and the pattern of acetaminophen metabolism (i.e. the relative

amounts of sulfate and glucuronide metabolites formed) were different after administration of single and multiple doses of the drug to humans. Some preliminary information relating to the effects of chronic exposure to acetaminophen on sulfate levels in humans was also obtained from patients receiving acetaminophen for treatment of chronic pain.

Materials and Methods

Subjects

The study population consisted of 9 healthy volunteers (5 males, 4 females) and 9 patients (3 males, 6 females) receiving acetaminophen for the treatment of chronic pain. Informed consent was received from all volunteers participating in the study.

Volunteers participated on 2 occasions. On the first, each received a single 650 mg oral dose of acetaminophen (2 × 325 mg capsules) with 100 ml of water following a 9-h fast. Food was restricted for an additional 1.5 h after the first dose. One week later, the same volunteers received 5 sequential 650 mg doses of acetaminophen (every 6 h for a 30-h period). Volunteers ranged in age from 17 to 33 years (mean 22.4 years ± 4.5 SD) and weighed between 54.9 and 92 kg (mean 72.5 kg ± 9.8 SD). All were nonsmokers and drug free for 2 weeks prior to the beginning of the study. Alcohol was not permitted 48 h before and throughout the study period. Diet was not controlled. Medical histories, physical examination and haematological tests were completed prior to the study.

Patients participated as part of a regular checkup at the Pain Management Clinic, University Hospital, Saskatoon, Saskatchewan. The patients suffered from a variety of chronic conditions but none showed evidence of kidney or liver damage (confirmed by laboratory data). A variety of medications were being consumed, depending on the medical condition, but all were receiving acetaminophen in a liquid oral dosage form[1] on a regular basis. The dosage of acetaminophen had been adjusted by the physician according to the need of individual patients. Dosage schedules remained unchanged for the study. Duration of acetaminophen therapy for the patients ranged from 6 days to 5 years. Patients in the study ranged in age from 39 to 61 years (mean 48.8 years ± 6.4 SD). Medical histories and medication profiles were obtained from hospital records.

[1] "Pain cocktail", prepared by the Department of Pharmaceutical Services, University Hospital, Saskatoon contained 300 mg acetaminophen per 5 ml and other drugs (diphenhydramine, chlorpromazine) as required for pain management

Collection of Biological Samples

Samples of blood and urine (4-h void) were collected one day prior to the start of the volunteer study. Further blood samples were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 h after ingestion of the single dose. Blood samples were also collected immediately before and at the same times after administration of the last dose in the multiple dose series. Urine was collected after administration of the single dose (0–4 h, 4–8 h) and after the last dose in the multiple dose series (0–4 h, 4–8 h, 8–24 h). For the patient study, single blood and urine samples were collected during the patient's clinical appointment. Most blood samples were collected approximately 2 h after a dose.

Venous blood samples were collected in plain silicone-coated vacutainers (7 ml) and separated by centrifugation. All volumes of urine were recorded and biological samples were immediately frozen (−8 °C).

Analysis of Samples

Concentrations of acetaminophen in serum and acetaminophen and its metabolites in urine were measured using a high pressure liquid chromatographic (HPLC) assay. Acetaminophen in serum was separated using a Varian 8500 Liquid Chromatograph and a bonded reverse-phase C_{18} column (25 cm × 4.6 mm; Beckman) using an eluent mixture of methanol (20%), glacial acetic acid (0.2%) and acetonitrile (5%) in water. The ultraviolet absorbance of the column eluent was monitored at 249 nm with a multiple-wavelengh spectrophotometer (Lambda Max 480). Samples were thawed (room temperature) immediately prior to analysis. Duplicate aliquots (0.5 ml) of each serum sample, containing 25 µg of the internal standard (3-acetamidophenol), were extracted with 4.0 ml of an ether:methylene chloride:isopropanol (4:2:1) solvent mixture. The samples were mixed (Vortex, Fisher Scientific) for 60 s and then agitated (Multipurpose Rotator, Scientific Industries) for 30 min. After centrifugation (2000 g; 10 min), the organic layer was removed and evaporated to dryness (Dri-Bath) using a gentle stream of nitrogen. The residue was then dissolved in methanol (0.5 ml) and an aliquot (5 µl) injected onto the HPLC column. For calibration curves, standard samples were prepared by adding known amounts of acetaminophen to 0.5 ml of serum and processed as described above.

