



3498325-X-00-01

REPORT

The Purdue Frederick Company

FDA Approved 11/08/93

Mfr report #	200212
UF/Dist report #	
FDA Use Only	

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 5

A. PATIENT INFORMATION

1. Patient identifier N/I	2. Age at event 55 YEARS or DOB:	3. Sex <input checked="" type="checkbox"/> female <input type="checkbox"/> male	4. Weight lbs or kgs
------------------------------	---	---	-------------------------------

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. <input checked="" type="checkbox"/> Adverse Event and/or	<input type="checkbox"/> Product problem
2. Outcomes attrib. to event <input type="checkbox"/> death <input type="checkbox"/> life-threatening <input checked="" type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> disability <input type="checkbox"/> congen anomaly <input type="checkbox"/> required intervention to prevent perm damage <input type="checkbox"/> other:
3. Date of event	4. Date of this Rept 05/05/2000

5. Describe event or problem

"Interaction with concomitant phenytoin leading to liver dysfunction." A Case Report: "A 55-year-old woman, who was taking phenytoin for post-traumatic seizures, developed liver dysfunction after she took large doses of paracetamol (acetaminophen) for analgesia during treatment for pneumonia. She also had a history of thrombosis and was receiving warfarin. The patient was taking phenytoin 400mg every other day alternating with 300mg. She was initially treated as an outpatient for pneumonia with cefprozil and hydrocodone with paracetamol 1-2 tablets every 6 hours as needed. However, her condition worsened and she developed new-onset haemoptysis and she was admitted to hospital. Warfarin was stopped and she was transferred to another facility for placement of an inferior vena cava filter. Routine laboratory tests revealed elevated levels of hepatic transaminases, lactate dehydrogenase and alkaline phosphatase. A review of the patient's medications indicated that she had been prescribed several agents for musculoskeletal pain during her hospitalisation. These included oxycodone with paracetamol 1-2 tablets every 4 hours as required (325mg paracetamol per tablet), propoxyphene napsylate with paracetamol 1-2 tablets every 4-6 hours (650mg paracetamol per tablet) and paracetamol 500 mg 1-2 tablets every 4-6 hours as needed. Overall, she had received dosages of 1300-6200 mg/day of paracetamol over a 10-day period. All paracetamol-containing agents were stopped and propoxyphene alone was given for musculoskeletal pain. At discharge, the woman was warned to avoid paracetamol-containing products. Her liver (CONTINUED)

6. Relevant tests/laboratory data, including dates

RELEVANT TEST/LAB DATA: See narrative

DSS
MAY 10 2000

7. Other relevant history, including pre-existing conditions

See Narrative

REC'D
MAY 09 2000
CDR
EVALUATION AND RESEARCH

C. SUSPECT MEDICATION(S)

1. Name (give labeled strength & mfr/labeler, if known) (CONT)	
#1 dihydrocodeine (similar to ANDA 88-584) #2 oxycodone hydrochloride (similar to NDA 20-553)	
2. Dose, frequency & route	3. Therapy dates (if unk, give dur)
#1 2 TAB Q6H PO #2 2 TAB Q4H PO	#1 UNKNOWN (STOP'D) #2 UNKNOWN
4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 ANALGESIA #2 SUICIDE	#1 <input checked="" type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A #2 <input checked="" type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A
6. Lot # (if known)	7. Exp. Date
#1 UNKNOWN #2 UNKNOWN	#1 #2
9. NDC # for prod problems only	
10. Concomitant medical products and therapy dates CEFPROZIL (STOP'D), WARFARIN (STOP'D), DILTIAZEM HCL, CISAPRIDE, FANOTIDINE, PAROKETINE HCL, IBUPROFEN (STOP'D)	

G. ALL MANUFACTURERS

1. Contact office - name/address	2. Phone number
The Purdue Frederick Company 100 Connecticut Avenue Norwalk, CT 06850-3590	203-853-0123
3. Report Source (check all that apply)	
<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:	
4. Date Rec'd by Mfr.	5. (A)NDA#
05/01/2000	
6. If IND, protocol #	IND#
	PLA#
7. Type of report (check all that apply)	pre-1938 <input type="checkbox"/> yes OTC <input type="checkbox"/> yes product <input type="checkbox"/> yes
<input type="checkbox"/> 15-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 110-day <input type="checkbox"/> periodic <input type="checkbox"/> Init <input checked="" type="checkbox"/> follow-up # 1	8. Adverse event term(s)
	LIVER DAMAGE DRUG INTERACTION
9. Mfr. report number	
200212	

E. INITIAL REPORTER

1. Name, address & phone #		
BRACKETT CC, BLOCH JD ET AL PHARMACOTHERAPY FEB 2000; 20:229-233 ; USA		
2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
<input checked="" type="checkbox"/> yes <input type="checkbox"/> no	CLINICAL PHARMACIST	<input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> unk

