



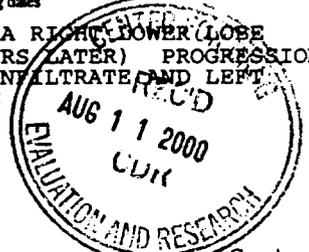
Mfr report # 001-0073-M0000267
UD/Date report #
FDA Use Only

Patient information			
1. Patient identifier UNK	2. Age at time of event: 55 Y	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight ____ lbs or ____ kgs
In confidence Date of birth: _____			

B. Adverse event or product problem	
1. <input checked="" type="checkbox"/> Adverse event and/or	<input type="checkbox"/> Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)	
<input type="checkbox"/> death (m/d/yyyy)	<input type="checkbox"/> disability
<input type="checkbox"/> life-threatening	<input type="checkbox"/> congenital anomaly
<input type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
	<input checked="" type="checkbox"/> other: MED SIGNIFICANT
3. Date of event (m/d/yyyy) 02/09/00	4. Date of this report (m/d/yyyy) 08/09/00

5. Describe event or problem

A literature article published in 2000 reported that a patient developed hepatotoxicity, considered medically significant, and a possible drug interaction while taking phenytoin and acetaminophen (paracetamol). The patient was admitted to the hospital for placement of an inferior vena cava filter. Upon admission her hepatic transaminases, lactose dehydrogenase, and alkaline phosphatase levels were all elevated. On 09FEB00, her alkaline phosphatase (AKL-P) level was 213 IU/L, aspartate aminotransferase (AST) level was 133 IU/L her alanine aminotransferase (ALT) level was 181 IU/L and her lactate dehydrogenase (LD) level was 162 IU/L. These laboratory elevations failed to resolve. All laboratory and serologic test for hepatitis were negative. The most recent addition to her medication regime was paroxetine, all other agents were unchanged for at least six months. None of her current medications were strongly associated with drug induced etiology. The patient's AST and ALT elevations were greater than those associated with heparin use and elevations occurred prior to heparin

6. Relevant tests/laboratory data, including dates	
CHEST XRAY: PNEUMONIA RIGHT LOWER LOBE CHEST XRAY: (36 HOURS LATER) PROGRESSION OF RIGHT LOWER LOBE INFILTRATE AND LEFT LOWER LOBE INFILTRATE	
	

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

CHRONIC OBSTRUCTIVE PULMONARY DISEASE
GASTROESOPHOGEAL REFLUX DISEASE
HYPERLIPIDEMIA
HEAD INJURY
HYPERCOAGULABLE STATE
MYOCARDIAL INFARCTION SEVERAL TIMES
RECURRENT DEEP VEIN THROMBOSIS
RECURRENT PULMONARY EMBOLI
SMOKER
DENIES ILLICIT DRUG USE OR ALCOHOL USE

C. Suspect medication(s)	
1. Name (give labeled strength & mfr/labeler, if known)	
#1 PHENYTOIN (PHENYTOIN)	
#2 ACETAMINOPHEN (PARACETAMOL)	
Cont.	
2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) (month or best estimate)
#1 300 mg (QOD), Per oral	#1 UNK
#2 2800 mg (DAILY), Per oral	#2 02/08/00 - 02/08/00
4. Diagnosis for use (indication)	
#1 SEIZURES	
#2 MUSCULOSKELETAL PAIN	
5. Event abated after use stopped or dose reduced	#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply
	#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply
6. Lot # (if known)	7. Exp. date (if known)
#1 UNK	#1 UNK
#2 UNK	#2 UNK
9. NDC # - for product problems only (if known)	
10. Concomitant medical products and therapy dates (exclude treatment of event)	
1) PROPOXYPHENE NAPSYLATE WITH ACETAMINOPHEN (PAR-ACETAMOL, DEXTROPROPOXYPHENE)	