For analysis of acetaminophen and its metabolites in urine, urine (20–150 µl) was diluted with distilled water (2–45 ×), the internal standard (25 µg of 3-acetamidophenol) added and an aliquot injected directly onto the HPLC column. Each sample was

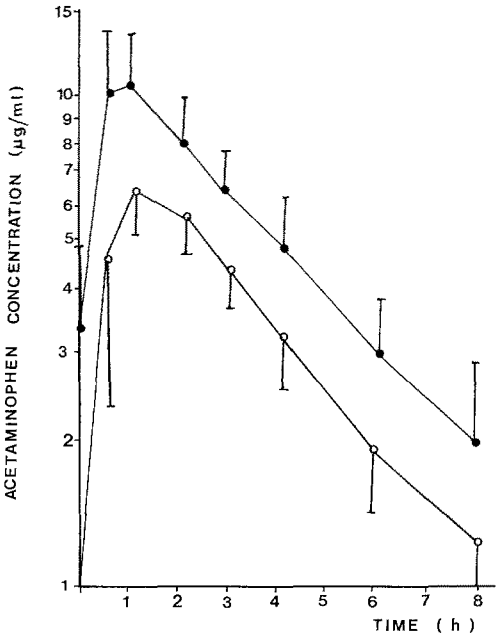

Fig. 1. Acetaminophen concentration-time profile of volunteers (mean values), patient J. M. excluded, O single dose, ● multiple dose

analyzed in duplicate. The same column described for serum separation was used for urine, the eluent mixture consisted of methanol (15%) and glacial acetic acid (0.2%) in water. For calibration curves, standard samples were prepared by adding acetaminophen (or metabolite) and internal standard to 75 µl of urine. The urine was diluted to 225 µl with water and a 1 µl aliquot injected for analysis.

Calibration curves were constructed by plotting the peak height ratio (acetaminophen/internal standard) against known concentrations of acetaminophen in serum or urine. Calibration curves for the sulfate and glucuronide conjugates were constructed in the same manner (i. e. peak height ratio of metabolite/internal standard vs. concentration).

Inorganic sulfate concentrations in serum (0.5 ml samples) and urine (0.1 ml samples) were determined using a modified turbidimetric assay [8, 9, 10]. Sodium sulfate, rather than ammonium sulfate, was used as the source of sulfate for preparation of calibration curves. Absorbance at 360 nm was read at 15 min (for urine) and 25 min (for serum) after addition of the barium chloride. Samples were filtered through filter pape rather than cotton.

Statistical Analysis

The apparent first-order elimination rate constant (k_d) was calculated by log-linear regression analysis using experimental points from 2 to 8 h after dosing and half-life ($t_{½}$) calculated as $0.693/k_d$. The area under the serum concentration-time curve for acetaminophen were calculated using the trapezoidal rule (AUC_0^∞ for single dose and AUC_0^τ for last dose of the multiple dose series). The accumulation ratio of acetaminophen in serum was calculated as C_{min_∞}/C_{min_1} (where C_{min_∞} represents the acetaminophen concentration 6 h after administration of the last dose; C_{min_1} 6 h after administration of the single dose) and predicted from the formula $1/1-e^{-k}d^{\tau}$.

Data were analyzed using the appropriate statistical test: Student's *t*-test, one-way or two-way analysis of variance (ANOVA). A multiple comparison test (Least Significance Difference) was used to examine differences between specific pairs of values. A probability value *(p)* of 0.05 or less was considered significant.

Results

Analytical

Acetaminophen and 3-acetamidophenol had retention times of 3.3 min and 4.8 min respectively on extraction and HPLC analyses of the serum extracts. No interfering peaks were observed on chromatographic analysis of the extract of drug-free serum. The total analysis time was 5-6 min.

Using the mobile phase described for analysis of urine samples, acetaminophen and its metabolites had retention times of 1.8, 2.6, 5.0 and 7.4 min for acetaminophen sulfate, acetaminophen glucuronide, acetaminophen and 3-acetamidophenol, respectively. Total analysis time was 8-9 min.

Calibration curves for determination of acetaminophen in serum were linear over a concentration range of 0.5-15 mg/l (coefficient of variation for analysis, 6%). Recovery of acetaminophen from serum averaged 82.5(±2.5)%. Calibration curves for determination of acetaminophen (0.9-4.5 µg), acetaminophen sulfate (5-36 µg) and acetaminophen glucuronide (12-58 µg) in urine were linear. The lower limits of the calibration curves corresponded to minimum detectable quantities (injected on column) of 4, 22 and 53 ng for acetaminophen, its sulfate and glucuronide metabolites.

