

Memorandum

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To: The APAP Hepatotoxicity Working Group Committee
Division of Over the Counter Drug Products (HFD-560)
Re: Acetaminophen Hepatotoxicity working group PK consult for metabolic issues
and drug interactions (from meeting held on July 13th, 2001)

Introduction:

The relative safety of acetaminophen (APAP) induced hepatotoxicity is still a major area of concern. These hepatotoxic effects are dose-related and generally occur in patients that ingest large single and/or multiple doses exceeding 150-mg/kg body weight. In the case of pediatric use, the major cause of APAP hepatotoxicity identified in retrospective reviews of case reports was dosing errors by parents or caregivers^{1,2}.

In addition to the acute suicidal or accidental intoxication, recent literature reviews suggest that long-term administration of "therapeutic" doses of acetaminophen in patients compromised by illness, chronic ethanol use, genetic predisposition, and co-ingestion with substances metabolized by the liver and other factors, may also cause hepatic injury particularly in adolescents and adults^{1, 2, 3}. Thus it is possible that certain patients who receive only normal doses of APAP may be at increased risk for hepatocellular injury. The main objective of this review is to review the literature on the metabolic issues and, clinically relevant drug-drug interactions related to APAP hepatotoxicity.

Methods:

This was primarily a review of past and current literature obtained from different databases as described below:

Data Source: (1) A MEDLINE search (January 1st 1985 - May 18th, 2001) of English-language articles was performed using the terms acetaminophen/adverse effects OR acetaminophen/poisoning OR acetaminophen/toxicity AND "liver diseases/chemically induced. Also the terms acetaminophen and "biological markers" and "[molecular probes and acetaminophen] were used. (2) An EMBASE search (1990 to May 2001) of English language articles in humans was also performed using the terms 'liver toxicity and 'paracetamol'. (3) A Micromedex Integrated Index Database search looking at the following specific files: Toxicological Managements, Martindale, Hazardous Substances Data Bank, DrugDex Drug Evaluations.

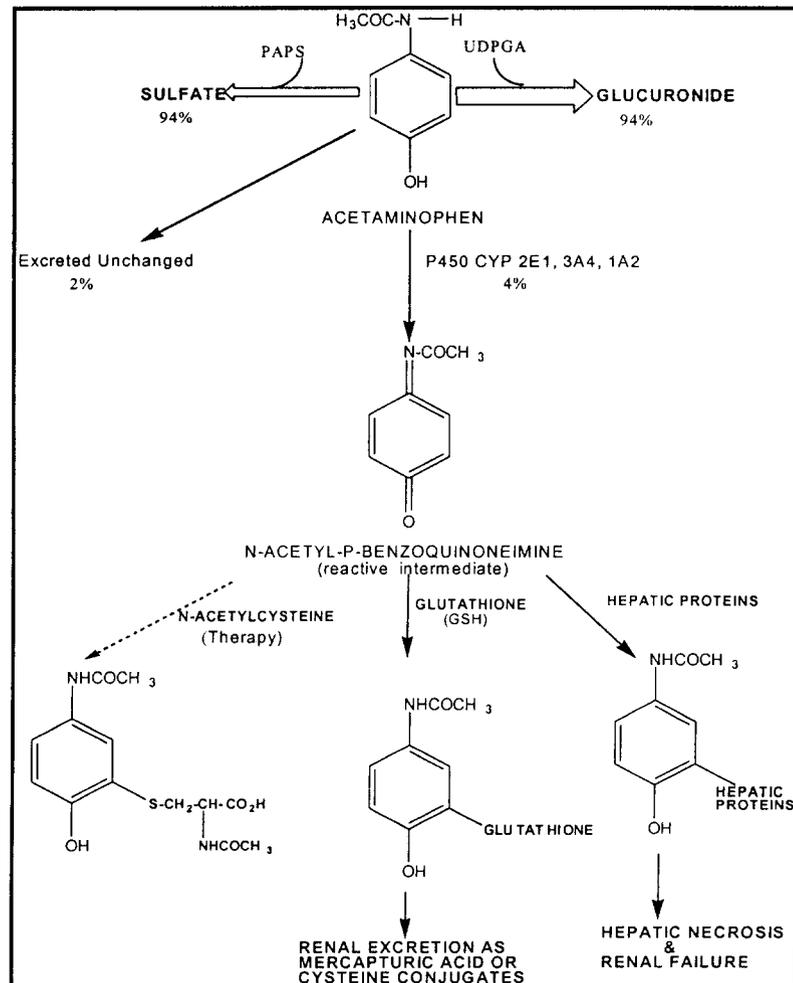
Data Extraction: The articles relevant to metabolic issues related to APAP hepatotoxicity and, drug-drug interactions that potentiate or may potentiate APAP hepatotoxicity were abstracted in terms of their clinical significance. Since the quality of data reported in the literature vary considerably, controlled clinical studies would allow for better verification and