G. All manufacturers	
1. Contact office - name/address (& mfring site for devices)	2. Phone number
PARKE-DAVIS PHARM. RESEARCH, DIV W-L CO. ATTN: DAVID PALAN, RPH, M.H.P. 2800 PLYMOUTH ROAD ANN ARBOR MI. 48105 USA (Printing Unit)	734-622-7663
4. Date received by manufacturer (m/d/yyyy) 07/06/00	3. Report source (check all that apply)
6. If IND, protocol #	<input type="checkbox"/> foreign <input type="checkbox"/> study <input checked="" type="checkbox"/> literature <input type="checkbox"/> consumer <input checked="" type="checkbox"/> health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:
7. Type of report (check all that apply)	5. (A)NDA # 84-349
<input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 10-day <input type="checkbox"/> periodic <input checked="" type="checkbox"/> Initial <input type="checkbox"/> follow-up # _____	IND # _____ PLA # _____ pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes
9. Mfr. report number 001-0073-M0000267	8. Adverse event term(s) 1) ACETAMINOPHEN-POSS INTERACTION 2) HEPATOTOXICITY AUG 11 2000

F. Initial reporter			
1. Name, address & phone # CAROLYN BRACKETT, PHARM D COLLEGE OF PHARMACY OHIO STATE UNIV. DIVISION OF PHARMACY PRACTICE AND ADMIN. 500 WEST 12TH AVENUE COLUMBUS, OH 43210 USA			
2. Health professional? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation Pharmacist	4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> unk	

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.



B. Adverse event or product problem

B.5 Describe event or problem (Cont...)

administration (intravenous and subcutaneous). After continued review of her concomitant medications it was noted that she received the following analgesics oxycodone with acetaminophen, propoxyphene napsylate with acetaminophen, and acetaminophen. The patient received doses of acetaminophen of 1300-6200 mg per day. All products containing acetaminophen were discontinued. Phenytoin therapy was maintained. The patient's laboratory levels returned to normal and she recovered from the hepatotoxicity. On 19FEB00, her LD level was 203 IU/L. On 15APR00, her ALK-P level was 120 IU/L, ALT level was 10 IU/L, and her AST level was 14 IU/L. [Brackett, C. et al. Phenytoin as a possible cause of acetaminophen hepatotoxicity: Case report and review of the literature. Pharmacotherapy 20(s): 229-233, 2000.]

B.6 Relevant tests/laboratory data, including dates (Cont...)

Lab Result :

Sl.No.	Test name	Test date	Test result	Normal value
1	ALANINE AMINOTRANSFERASE	02/09/00	181 IU/L	0-45 IU/L
		02/10/00	112 IU/L	0-45 IU/L
		02/11/00	81 IU/L	0-45 IU/L
		02/12/00	79 IU/L	0-45 IU/L
		02/16/00	335 IU/L	0-45 IU/L
		02/18/00	217 IU/L	0-45 IU/L
		02/19/00	181 IU/L	0-45 IU/L
		03/05/00	28 IU/L	0-45 IU/L
2	ALKALINE PHOSPHATASE	04/15/00	10 IU/L	0-45 IU/L
		02/09/00	213 IU/L	30-115 IU/L
		02/10/00	190 IU/L	30-115 IU/L
		02/11/00	186 IU/L	30-115 IU/L
		02/12/00	195 IU/L	30-115 IU/L
		02/16/00	389 IU/L	30-115 IU/L
		02/18/00	327 IU/L	30-115 IU/L
		02/19/00	314 IU/L	30-115 IU/L
3	ASPARTATE AMINOTRANSFERASE	04/15/00	120 IU/L	30-115 IU/L
		02/09/00	133 IU/L	0-41 IU/L
		02/10/00	190 IU/L	0-41 IU/L
		02/11/00	31 IU/L	0-41 IU/L
		02/12/00	49 IU/L	0-41 IU/L
		02/16/00	305 IU/L	0-41 IU/L
		02/18/00	95 IU/L	0-41 IU/L
		02/19/00	70 IU/L	0-41 IU/L
4	CHEST X-RAY	03/05/00	19 IU/L	0-41 IU/L
		04/15/00	14 IU/L	0-41 IU/L
5	HEPATITIS SCREEN		SEE TEXT	
6	LACTATE DEHYDROGENASE		NEGATIVE	
		02/09/00	162 IU/L	60-200 IU/L
		02/10/00	170 IU/L	60-200 IU/L
		02/11/00	166 IU/L	60-200 IU/L
		02/12/00	199 IU/L	60-200 IU/L
		02/16/00	472 U/L	60-200 IU/L
		02/18/00	209 IU/L	60-200 IU/L
		02/19/00	203 IU/L	60-200 IU/L