Acetaminophen and its metabolites, in particular the sulphate metabolite, did not interfere with determination of inorganic sulphate.

Disposition of Acetaminophen

The maximum serum acetaminophen concentration (C_{max}) varied considerably between individual volunteers, with a range of 3.79-8.63 mg/l for single dosing and 6.81-29.63 mg/l for multiple dosing. The

C_{max} was significantly higher in the multiple dose study compared to the single dose ($p < 0.05$) (Fig. 1). The serum half-live ($t_{½}$) (2.69 ± 0.40 h - single; 2.77 ± 0.44 h - multiple), area under the curve (AUC_0^∞ - 33.2 ± 5.2 mg/l × h; AUC_0^τ - 37.1 ± 16.2 mg/l × h) and time required to reach peak acetaminophen serum concentrations (t_{max}) (1.3 ± 0.8 h - single; 1.0 ± 0.8 h - multiple) did not differ between single and multiple dose studies ($p > 0.05$). The extent of accumulation of acetaminophen (R_{AC}) on multiple dosing, calculated as the ratio of (C_{min_∞}) to (C_{min_l}) (1.64 ± 0.54), was not different from that predicted by the half-life and dosing interval (1.28 ± 0.09); ($p > 0.05$); (Table 1).

In patients, serum levels varied considerably ranging from 2.1-14.8 mg/l in samples taken 1.5-2.5 h after the previous acetaminophen dose (Table 2). One patient, taking acetaminophen once daily, retained a serum level of 0.5 mg/l 15 h after the last dose.

Table 1. Disposition of acetaminophen in healthy volunteers[a]

	Single Dose (650 mg)	Multiple Dose (650 mg every 6 h)	Sig[b]
C_{max} (mg/l)	7.12 ± 1.36	13.39 ± 6.35	Sig
C_{min} (mg/l)[c]	1.98 ± 0.53	3.14 ± 1.02	Sig
AUC (mg/l × h)[d]	33.2 ± 5.2	37.1 ± 16.2	NS
t_{max} (h)	1.3 ± 0.8	1.0 ± 0.8	NS
$t_{½}$ (h)	2.7 ± 0.4	2.8 ± 0.4	NS
R_{AC}[e]	1.3 ± 0.09	1.6 ± 0.5	NS
Renal excretion (0-24 h)			
% acetaminophen	5.4 ± 5.7	3.7 ± 1.8	NS
% acetaminophen glucuronide	47.7 ± 9.3	55.6 ± 6.8	Sig
% acetaminophen sulfate	46.9 ± 9.4	40.5 ± 7.3	Sig
Sulfate/glucuronide ratio	1.05 ± 0.43	0.76 ± 0.25	Sig

[a] Values represent mean standard deviation for 9 subjects (4 males, 5 females); [b] Paired t-test; NS = $p > 0.05$; Sig = $p < 0.05$; [c] C_{min}, plasma level 6 h after dose administered; [d] AUC_0^{6h} for multiple dose, AUC_0^∞ for single dose; [e] R_{AC} predicted from single dose ($1/1 - e^{-k}d^{\tau}$), R_{AC} measured for multiple dose (C_{min_∞}/C_{min_l})

Effect of Multiple Dosing on Urinary Excretion of Acetaminophen

In the volunteer study, an average of 86.8% (± 7.2 SD) of the 650 mg oral dose was recovered in the urine during the 24-h period following the single dose. Of this, 47.7 (± 9.3)% of the total acetaminophen recovered in the urine was the glucuronide conjugate, 46.9(± 9.4)% was acetaminophen sulfate and 5.4(± 5.7)% the parent drug (Table 1). The fraction excreted as the sulfate conjugate was lower after multiple dosing (40.5 ± 7.3%) than after single dosing ($p < 0.05$) with a reciprocal increase in the percentage of the glucuronide excreted after multiple dosing (55.6 ± 6.8%) as compared to the single dose. The ratio of sulfate/glucuronide excretion in urine averaged 1.05 (± 0.43) for the 24-h period following a single acetaminophen dose and 0.76 (± 0.25) following multiple doses. The fraction excreted as the parent drug was not different after multiple dosing ($p > 0.10$).