determination of the clinical importance of the potential drug interactions as opposed to case reports which are usually anecdotal. Therefore, the categories in descending order of quality of data were as follows: Class A data (randomized, controlled trials), Class B data (retrospective, nonrandomized trials) and Class C data (retrospective case reviews and case reports).

Results:

Metabolic Issues Related to APAP Hepatotoxicity

At therapeutic doses, acetaminophen is metabolized primarily in the liver. Toxicity following overdose with APAP has been attributed to the production of a minor, but highly reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI) by mixed function oxidase enzymes in the liver and kidney. Ninety-four percent of APAP (94%) is metabolized via two conjugation (phase II) pathways: sulfation and glucuronidation; a small fraction (~4%) is hepatically metabolized in man by the cytochromes P450 (currently identified as predominantly CYP 2E1 and less of CYP 1A2 and CYP 3A4) producing the reactive (toxic) intermediate NAPQI. NAPQI is then detoxified by glutathione (GSH) to form 3-(glutathion-S-yl)-acetaminophen a non-toxic intermediate that is renally excreted as mercapturic acid or cysteine conjugates^{4, 5, 6}. At therapeutic doses, APAP is perceived as having a wide margin of safety because only a small amount of NAPQI is formed and there is an adequate supply of GSH for detoxification⁶. A schematic presentation of the pathways of APAP metabolism is shown below:



When sustained therapeutic or single toxic doses (>7.5-10 grams) of APAP are ingested, the sulfation and glucuronidation pathways become saturated, and the P450 pathway assumes a larger role, leading to the production of greater amounts of NAPQI. If hepatic GSH stores are depleted by more than 70% from normal because of fasting or excess production of NAPQI, then NAPQI will bind covalently to thiols in hepatocyte proteins leading to hepatotoxicity.

Published literature on the analgesic and antipyretic effects of APAP revealed a therapeutically effective plasma concentration range of 10-30 mcg/mL⁷. In adults chronic APAP doses > 5gm/day usually result in hepatotoxicity. Acute APAP hepatotoxicity in adults usually occurs at doses > 15gm. In children, risk is defined as doses > 150 mg/kg. The Rumack and Matthew nomogram is used to estimate the potential for hepatotoxicity by correlating APAP plasma concentration with time after exposure following ingestion of a single dose. Patients with concentrations > than 300 mcg/mL at 4 hours or 50 mcg/mL at 12 hours have a 90 % chance of developing severe and often fatal liver damage as defined by elevation of the plasma transaminase activities above 1000 IU/L. Minimal hepatic damage can be anticipated when the drug concentration is less than 125 mcg/mL at 4 hours after ingestion. Pharmacokinetic data also suggest that the hepatic supply of reduced GSH begin to be depleted in humans after ingestion of 0.5g to 3.0g APAP⁸.