C. Suspect medication (Cont...)

Seq No. : 1
 C.1 Suspect medication : PHENYTOIN (PHENYTOIN)
 C.2 Dose, frequency & route used : 2) 400 mg (QOD), Per oral
 C.4 Diagnosis for use(indication) : 2) SEIZURES

Seq No. : 2
 C.1 Suspect medication : ACETAMINOPHEN (PARACETAMOL)
 C.2 Dose, frequency & route used : 2) 5200 mg (DAILY), Per oral
 3) 6200 mg (DAILY), Per oral
 4) 5200 mg (DAILY), Per oral
 5) 2600 mg (DAILY), Per oral
 6) 2600 mg (DAILY), Per oral
 7) 1400 mg (DAILY), Per oral
 8) 1950 mg (DAILY), Per oral
 9) 2600 mg (DAILY), Per oral
 10) 2600 mg (DAILY), Per oral

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PARKE-DAVIS PHARM. RESEARCH, DIV W-L CO.
ATTN: DAVID PALAN, RPH, M.H.P.
2800 PLYMOUTH ROAD
ANN ARBOR MI. 48105
USA



Continuation Sheet for FDA-3500A Form

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Mfr. report #: 001-0073-M0000267

Date of this report: 08/09/00

C3 Therapy Dates (or duration)

- 11) 1300 mg (DAILY), Per oral
- 2) 02/09/00 - 02/09/00
- 3) 02/10/00 - 02/10/00
- 4) 02/11/00 - 02/11/00
- 5) 02/12/00 - 02/12/00
- 6) 02/13/00 - 02/13/00
- 7) 02/14/00 - 02/14/00
- 8) 02/15/00 - 02/15/00
- 9) 02/16/00 - 02/16/00
- 10) 02/17/00 - 02/17/00
- 11) 02/18/00 - 02/19/00

C10. Concomitant medical products

- Seq No. : 1
Concomitant Medical Product : PROPOXYPHENE NAPSYLATE WITH ACETAMINOPHEN (PARACETAMOL, DEXTROPROPOXYPHENE NAPSILATE)
Therapy Dates : 1) UNK - Stopped
- Seq No. : 2
Concomitant Medical Product : OXYCODONE WITH ACETAMINOPHEN
Therapy Dates : 1) UNK - Stopped
- Seq No. : 3
Concomitant Medical Product : (WARFARIN SODIUM)
Therapy Dates : 1) UNK - STOPPED
2) UNK - Ongoing
- Seq No. : 4
Concomitant Medical Product : (DILTIAZEM)
Therapy Duration : UNK
- Seq No. : 5
Concomitant Medical Product : (CISAPRIDE)
Therapy Duration : UNK
- Seq No. : 6
Concomitant Medical Product : (FAMOTIDINE)
Therapy Duration : UNK
- Seq No. : 7
Concomitant Medical Product : (PAROXETINE)
Therapy Duration : UNK
- Seq No. : 8
Concomitant Medical Product : (CEFPROZIL)
Therapy Dates : 1) UNK - Stopped
- Seq No. : 9
Concomitant Medical Product : (IBUPROFEN)
Therapy Dates : 1) UNK - Stopped
- Seq No. : 10
Concomitant Medical Product : HYDROCODONE (PARACETAMOL, HYDROCODONE BITARTRATE)
Therapy Dates : 1) UNK - Stopped

Source of report (Literature):

- Seq No. : 1
- Author : PHARM D CAROL BRACKETT
- Journal title : PHARMACOTHERAPY
- Year : 00
- Edition : 20(2)
- Page number : From 229 To 233
- Article title : PHENYTOIN AS A POSSIBLE CAUSE OF ACETAMINOPHEN HEPATOTOXICITY: CASE REPORT AND REVIEW LITERATURE

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CASE REPORTS



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Phenytoin as a Possible Cause of Acetaminophen Hepatotoxicity: Case Report and Review of the Literature

Carolyn C. Brackett, Pharm.D., and James D. Bloch, D.O.