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

Facsimile Form 3500A



3498325-X-80-02

REPORT

FDA Approved 11/08/93

MEDWATCH

The Purdue Frederick Company

Mfr report #	200212
UF/Dist report #	
FDA Use Only	

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 2 of 5

A. PATIENT INFORMATION

1. Patient identifier	2. Age at event or _____ DOB: _____	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight (lbs or kgs)
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B. ADVERSE EVENT OR PRODUCT PROBLEM

1. <input type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product problem	2. Outcomes attrib. to event <input type="checkbox"/> death (mo/day/yy) <input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> disability <input type="checkbox"/> congen anomaly <input type="checkbox"/> required intervention to prevent perm damage <input type="checkbox"/> other: _____
3. Date of event	4. Date of this Rept 05/05/2000	

5. Describe event or problem

transaminase levels were normal at follow-up 2 and 6 weeks later." Literature Citation: "Interaction with concomitant phenytoin leading to liver dysfunction": Report of A Case, Pharmacotherapy Feb 2000; 20:229-233. A copy of the complete article is being requested.

***Follow up information received on 01MAY00 in the form of the complete article revealed that, "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 36 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 (CONTINUED)

6. Relevant tests/laboratory data, including dates

DSS

MAY 10 2000

7. Other relevant history, including preexist. med. conditions

C. SUSPECT MEDICATION(S)

1. Name (give labeled strength & mfr/labeler, if known) (CONT)		
#3 OXYCODONE W/ACETAMINOPHEN #4 HYDROCODONE W/ACETAMINOPHEN		
2. Dose, frequency & route	3. Therapy dates (if unk, give dur)	
#3 2 TAB Q4H PO #4 2 TAB Q6H PO	#3 UNKNOWN (STOP'D) #4 UNKNOWN (STOP'D)	
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced
#3 MUSCULOSKELETAL PAIN #4 ANALGESIA		#3 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A #4 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A
6. Lot # (if known)	7. Exp. Date	8. Event reappeared after reintroduction
#3 UNKNOWN #4 UNKNOWN	#3 _____ #4 _____	#3 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A #4 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A
9. NDC # for prod problems only		
10. Concomitant medical products and therapy dates		

G. ALL MANUFACTURERS

1. Contact office - name/address		2. Phone number
The Purdue Frederick Company 100 Connecticut Avenue Norwalk, CT 06850-3590		203-853-0123
4. Date Rec'd by Mfr.		3. Report Source (check all that apply)
		<input type="checkbox"/> foreign <input type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer <input type="checkbox"/> health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:
5. (A)NDA#	6. If IND, protocol #	
	IND# _____ PLA# _____	
7. Type of report (check all that apply)	8. Adverse event term(s)	
<input type="checkbox"/> 15-day <input type="checkbox"/> 115-day <input type="checkbox"/> 110-day <input type="checkbox"/> periodic <input type="checkbox"/> Init <input type="checkbox"/> follow-up # _____		
9. Mfr. report number		
200212		

E. INITIAL REPORTER

1. Name, address & phone #			
2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA	
<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk	

MED INFO ASSOC Facsimile Form 3500A Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Individual Safety Report



3498325-X-00-03

EPORT

FDA Approved 11/08/93

MEDWATCH

The Purdue Frederick Company

Mfr report #	200212
UF/Dist report #	
FDA Use Only	

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 3 of 5

A. PATIENT INFORMATION

1. Patient identifier	2. Age at event	3. Sex [] female [] male	4. Weight (lbs or kgs)
-----------------------	-----------------	----------------------------------	------------------------

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. [] Adverse Event and/or	[] Product problem
2. Outcomes attrib. to event [] death (mo/day/yy) [] life-threatening [] hospitalization - initial or prolonged	[] disability [] congen anomaly [] required intervention to prevent perm damage [] other:

3. Date of event	4. Date of this Rept 05/05/2000
------------------	---------------------------------

5. Describe event or problem

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 larger than available 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...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 (CONTINUED)

6. Relevant tests/laboratory data, including dates

DSS
MAY 10 2000

7. Other relevant history, including preexist. med. conditions

C. SUSPECT MEDICATION(S)

1. Name (give labeled strength & mfr/labeler, if known) (CONT)		
#5 PHENYTOIN #6 PROPOXYPHENE HCL W/APAP		
2. Dose, frequency & route	3. Therapy dates (if unk, give dur)	
#5 400 MG QOD PO #6 2 TAB Q4-6H PO	#5 UNKNOWN #6 UNKNOWN (STOP'D)	
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced
#5 POST-TRAUMATIC SEIZURES #6 MUSCULOSKELETAL PAIN		#5 [] yes [] no [] N/A #6 [] yes [] no [] N/A
6. Lot # (if known)	7. Exp. Date	8. Event reappeared after reintroduction
#5 UNKNOWN #6 UNKNOWN	#5 #6	
9. NDC # for prod problems only		
- - -		
10. Concomitant medical products and therapy dates		