It is proposed that conditions that reduce glutathione stores or enhance the induction of enzymes involved in the bioactivation of acetaminophen to NAPQI (e.g., the cytochrome P450: CYP2E1, CYP3A4, CYP1A2) can potentiate the hepatotoxic effect of acetaminophen. Proposed risk factors that have been associated with APAP hepatotoxicity with chronic use include age, total dose, duration, presence of intercurrent febrile illness, chronic alcoholics and binge drinkers, starvation, co-administration of cytochrome P450-inducing drugs, underlying hepatic disease and unique genetic makeup¹.

Published reports suggest that the risk of developing APAP induced hepatotoxicity is lower in children (< 10 years old) than in adults. This is probably because Infants and children (0-9 years) metabolize acetaminophen differently from adults and children 12 years and older. Because of an increased capacity to conjugate the drug with sulfate on a mg/kg basis they may be afforded relative "protection" from acute acetaminophen intoxication. However, it is unclear at what age this relative protection from acetaminophen toxicity declines, but based on several studies, the transition may occur between 9 and 12 years⁹.

There is also a report in the literature indicating that subjects with genetic deficiency in glutathione synthetase deficiency, a rare disorder, may have a limited capacity for detoxification of NAPQI by conjugation with GSH resulting in increased risk of hepatotoxicity¹⁰.

Drug-Drug Interactions

Reproduced in the table below are concomitant drug therapy identified in the literature that may increase susceptibility to APAP hepatotoxicity. The review of the case reports and controlled clinical studies abstracted from the literature are included as Tables in the Appendix, pages 7-12.

Table 1: Summary of the Literature Reports of Concomitant Drug Therapy that may increase the Susceptibility to Acetaminophen Hepatotoxicity

| Drug Name | Probable Mechanism | Reference Number |
|--|---|-------------------------|
| Anticonvulsants | | |
| Phenytoin | Phenytoin induction of CYP3A4. | 11, 12, 13 |
| Fosphenytoin | Same as phenytoin. | 14 |
| Carbamazepine | Carbamazepine induction of CYP 3A4 and 1A2. | 15 |
| Antibacterials | | |
| Isoniazid | Variable, first inhibits then enhances NAPQI formation as it is cleared by induction of CYP 2E1 | 16, 17, 18,19 |
| Combination Therapy (Isoniazid, Rifampicin and Pyrazinamide) | INH induction of CYP2E1 and Rifampicin induction of CYP 1A2 and 3A4. | 20 |
| Antivirals | | |
| Zidovudine | Not Known. Possibly diminished stores of GSH due to poor nutrition in patients with AIDS. | 21,22 |
| Interferon | Hepatotoxic reactions observed. Mechanism Unknown. | 23 |
| Uricosuric Agents | | |
| Probenecid | Mechanism unknown. May be combination of inhibition of APAP glucuronidation and impairment of the renal active transport of APAP glucuronide. | 33, 34 |
| Sulfinpyrazone | Mechanism unknown. Increased metabolism of APAP by about 22% reported. | 35 |
| Other Drugs | | |
| Alcohol | Unknown. With chronic ethanol intake it may be due to alcohol induction of CYP 2E1 and depletion of GSH stores due to malnourished status. Acute alcohol intake inhibits microsomal oxidation of APAP in man and is hepatoprotective. | 27, 28, 29, 30 |
| Diflunisal (Analgesic, Anti-inflammatory and Antipyretic) | Mechanism unknown. 50% increase in plasma concentrations of APAP reported. | 31 |
| Metyraprone (an oral agent used for pituitary function ACTH tests) | Inhibition of APAP glucuronide formation | 32 |
| Lansoprazole (An acid proton inhibitor for TX of ulcers) | Increased peak plasma concentrations of APAP. Mechanism unknown | 36 |
| Thyroxine | Patient developed centrolobular hepatic necrosis. Mechanism unknown | 37 |
| Mercury Poisoning | Potential of APAP hepatotoxicity. Mechanism unknown | 38 |
| Total Parenteral Nutrition | TPN may have diminished patient's hepatic reserve making him more susceptible to hepatotoxicity from chronic APAP usage. | 39 |