A 55-year-old woman was hospitalized for treatment of community-acquired pneumonia. Unexplained, moderate elevations in hepatic transaminase and enzyme levels prompted review of her drug regimen. She had taken acetaminophen 1300-6200 mg/day during the hospitalization. She also received phenytoin for posttraumatic seizures. Acetaminophen was discontinued, and the patient's liver chemistries returned to normal within 2 weeks of discharge. Acetaminophen is metabolized in part by cytochrome P450 (CYP) 2E1, and inducers of CYP2E1 are known to predispose patients to acetaminophen-related hepatotoxicity. Phenytoin induces CYP2C and CYP3A4 isoforms, but not CYP2E1. The literature suggests, however, that CYP3A4 may participate in acetaminophen metabolism to a greater extent than previously realized, and induction of this isoform may predispose patients to acetaminophen-induced hepatotoxicity. (Pharmacotherapy 2000;20(2):229-233)

A 55-year-old woman came to the emergency department of an outlying hospital because of severe right-sided chest pain and dyspnea of 24 hours' duration. Physical examination and chest radiograph were suggestive of right lower lobe pneumonia. The patient declined hospitalization and was released with prescriptions for cefprozil and hydrocodone with acetaminophen. She returned to the same emergency department 30 hours later with continued severe chest pain and new-onset hemoptysis. The chest radiograph now revealed progression of the right lower lobe infiltrate and a new left lower lobe infiltrate. She was admitted for treatment of community-acquired pneumonia.

The patient's medical history was significant for chronic obstructive pulmonary disease with

continued smoking, gastroesophageal reflux disease, hyperlipidemia, seizures secondary to a head injury 2 years earlier, and a hypercoagulable state with several myocardial infarctions, recurrent deep vein thromboses (DVTs), and pulmonary emboli. She had been hospitalized several weeks previously for recurrent DVT. Drug therapy consisted of phenytoin sodium 400 mg every other day alternating with 300 mg warfarin sodium 6 mg/day, diltiazem 30 mg 4 times/day, cisapride 20 mg 4 times/day, famotidine 40 mg/day, paroxetine 20 mg/day, cefprozil 500 mg twice/day, ibuprofen 400 mg every 6 hours as needed, and hydrocodone with acetaminophen 1-2 tablets every 6 hours as needed. She denied use of over-the-counter agents, illicit drugs, or alcohol.

On admission, ibuprofen, cefprozil, and hydrocodone with acetaminophen were discontinued; because of hemoptysis, warfarin was discontinued as well. In light of her history of thrombosis and recent episode of DVT, placement of an inferior vena cava (IVC) filter was attempted. This was initially unsuccessful because her vena cava was

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From the Division of Pharmacy Practice and Administration, College of Pharmacy, The Ohio State University (Dr. Brackett), and the Department of Internal Medicine, Doctors Hospital (Dr. Bloch), Columbus, Ohio. Address reprint requests to Carolyn C. Brackett, Pharm.D., Division of Pharmacy Practice and Administration, College of Pharmacy, The Ohio State University, 500 West 12th Avenue, Columbus, OH 43210.

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Table 1. Hepatic Chemistry Values

Test	Date									
	2/09	2/10	2/11	2/12	2/16	2/18	2/19	3/05	4/15	
Alkaline phosphatase (normal 30-115 IU/L)	213	190	186	195	389	327	314	ND	120	
Aspartate aminotransferase (normal 0-41 IU/L)	133	190	31	49	305	95	70	19	14	
Alanine aminotransferase (normal 0-45 IU/L)	181	112	81	79	335	217	181	28	10	
Lactate dehydrogenase (normal 60-200 IU/L)	162	170	166	199	472	209	203	ND	ND	



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filters. As a result, and at the patient's request, she was transferred to our institution for IVC placement. On arrival, she was fully anticoagulated with intravenous unfractionated heparin, which was continued for 1 week, when enoxaparin 110 mg subcutaneously every 12 hours was begun. After stabilization with antibiotics and heparin, an IVC filter was placed successfully on hospital day 8. Warfarin was reinstated the day after this procedure, and the patient was discharged 2 days later.