Comparison of urinary excretion of acetaminophen metabolites in patients receiving chronic acetaminophen therapy and volunteers receiving single and multiple doses was difficult because of the varying length of therapy and time of sampling. However, of the seven patients who provided serum and urine samples in the 0 to 4-h period following a dose, 4 patients had a sulfate/glucuronide ratio of less than 0.5 with the highest ratio being 0.71. Of the 9 volunteers, none had a sulfate/glucuronide ratio less than 0.5 after a single dose and only one after multiple doses of acetaminophen, whereas 9 and 4 volunteers respectively had ratios of 0.7 or greater for single and multiple dosing. These data suggest less

Table 2. Acetaminophen disposition and serum levels of inorganic sulphate in patients

Patients[a]	Sex	Age (year)	Acetaminophen dosage	Time since last dose (h)	Acetaminophen		Inorganic Sulphate Serum Level (mM)
					Serum level (mg/l)	Sulphate/Glucuronide Ratio in Urine	
1	M	61	600 mg q8h for 1.6 years	1.5	10.7	0.59	-
2	F	53	600 mg q4h for 4 months	2.0	14.0	0.71	0.88
3	M	54	600 mg q3h for 3 weeks	2.0	14.8	0.28	-
4	F	45	600 mg q4h for 5 years	2.2	2.1	0.48	0.94
5	M	39	600 mg q4h for 1 week	2.3	3.6	0.40	0.80
6	F	49	600 mg q4h for 1.5 years	2.3	9.1	0.38	0.84
7	F	47	600 mg q4h for 10 months	2.5	6.2	0.56	0.99
8	F	46	600 mg q6h for 4 years	5.5	3.8	0.55	1.18
9	F	46	600 mg at bedtime	15.0	0.5	0.30	0.93
Mean ± SD		48.8 ± 6.4				0.47 ± 0.14	0.91 ± 0.12

[a] Patients' diagnoses included arthritis (3, 5), multiple sclerosis (9), low back pain (7), brachial flexis fibrosis (2), demyelinating neuropathy (8), diffuse skeletal pain (6), poliomyelitis (4). One patient (1) had chronic pain of unknown etiology

Table 3. Status of inorganic sulfate in healthy volunteers after acetaminophen dosing

Dose	Serum Sulfate Concentration (mM)		Renal Clearance of Inorganic Sulfate[a] (l/h)	
	Maximum	Average over 6-h interval	0-4 h	0-24 h
Control	-	0.55 ± 0.08[b]	2.00 ± 0.57	-
Single dose	0.69 ± 0.12	0.58 ± 0.11	1.05 ± 0.54[d]	1.36 ± 0.49
Multiple dose	0.56 ± 0.13	0.48 ± 0.10[d, e]	0.89 ± 0.53[d, e]	1.39 ± 0.44

[a] Renal clearance calculated as the amount excreted in the urine divided by the average serum sulfate level during a given interval. [b] Control samples collected at 9 A.M. the day before the single dose study. [c] Statistical comparison by ANOVA and multiple range tests. [d] Different from control values ($p < 0.05$). [e] Different from single dose ($p < 0.05$)

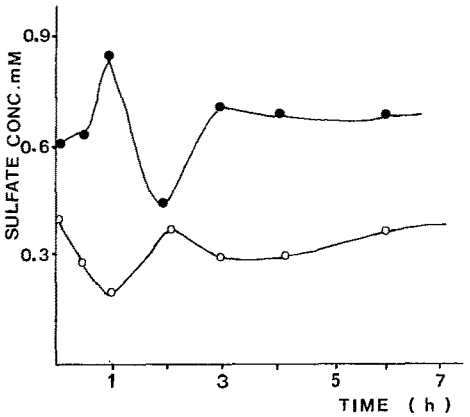

Fig. 2. Concentration-time curves, for one volunteer, of inorganic sulfate in the body (single dose (●) and multiple dose study (○)

sulphate and more glucuronide metabolite was excreted in patients receiving chronic acetaminophen therapy than in volunteers receiving single or multiple doses of the drug.