Reproduced in Table 2 below is a categorization of the abstracts in terms of the quality of the **literature data** on drug-drug interactions that may potentially increase the risk of APAP hepatotoxicity:

Table 2: Summary of the Categorization of the Literature Reports on Drug-Drug Interactions with APAP associated Hepatotoxicity

| Drug | ¹Category of Data | APAP Dose (Plasma APAP concentration) |
|----------------------------------|-------------------------------------|--|
| Phenytoin | Class C | 1300 - 6200 mg/day |
| Carbamazepine | Class C | 7800 mg (15 mcg/mL) |
| Isoniazid (INH) | Class C | 11.5 g |
| Rifampicin | Class C | Not reported |
| Interferon | Class C | 2-3g three times a week |
| Alcohol | Class C | Chronic ingestion 1-3g daily (both patients consumed large quantities of alcohol) |
| | Class C | Patient 1: 14 x 30mLs of Nyquil [(1g/30mL) APAP & 25% Ethanol] over 1-day Patient 2: 8-10 Tylenol ES (500mg/tab/day) x1 week + 14 x 30mLs of Nyquil over 3-days (Both patients had a history of alcohol abuse) |
| | Class C | 360 mL of Nyquil (~ 12g) over a 12 hour period (patient was alcoholic, had ingested 1-2 cases of beer daily 3 days prior to Nyquil ingestion) |
| | Class C | 4-6.1g/day (All regular users of alcohol, 64% were chronic alcoholics) |
| | Class B | 4-10g/day |
| | Class A | Ten healthy volunteers ingested 500 mg APAP 8 hours after infusion of ethanol (to achieve a blood concentration of 100 mg/dL of ethanol). |
| Probenecid | Class A | 1500 mg orally one hour after probenecid dose |
| | Class A | 650 mg I.V. on 2 occasions with concurrent administration of probenecid (500 mg) Q6h |
| Sulfinpyrazone | Class C | 1 g oral dose |
| Diflunisal | Class C | Not reported |
| Lansoprazole | Class C | Not reported |
| Metyrapone | Class A | 1g on two separate occasions |
| Thyroxine | Class C | 1.5-2g daily for 12 days |
| Total Parenteral Nutrition (TPN) | Class C | 160 mg/5 mL ~ 19.5 mg per kg every 4 hours for 4 days (APAP level = 46 mcg/mL) |

¹ Class A data (randomized, controlled trials); Class B data (retrospective, nonrandomized trials) and Class C data (retrospective case reviews and case reports)

Literature Reports of Disease states and APAP Hepatotoxicity

Reproduced in the table below are the disease and dietary states that may increase the risk of APAP hepatotoxicity identified in the literature. The review of the literature on the disease states and nutritional status is included in the Appendix on page 12. Some information on the nutritional status was also extracted from the drug-drug interaction data.

Table 3: Disease and Dietary States that may increase the risk of APAP hepatotoxicity

| Disease State or Dietary States | Reference Number |
|--|-------------------------|
| Gilbert's syndrome (benign, mild, chronic unconjugated hyperbilirubinemia) | 40 |
| Chronic Renal, Cardiac and Pulmonary disease | 41 |
| Prolonged Fasting or Starvation | 28, 42 |
| Poorly Controlled Diabetes Mellitus | 43 |
| Obesity | 44 |

Conclusions:

Hepatotoxicity of APAP depends largely upon the rate of formation of the toxic metabolite, NAPQI and the rate of depletion of hepatic GSH. In conclusion, the literature review revealed that those drugs and or disease states that affect normal homeostatic liver function places those subjects at a higher risk of APAP associated liver toxicity.