G. ALL MANUFACTURERS

1. Contact office - name/address		2. Phone number
The Purdue Frederick Company 100 Connecticut Avenue Norwalk, CT 06850-3590		203-853-0123
4. Date Rec'd by Mfr.		3. Report Source (check all that apply)
6. If IND, protocol #	IND#	[] foreign [] study [] literature [] consumer [] health professional [] user facility [] company representative [] distributor [] other:
7. Type of report (check all that apply)	PLA#	
[] 15-day [] 15-day [] 10-day [] periodic [] Init [] follow-up	pre-1938 [] yes OTC [] yes product [] yes	
9. Mfr. report number		8. Adverse event term(s)
200212		

E. INITIAL REPORTER

1. Name, address & phone #			
2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA	
[] yes [] no		[] yes [] no [] unk	

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

Facsimile Form 3500A

Individual Safety Report



3498328-X-06-04

RT

FDA Approved 11/08/93

MEDWATCH

The Purdue Frederick Company

Mfr report # 200212

UF/Dist report #

FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 4 of 5

A. PATIENT INFORMATION			
1. Patient identifier	2. Age at event or _____ DOB:	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight lbs or kgs
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product problem			
2. Outcomes attrib. to event <input type="checkbox"/> death <input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalization - initial or prolonged		<input type="checkbox"/> disability <input type="checkbox"/> congen anomaly <input type="checkbox"/> required intervention to prevent perm damage <input type="checkbox"/> other: _____	
3. Date of event		4. Date of this Rept 05/05/2000	
5. Describe event or problem			
<p>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 18-87% of patients. 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...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. (CONTINUED)</p>			
6. Relevant tests/laboratory data, including dates			
<p>DSS MAY 10 2000</p>			
7. Other relevant history, including preexist. med. conditions			

C. SUSPECT MEDICATION(S)	
1. Name (give labeled strength & mfr/labeler, if known) #7 ACETAMINOPHEN #	
2. Dose, frequency & route #7 2 TAB Q4-6H PO #	3. Therapy dates (if unk, give dur) #7 UNKNOWN (STOP'D) #
4. Diagnosis for use (indication) #7 MUSCULOSKELETAL PAIN #	5. Event abated after use stopped or dose reduced #7 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A # <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A
6. Lot # (if known) #7 UNKNOWN #	7. Exp. Date #7 #
9. NDC # for prod problems only - -	
8. Event reappeared after reintroduction #7 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A # <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> N/A	
10. Concomitant medical products and therapy dates	

G. ALL MANUFACTURERS	
1. Contact office - name/address The Purdue Frederick Company 100 Connecticut Avenue Norwalk, CT 06850-3590	
2. Phone number 203-853-0123	
3. Report Source (check all that apply) <input type="checkbox"/> foreign <input type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer <input type="checkbox"/> health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:	
4. Date Rec'd by Mfr.	5. (A)NDA# IND# PLA# pre-1938 <input type="checkbox"/> yes OTC <input type="checkbox"/> yes product <input type="checkbox"/> yes
6. If IND, protocol #	8. Adverse event term(s)
7. Type of report (check all that apply) <input type="checkbox"/> 15-day <input type="checkbox"/> 15-day <input type="checkbox"/> 110-day <input type="checkbox"/> periodic <input type="checkbox"/> Init <input type="checkbox"/> follow-up	9. Mfr. report number 200212

E. INITIAL REPORTER			
1. Name, address & phone #			
2. Health professional? <input type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation	4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk	

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



3496325-X-00-05

The Purdue Frederick Company
Ref. report # 200212
Page 5 of 5

3500A Continuation Page

B5. DESCRIBE EVENT OR PROBLEM (continued)

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." The authors commented that "...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."

MAY 09 2000

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MAY 10 2000



CASE REPORTS

J00010

 MAY 01 2000
 MAYRA BALLINA, M.D.

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)

MAY 09 2000

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MAY 10 2000

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 36 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 larger than available

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.



Table 1. Hepatic Chemistry Values

Test	Date								
	2/09	2/10	2/11	2/12	2/16	2/18	2/19	3/03	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

ND = not done.

DSS

MAY 09 2000

MAY 10 2000

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



Table 2. Acetaminophen Doses

Dose (mg)	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
	2800	5200	6200	5200	2600	2600	1950	2600	2600	2600	1300	0

MAY 10 2000

MAY 09 2000

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} Induction of the cytochrome system increases the

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 only 4-6 g/day.¹⁰ They were all alcoholic, and



MAY 09 2000

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 enzyme 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

MAY 10 2000



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.

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MAY 10 2000

MAY 09 2000