When the patient was admitted to our institution, hepatic transaminases, lactose dehydrogenase, and alkaline phosphatase were elevated (Table 1). Because the elevations failed to resolve, the internal medicine service was consulted. All laboratory and serologic tests for hepatitis were negative. The most recent addition to her regimen was paroxetine, which had been started 4 months before admission; all other agents were unchanged for at least 6 months. None of her current drugs is strongly associated with drug-induced hepatitis and, with the exception of heparin, the time course of her regimen argued against a drug-induced etiology.

Heparin frequently is associated with increased transaminase levels, with significant elevations in aspartate and alanine aminotransferases reported in 18-89% of patients.¹⁻³ The phenomenon appears to be dosage related and reversible, and almost never causes increases of more than twice the baseline value. Elevations in this patient were greater than those typically associated with heparin. Furthermore, although she received both intravenous and subcutaneous heparin at our institution, her transaminases were elevated on admission, before the initiation of heparin.

Continued review of drugs that she received indicated that, in addition to those listed above, the following analgesic orders were active

concurrently: oxycodone with acetaminophen 1-2 tablets every 4 hours as needed (325 mg acetaminophen/tablet), propoxyphene napsylate with acetaminophen 1-2 tablets every 4-6 hours (650 mg acetaminophen/tablet), and acetaminophen 500 mg 1-2 tablets every 4-6 hours as needed. The patient experienced significant musculoskeletal pain during hospitalization and received many doses of different oral analgesics, which resulted in unintended administration of substantial amounts of acetaminophen. In fact, she received dosages of 1300-6200 mg/day (Table 2).

The patient had taken phenytoin for several years because of a closed head injury. Phenytoin is a potent inducer of the hepatic cytochrome system, and thus possible acetaminophen-induced liver injury secondary to enzyme induction was questioned. Because of this concern, all acetaminophen-containing products were discontinued and plain propoxyphene was prescribed for musculoskeletal discomfort. The patient stated that she typically did not take acetaminophen; however, she had received a prescription for hydrocodone and acetaminophen at her first visit to the emergency department and had taken it as ordered. When she was discharged from our institution she was warned to avoid acetaminophen-containing products. Hepatic transaminases measured by her primary care physician 2 and 6 weeks after discharge were normal.

Review of the Literature

Acetaminophen is metabolized in the liver by two pathways. Eighty to 90% of a dose is conjugated by a phase II reaction with either glucuronic acid or sulfate. These conjugation reactions produce nontoxic metabolites that are eliminated in urine. A small proportion of a dose

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two of them were taking enzyme-inducing drugs—one phenytoin and one phenobarbital.

Phenytoin is a strong inducer of the CYP3A4 and CYP2C isoforms but has no effect on CYP2E1.^{16, 17} Evidence shows, however, that cytochrome induction by phenytoin may affect acetaminophen clearance. Typically considered a restrictively cleared drug, the extraction ratio of acetaminophen increases significantly from 0.17 to 0.27 when administered to patients taking phenytoin.¹⁸ The increase in extraction ratio signifies increased hepatic clearance of acetaminophen, probably due to enzyme induction. Several studies also documented increases in acetaminophen's oral clearance after treatment with phenytoin, strongly suggesting heightened metabolic capacity.¹⁸⁻²⁰ The CYP2E1 isoform is considered responsible for most of acetaminophen's phase I metabolism, but because phenytoin induces only the CYP3A4 and CYP2C isoforms, studies suggest that additional isoforms may participate. In support of this hypothesis, monospecific IgG antibodies directed against human CYP2E1 inhibited phase I transformation of acetaminophen to NAPQI by only 50%, which suggests significant participation of additional metabolic routes.²¹

Cytochrome P450 1A2 was investigated as a potential participant in the metabolic conversion of acetaminophen to NAPQI in humans. Anti-CYP1A2 IgG partially inhibits acetaminophen metabolism, indicating that CYP1A2 may be an additional contributor to NAPQI formation.²¹ Other studies confirmed the participation of CYP1A2 in acetaminophen metabolism but proposed that it contributes significantly to bioactivation and toxicity only when acetaminophen is given at high doses or when the isoform is enzyme induced.²² Phenytoin does not induce CYP1A2, but cigarette smoking does, and our patient had been a heavy smoker for many years.