Recommendations:

The following areas of drugs and disease states that may potentiate the risk of APAP hepatotoxicity that would require further research have been identified as follows:

- 1) Drugs that induce cytochrome P450 enzymes CYP 2E1, CYP 3A4 and CYP 1A2 that are primarily involved in the bioactivation of APAP to NAPQI, the toxic metabolite
- 2) The drugs that inhibit glucuronide formation
- 3) Lifestyle factors e.g. alcohol intake
- 4) Education of the healthcare providers and consumers on the different medications, chronic disease states and dietary status that may increase the risk of developing APAP hepatotoxicity.

APPENDIX

A. Drug-Drug interactions:
 1. Anticonvulsants

| Drug | Case Report or Study design | Probable Mechanism of Action/Recommendations |
|------------------------|--|--|
| Anticonvulsants | | |
| Phenytoin | <p>A. A 55-year-old female smoker with chronic obstructive pulmonary disease developed community-acquired pneumonia. A 55-year old woman hospitalized for the treatment of community-acquired pneumonia. Drug regimen reviewed due to elevations in hepatic transaminase and enzyme levels. APAP 1300 - 6200 mg /day from three different analgesics was given during hospitalization along with phenytoin 400 mg alternating every other day with 300 mg for posttraumatic seizures. APAP was discontinued and patient's liver chemistry returned to normal within 2 weeks of discharge.¹¹.</p> <p>B. Liver failure and subsequent morbidity was caused by acetaminophen induction by phenytoin (Dilantin) and butalbital (Isocet)¹².</p> <p>C. The percentage urinary recovery of paracetamol and its metabolites after a dose of 20 mg/kg (syrup), and the excretion of 6β-hydroxycortisol as a ratio to urinary free cortisol (an increase will suggest induction of CYP3A3 and CYP3A4) in Chinese epileptic patients maintained on long term therapy with carbamazepine (N = 6; Age range 23-65; Dose range 300-100 mg/day) or phenytoin (N = 6; Age range = 17-40; Dose range = 100-300mg/day) was measured. Patients on phenytoin had lower recoveries of the GSH metabolites but higher recoveries of the glucuronide metabolites on comparison of the data with controls (n=20). The recoveries of paracetamol metabolites in patients on carbamazepine were no different from controls. 6β-hydroxycortisol as a ratio to urinary free cortisol was higher in patients on carbamazepine (3 fold) or phenytoin (2-fold) compared to controls. Results suggest that with both anticonvulsants there is no significant induction of the isoenzymes responsible for the metabolic bioactivation of APAP when given in therapeutic doses. Also no increased risk of APAP-induced hepatotoxicity in Chinese patients on anticonvulsants¹³.</p> | Acetaminophen-induced liver injury secondary to enzyme induction was suspected. Phenytoin induces CYP3A4. CYP3A4 participates in APAP hepatotoxicity and induction of this isoform may predispose patients to APAP induced hepatotoxicity. |
| Fosphenytoin | Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin are expected to occur with fosphenytoin ¹⁴ . | Acetaminophen-induced liver injury secondary to enzyme induction was suspected. |
| Carbamazepine | A 17-year-old female with a history of anorexia nervosa and who was receiving carbamazepine 300 mg daily for mood stabilization ingested acetaminophen 7800 mg in a suicide attempt. Upon admission to the hospital, her liver function tests were significantly elevated and her serum acetaminophen | Carbamazepine is known to induce the cytochrome P450 system (2C19, 3A4 1A2), and her malnutrition status depleted her glutathione |