Effect of Acetaminophen Administration on Inorganic Sulfate Kinetics

Over an 8-h period following administration of a single acetaminophen dose to volunteers, serum levels of inorganic sulfate fluctuated, dropping to a minimum level between 1-2 h after administration (Fig. 2). Data from volunteers also demonstrated a rise in serum sulfate prior to the drop at 1-2 h. After multiple dosing, a similar drop in serum sulfate levels, extending over a period of 0.5-2.0 h after the last dose, was noted. There was no transient rise preceding the drop in serum sulfate. In all volunteers, except one, the mean serum inorganic sulfate levels was lower after multiple doses (0.48 ± 0.10 mM) than after a single dose (0.58 ± 0.10 mM). Renal clearance of inorganic sulfate for the 0 to 4-h interval was significantly less after multiple dosing (0.89 ± 5.3 l/h) compared to the single dose (1.05 ± 0.54 l/h) or the control period (2.0 ± 0.57 l/h) (Table 3). Differences in renal sulfate clearance after single and multiple doses of acetaminophen were not apparent if clearance was calculated over a longer interval; i.e. 0-24 h.

Serum sulfate levels (0.91 ± 0.12 mM) in patients were significantly higher than levels in volunteers ($p < 0.05$) - whether the comparison was made with the average sulfate level (0.48 ± 0.10 mM) or the maximum sulfate level over the 8-h period (0.56 ± 0.13 mM) (Tables 1 and 2). All patients, except number 5, had serum sulfate levels in the range of 0.75-0.99 mM.

Discussion

Acetaminophen serum levels were measured in healthy volunteers over an 8-h period, following single and multiple oral doses. C_{max}, t_{max} and $t_{½}$ values following a single dose study were similar to values reported in the literature [11, 12, 13]. Acetaminophen accumulated when administered every 6 h. The extent of accumulation (R_{AC}), however, was not greater than predicted from the single dose $t_{½}$; nor was the $t_{½}$ after a single dose different from the $t_{½}$ after multiple dosing.

In the single dose volunteer study, acetaminophen glucuronide constituted 47.7(±9.3)% of the dose recovered in the urine, acetaminophen sulfate 46.9(±9.4)% and acetaminophen 5.4(±5.7)%. In the literature, reports of the percentage excreted as acetaminophen and metabolites after a single therapeutic dose vary from 40-75% for the glucuronide, 20-40% for the sulfate conjugate and 1-4% for the parent drug [14-18]. Doses used in these studies ranged from 5 mg/kg to 20 mg/kg.

Although the overall elimination rate of acetaminophen, as monitored by the $t_{½}$, did not change with multiple dosing, the pattern of metabolite excretion was significantly different. In the volunteer multiple dose study, the fraction eliminated as the sulfate conjugate decreased while that excreted as the glucuronide increased when compared to the single dose study ($p < 0.05$). There was no change in the percentage excreted as the parent drug. The decrease in the fraction recovered as acetaminophen sulfate in urine was consistent with saturation of the sulfate metabolic pathway and subsequent shunting to glucuronidation, the predominant metabolic route at higher concentrations of acetaminophen [6]. The limited capacity to produce sulfate conjugates may reflect either saturation of the enzyme systems responsible for activation of inorganic sulfate or for transfer of activated sulfate to the drug (i.e. sulfotransferase), [3].

Serum levels of inorganic sulfate in control samples from volunteers (i.e. before any drug was ingest-

ed) averaged 0.55 mM (±0.08 mM). This is somewhat higher than mean values for inorganic sulfate in man reported in the literature; 0.3-0.4 mM [7, 9]. This higher value may be partially explained by the high natural sulfate content of soil and water in our area, Because both groups - volunteers and patients - were resident in the same geographic area, it was felt that comparisons of differences in sulfate levels within the volunteer group and between the volunteer and patient groups would still be valid.

The immediate response of a drop in serum levels approximately 2 h after administration of a single acetaminophen dose is similar to the decrease in urinary sulfate excretion 2 h after oral administration of acetaminophen reported by Levy et al. [2]. A decrease in the serum sulfate levels after single doses of acetaminophen has been reported previously [2, 3] and is presumed to reflect a depletion of the total body stores of inorganic sulfate. Corresponding to the lowering of serum sulfate levels, renal sulfate clearance from 0-4 h is reduced (Table 3) presumably as part of a homeostatic mechanism to conserve sulfate [3]. Serum sulfate levels, after a single acetaminophen dose, returned to their control value within the six hour observation period.