Cytochrome P450 3A4 is the predominant isoform in human liver. An investigation of the kinetics of NAPQI formation in human liver microsomal preparations showed that, at therapeutic acetaminophen concentrations, the contribution of CYP3A4 to total NAPQI formation varied from 1-20%.²³ As noted, CYP2E1 typically is implicated in alcoholics' predisposition to acetaminophen-induced hepatotoxicity for two reasons. First, CYP2E1 contributes substantially to NAPQI production,

and second, ethanol is a potent inducer of this isoform. However, short-term alcohol ingestion

is also a CYP2E1 inhibitor. Thus, in an attempt to avoid the confounding effects of ethanol inhibition during animal studies, most investigators require that alcohol be withdrawn from enzyme-induced animals for 16-24 hours before administration of test compounds. However, enzyme induction of the CYP2E1 system apparently reverses very rapidly, and 24-hour withdrawal from ethanol resulted in CYP2E1 levels that were not different from those in noninduced controls.⁹ Thus, at least in animal studies, augmented acetaminophen hepatotoxicity attributed to CYP2E1 induction may be related in part to induction of other enzyme systems.

Ethanol also induces CYP3A4, although not to the same magnitude as CYP2E1. Another investigation used ethanol as an enzyme inducer in rats.⁹ Ethanol was withdrawn 11 hours before acetaminophen administration and troleandomycin (TAO), a potent and selective inhibitor of CYP3A4, was administered to some animals immediately before they received moderate doses of acetaminophen. Animals that did not receive ethanol pretreatment experienced no histologic damage. In pretreated rats, administration of acetaminophen 11 hours after withdrawal from ethanol resulted in moderate histologic hepatic damage. However, in a second group of ethanol-pretreated animals, administration of TAO to inhibit CYP3A4 completely prevented histologic evidence of acetaminophen damage, suggesting that in the enzyme-induced state CYP3A4 is a major contributor to NAPQI production and hepatotoxicity.

Discussion

Our patient's abnormal hepatic chemistries may have been related to other factors, but we believe that they were associated with acetaminophen taken in combination with phenytoin. Induction of CYP1A2 caused by her smoking may have contributed as well. Prospective recognition of such an interaction may prove problematic. Some standard reference texts and computerized information systems note and clearly describe the combination, and others do not identify it at all. Some references consider the interaction to be merely potential, and some identify it only under the listing for acetaminophen. Furthermore, since many acetaminophen-containing products are nonprescription items, the agent often is not included by pharmacists when they perform manual or electronic screens for interactions. We

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Table 2. Acetaminophen Doses

	Date											
	2/08	2/09	2/10	2/11	2/12	2/13	2/14	2/15	2/16	2/17	2/18	2/19
Dose (mg)	2800	5200	6200	5200	2600	2600	1400	1950	2600	2600	1300	0

is metabolized by a phase I cytochrome P450 (CYP) reaction to a reactive, electrophilic intermediate, *N*-acetyl-*p*-benzoquinone imine (NAPQI). Under normal conditions this intermediate is rapidly conjugated with glutathione (GSH) to form mercapturic acid and other related products that are nontoxic and are eliminated in urine. If, however, glutathione stores are depleted by malnutrition or if production of NAPQI is increased (as in acetaminophen overdose), insufficient glutathione is available to detoxify the intermediate. In this case, detoxification is capacity limited, and unconjugated NAPQI accumulates, binds covalently to hepatic tissue macromolecules, and causes oxidative stress, tissue damage, or necrosis.⁶

Acetaminophen-induced hepatotoxicity is associated most frequently with large, single ingestions, usually related to suicide attempts. In adults, dosages of less than 6 g/day usually are considered nontoxic, even though the upper limit recommended by most authorities is 4 g/day.⁷ Single doses of less than 10 g only rarely lead to significant liver injury.