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| | level was 15 mcg/mL (Reported serum concentration of APAP to achieve therapeutic benefits is 10-20 mcg/mL) ¹⁵ . | concentrations. These two factors resulted in a greater concentration of acetaminophen toxic metabolites, resulting in liver failure |
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2. Antibacterials

| Drug | Case Report or Study Design | Probable Mechanism of Action/Recommendations |
|-----------------|--|--|
| Isoniazid (INH) | <p>A. A 19-year-old woman being treated with isoniazid developed liver and renal toxicity following an ingestion of 11.5 grams acetaminophen. Liver function tests peaked 2-4 days post-ingestion while BUN and creatinine peaked at 7 and 10 days respectively. Liver function tests were within normal limits and renal function tests were nearly normal 130 days post-ingestion¹⁶.</p> <p>B. Four more cases of isoniazid-acetaminophen clinical interaction have been reported anecdotally. Two of the patients died of liver failure after taking unspecified amounts of acetaminophen while on maintenance isoniazid therapy; it is uncertain whether these cases represent acetaminophen overdose or true drug interaction^{17,18}.</p> <p>C. In a volunteer study (10 subjects) those who were fast isoniazid acetylators formed more of the toxic metabolite of acetaminophen (NAPQI) when acetaminophen was administered 12 hours after isoniazid agents¹⁹.</p> <p>D. COMBINATION THERAPY Three additional cases of hepatotoxicity in association with APAP use (overdose and therapeutic) in young adult women have been reported in patients on combination therapy for tuberculosis including isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin. Although clinical signs and symptoms varied among the 3 patients, all had greatly increased serum levels of hepatic enzymes. All signs and symptoms of hepatotoxicity resolved after discontinuation of all medications, and, when antituberculosis treatment was resumed, no further adverse effects were seen²⁰.</p> | Data suggest that INH or rifampin or both may potentiate the hepatotoxicity of APAP, perhaps by induction of cytochrome P450 isoenzymes. INH is an inducer of CYP 2E1 and, rifampin is an inducer of 1A2, 2C19, 2C9 and 3A4. |

3. Antivirals

| Drug | Case Report or Study Design | Probable Mechanism of Action |
|------------|--|--|
| Zidovudine | <p>A case of acute acetaminophen-related hepatotoxicity has been described with concurrent use of APAP and zidovudine. Malnutrition (perhaps disease-related) resulting in decreased hepatic reserves of glutathione was however suggested as a risk factor in the case of acetaminophen-associated hepatotoxicity²¹.</p> <p>B. A 43-year-old man with HIV-1 infection had used acetaminophen (along with codeine and diazepam) for more than</p> | Not Known. Patients with HIV may be at increased risk for APAP toxicity because of decreased GSH stores. |

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| | three years when he began zidovudine therapy. He used concurrent zidovudine 100 mg every six hours and acetaminophen 500 mg every four hours for eight months without experiencing zidovudine or acetaminophen toxicity. Although acetaminophen use might have accelerated the absorption of zidovudine, no other effect on zidovudine pharmacokinetics was seen. Zidovudine had no apparent effect on acetaminophen pharmacokinetics in this case ²² . | |
| Interferon | Hepatotoxic reactions were observed in 3 patients (in a series of 25) who received interferon, vinblastine, and acetaminophen 2 to 3 grams three times a week. Rechallenge with acetaminophen alone produced elevated liver enzymes, while rechallenge with the cytotoxic regimen did not ²³ . | Mechanism unknown. |