After administration of multiple doses of acetaminophen, serum levels of inorganic sulfate and the percentage of drug excreted as acetaminophen sulfate were less than after administration of a single dose (Table 1). Based on the decrease of inorganic sulfate levels in serum noted after acute administration of acetaminophen, we anticipated chronic acetaminophen therapy would produce further depletion of body stores of sulfate. However, our study suggests serum sulfate levels in patients exposed to acetaminophen on a chronic basis have higher serum sulfate levels than volunteers exposed to single or multiple doses of the drug. In contrast, the ratio of sulfate to glucuronide metabolite excreted in the urine did not appear to increase in relation to the serum sulfate level. Further studies are necessary to confirm these findings. However, the results suggest: (a) homeostatic mechanisms can mobilize inorganic sulfate in response to metabolic requirements if exposure to acetaminophen is prolonged, i.e. as in chronic dosing and (b) serum levels of inorganic sulfate may not always be rate controlling or reflect the supply of activated sulfate for the sulfation of acetaminophen.

Acknowledgements. The authors wish to express their appreciation to the Medical Research Council of Canada for financial assistance given in the form of a studentship to S. H-T.

References

1. Forrest JAH, Clements JA, Prescott LF (1982) Clinical pharmacokinetics of paracetamol. Clin Pharmacokinet 7: 93-107
2. Levy G, Galinsky R, Lin JH (1982) Pharmacokinetic consequences and toxicologic implications of endogenous cosubstrate depletion. Drug Metab Rev 13: 1009-1020
3. Morris M, Levy G (1983) Serum concentration and renal excretion by normal adults of inorganic sulfate after acetaminophen, ascorbic acid or sodium sulfate. Clin Pharmacol Ther 33: 529-536
4. Benson GD (1983) Acetaminophen in chronic liver disease Clin Pharmacol Ther 33: 95-101
5. Andreasen PB, Hutters L (1979) Paracetamol (acetaminophen) clearance in patients with cirrhosis of the liver. Acta Med Scand [Suppl] 624: 99-105
6. Galinsky RE, Levy G (1981) Dose and time-dependent elimination of acetaminophen in rats: Pharmacokinetic implications of cosubstrate depletion. J Pharmacol Exp Ther 219 [1] 14-20
7. Levy G, Matsuzawa T (1967) Pharmacokinetics of salicylamide elimination in man. J Pharmacol Exp Ther 156: 285
8. Berglund F, Sorbo B (1960) Turbidimetric analysis of inorganic sulfate in serum, plasma and urine. Scand J Clin Lab Invest 12 [2]: 147-153
9. Krijgsheld K, Franken H, Scholtens E, Zweens J, Mulder G (1979) Absorption, serum levels, and urinary excretion of inorganic sulfate after oral administration of sodium sulfate in the conscious rat. Biochim Biophys Acta 586: 492-500
10. Lundquist P, Martensson J, Sorbo B, Ohman S (1980) Turbidmetry of of inorganic sulfate, ester sulfate and total sulfur in urine. Clin Chem 26 [8]: 1178-1181
11. Ameer B, Greenblatt D, Divoll M, Abernathy D, Shargel L (1981) HPLC determination of acetaminophen in plasma: Single dose pharmacokinetic studies. J Chromatogra 226: 224-230
12. Miller RP, Roberts RJ, Fischer LJ (1976) Acetaminophen elimination kinetics in neonates, children and adults. Clin Pharmacol Ther 19: 284-294
13. Rawlins MD, Henderson D, Hijab AR (1977) Pharmacokinetics of paracetamol after i.v. and oral administration. Eur J Clin Pharmacol 11: 283-286
14. Levy G, Yamada H (1971) Drug biotransformation interactions in man (III): Acetaminophen and salicylamide. J Pharm Sci 60 [21]: 215-221
15. Cummings AJ, King ML, Martin BK (1967) A kinetic study of drug elimination and the excretion of paracetamol and its metabolites in man. Br J Pharmacol 29: 150-157
16. Mrochek JE, Kate S, Christie WH, Dinsmore SR (1974) Acetaminophen metabolism in man, as determined by high resolution liquid chromatography. Clin Chem 20: 1086-1096
17. Colwell BB, Thomas BH, Whitehouse LW, Wong LT, Hynie I (1976) Metabolism of 14-C acetaminophen in humans and laboratory animals. Proc Soc Toxicol 17: 269-276
18. Clements JA, Critchley JH, Prescott LF (1984) The role of sulphate conjugation in the metabolism and disposition of oral and intravenous paracetamol in man. Br J Clin Pharmacol 18: 481-485

Received: July 24, 1985
accepted in revised form: February 6, 1986

Dr. K. W. Hindmarsh
College of Pharmacy
University of Saskatchewan
Saskatoon, Saskatchewan S7N OWO
Canada