Considerable evidence indicates that acetaminophen is much more likely to cause hepatotoxicity in alcoholics, and that liver injury in these patients may occur at lower than expected doses. One author noted that among regular users of alcohol who developed symptomatic acetaminophen-related hepatotoxicity, 60% had taken 6 g/day or less, and 40% had taken less than 4 g/day.⁶ Most of these patients (77%) reported taking acetaminophen for 7 days or less, and a few took it for only 1 day. Estimation of patients' cumulative doses yielded a wide range, and hepatocellular damage did not appear to relate to the cumulative dose.

The predisposition for acetaminophen-induced hepatotoxicity among alcohol users is multifactorial. Poor nutrition may limit glutathione availability and result in accumulation of hepatotoxic NAPQI. In addition, whereas short-term alcohol ingestion results in inhibition of the hepatic cytochrome system, long-term use causes potent induction of these enzymes.^{6, 8-10}

rate of drug metabolism and consequently increases the rate of production of toxic intermediates. Thus the absolute amount of NAPQI produced by a therapeutic dose of acetaminophen taken by an enzyme-induced person may be the same as the amount of NAPQI produced by a toxic dose in a nonenzyme-induced individual. In either case, if glutathione stores are insufficient to detoxify the metabolite, NAPQI can accumulate, bind to tissue macromolecules, and cause hepatic injury.

In focusing on the potential contribution of enzyme induction to acetaminophen toxicity, it is important to note that conversion of acetaminophen to NAPQI usually is attributed to the CYP2E1 isoform. Ethanol is a potent inducer of CYP2E1. As with ethanol, drugs known to induce CYP2E1 have been associated with an apparent predisposition to acetaminophen hepatotoxicity. Acarbose potentiated both carbon tetrachloride- and acetaminophen-induced hepatotoxicity in rats.¹¹ When a second CYP2E1 inducer, ethanol, was administered in addition to acarbose, the severity of acetaminophen hepatotoxicity increased even more.

Case reports describe four patients who experienced serious acetaminophen-induced hepatotoxicity while taking isoniazid.^{12, 13} Isoniazid is also a potent inducer of the CYP2E1 isoform, and it is of particular note that in three of these four patients hepatotoxicity resulted from modest, therapeutic doses of acetaminophen.

In our patient the suspected enzyme inducer was phenytoin, and only a few reports and studies address this potential interaction. Three patients treated with phenytoin took intentional acetaminophen overdoses.^{14, 15} When given emergency care, however, their plasma acetaminophen concentrations were below the treatment action line and therefore they did not receive acetylcysteine.⁷ All patients experienced hepatic failure and one died. The authors attributed the unexpected hepatotoxicity to enzyme induction by phenytoin.

Although these patients intentionally took excessive doses of acetaminophen, three other individuals developed hepatotoxicity after taking

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believe that the literature suggests a strong and largely underappreciated potential for acetaminophen-induced hepatotoxicity in patients whose CYP3A4 isoform is induced by concurrent drugs. Thus, although our patient did not have clinical symptoms, we recommend that patients receiving known inducers of CYP2E1 or CYP3A4 be cautioned about even short-term, modest-dose acetaminophen.

Acknowledgment

We gratefully acknowledge the assistance of Joseph F. Dasta, M.S., in preparing this manuscript.

References

1. Minar E, Ehringer H, Hirschl M, et al. Transaminase increase: a largely unknown side-effect of heparin treatment. *Dtsch Med Wochenschr* 1980;105:1713-17.
2. Fagher B, Lundh B. Heparin treatment of deep vein thrombosis. Effects and complications after continuous or intermittent heparin administration. *Acta Med Scand* 1981;210:357-61.
3. Nielsen HK, Husted SE, Koopmann HD, et al. Heparin-induced increase in serum levels of aminotransferases. A controlled clinical trial. *Acta Med Scand* 1984;215:231-3.
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