4. Alcohol

| Drug | Case Report or Study Design | Probable Mechanism of Action |
|---------|--|---|
| Alcohol | <p>A. A report of hepatotoxicity occurring with therapeutic doses of acetaminophen was provided. Two female patients (Aged 58 and 46 years old) developed hepatic damage with clinical and morphological features of acetaminophen hepatotoxicity following chronic ingestion of therapeutic doses (1 to 3 grams daily). Both patients consumed large quantities of alcohol, although no signs of alcoholic liver disease were present²⁴.</p> <p>B. The occurrence of hepatic dysfunction was reported in 2 patients following ingestion of Nyquil(R), a nonprescription product containing acetaminophen 1 g/30 mL and ethanol 25%. The first patient, a 56-year-old male, ingested approximately 14 ounces of Nyquil(R) over a 1-day period (2 to 3 days prior to admission). The second patient, a 37-year-old female, ingested 8 to 10 Tylenol Extra Strength(R) tablets (acetaminophen 500 mg per tablet) daily for approximately 1 week prior to admission; the patient also consumed 14 ounces of Nyquil(R) during a 3-day period prior to admission. Both patients had a history of alcohol abuse²⁵.</p> <p>C. Massive hepatic necrosis occurred in a 45-year-old male following ingestion of 360 mL of Nyquil(R) over a 12 hour period (~7g of APAP). The patient was alcoholic and had ingested 1 to 2 cases of beer daily up to 3 days prior Nyquil(R) ingestion²⁶.</p> <p>D. This paper describes 67 patients who developed hepatic injury after ingestion of APAP with therapeutic intent. All were regular users of alcohol, with 64% being reported as alcoholics (> 80 g/day), 35% took 60g/day or less, and the remainder were vague. Doses of APAP were within the non-toxic range 4-6.1 g/day. Almost 20% of the patients died. This study provides further evidence of hepatic injury in regular users of alcohol, especially chronic alcoholics who take APAP with therapeutic intent²⁷.</p> <p>E. The objective of the study was to evaluate the association of fasting and alcohol use with hepatotoxicity from acetaminophen ingested for therapeutic reasons. Forty nine patients with APAP</p> | <p>Probable Mechanism: Unknown; possibly due to alcohol-induced cytochrome P450 2E1 (CYP2E1) enzyme induction and increased formation of hepatotoxic APAP metabolites and the depletion of GSH (especially in fasting or malnourished patients) in regular users of alcohol.</p> <p>APAP-alcohol interaction is complicated, because acute and chronic ethanol intakes have opposite effects. Acute ethanol intake inhibits the microsomal oxidation of APAP in man and protects the liver from its damage by the oxidized metabolites, while APAP hepatotoxicity is enhanced in chronic alcoholics (perhaps by impairing glutathione synthesis). Possibility remains that chronic consumption of alcohol does increase the risk of APAP hepatotoxicity³⁰.</p> |

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| | <p>hepatotoxicity were identified, 21 (45%) ingested APAP for therapeutic reasons. Recent fasting was more common than recent ethanol use in those who took a dose of 4 to 10 g/day. Recent ethanol use was more common than fasting in those who took more than 10 g/. All patients with hepatotoxicity took more than 4g/day. APAP after an overdose appears to be enhanced by fasting in addition to alcohol ingestion²⁸.</p> <p>F. Ten healthy volunteers each received a 6-hour intravenous infusion of ethanol (to achieve a blood concentration of 100 mg/dL ethanol) or 5% dextrose in water, administered in random order. Acetaminophen (500 mg) was ingested 8 hours after the end of the infusion. Blood and urine were collected for assessment of formation of N-acetyl-p-benzoquinone imine (NAPQI). Mean NAPQI formation was enhanced by 22% (range, 2% to 38%; P < .03) when the acetaminophen dose was given after an ethanol infusion, compared with after 5% dextrose in water infusion. This mean increase was similar in magnitude to that predicted by a mathematical model describing the induction of CYP2E1, the main enzyme catalyzing NAPQI formation, by a mechanism of enzyme stabilization. They concluded that consumption of up to one 750-mL bottle of wine, six 12-ounce cans of beer, or 9 ounces of 80-proof liquor over the course of a single evening modestly increases the fraction of an acetaminophen dose converted to its toxic metabolite, NAPQI, when acetaminophen is ingested soon after ethanol has been cleared from the body²⁹.</p> | <p>The data from this study suggests that if a lapse of at least 8 hours occurs from the last ethanol dose to the time of acetaminophen ingestion, the timing may be sufficient for the transition from inhibited to moderately enhanced N-acetyl-p-benzoquinone imine (toxic APAP metabolite) formation. This change in acetaminophen metabolism may present an incremental increase in the risk of acetaminophen hepatotoxicity.</p> |
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5. Other Drugs

| Drug | Case Report or Study Design | Probable Mechanism of Action |
|---|--|--|
| Diflunisal | Concomitant diflunisal and acetaminophen administration results in a 50% increase in plasma concentrations of acetaminophen ³¹ . | Unknown Mechanism Use caution if these agents are to be coadministered, especially in patients predisposed to hepatic dysfunction. Monitor liver function. |
| Metyrapone (an oral agent used for pituitary function (ACTH) tests) | Eight healthy male volunteers participated in a study to determine the effect of metyrapone on the elimination rate of acetaminophen and on the apparent formation rate of acetaminophen metabolites. This randomized crossover study involved subjects receiving a single oral dose of acetaminophen 1 gram on two separate occasions. On one occasion, subjects also received metyrapone 750 mg one hour before and three hours after the acetaminophen dose. Metyrapone increased the half-life of acetaminophen by 46% (from 2.4 hours to 3.5 hours). The fraction of the acetaminophen dose recovered as the glucuronide metabolite was decreased by 31% in the presence of metyrapone, while the fraction recovered as the sulfate and mercapturic acid conjugates were increased by 53% and 127%, respectively. These results suggest that metyrapone could potentiate acetaminophen toxicity by being a more potent inhibitor of glucuronide conjugation than of oxidation ³² . | Probably inhibition of APAP glucuronide formation. Use caution when administering acetaminophen to a patient on metyrapone therapy. Lower doses of acetaminophen may be warranted. Alternatively, an analgesic that does not contain acetaminophen could be administered. |
| Probenecid (uricosuric agent) | In a single-dose pharmacokinetic study in 10 healthy subjects, administered a single dose of acetaminophen 1500 mg orally, and two weeks later the subjects were administered the same dose of | The mechanism of action may be a combination of probenecid inhibition of acetaminophen |

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| | <p>acetaminophen one hour after probenecid 1000 mg. After probenecid, mean acetaminophen clearance decreased from 6.2 +/- 0.5 mL/min/kg to 3.4 +/- 0.3 mL/min/kg (P less than 0.05). Mean acetaminophen Cmax was increased from 18.2 +/- 1.9 mcg/mL to 23.5 +/- 1.1 mcg/mL (P less than 0.05) and mean half-life increased from 127 +/- 9 min to 206 +/- 32 min (P less than 0.05). The mean urinary excretion of acetaminophen sulfate and acetaminophen glucuronide was significantly reduced from 243.4 +/- 44.8 to 193.4 +/- 29 mg and 348.2 +/- 33.4 mg to 74.5 +/- 9.9 mg (P less than 0.05 for both), respectively. Free unconjugated acetaminophen did not decrease after probenecid administration (33.3 +/- 4 mg before and 37.9 +/- 4 mg after)³³. In another publication (of 11 subjects) it was also reported that concomitant probenecid and intravenous acetaminophen (650 mg) resulted in prolongation of the half-life (4.3 +/- 0.23 vs. 2.51 +/- 0.16 hrs) and a decreased clearance (1.78 +/- 13 vs. 329 +/- 24 mL/min) of acetaminophen with no change in the volume of distribution³⁴.</p> | <p>glucuronidation and impairment of the renal active transport of acetaminophen glucuronide.</p> <p>Suggests decreased dose threshold for APAP hepatotoxicity in patients taking probenecid (e.g. gout patients)</p> |
| Sulfinpyrazone (uricosuric agent) | <p>Pretreatment with sulfinpyrazone 800 mg daily for 1 week, followed by 1g oral dose of APAP, increased APAP clearance 22.8% and decreased elimination half-life 18.8%³⁵.</p> | <p>Clinical importance of accelerated APAP metabolism unknown. Concurrent use should be avoided if possible since patients may be at greater risk of acetaminophen hepatotoxicity. However, if used concurrently, the physician may consider monitoring liver function carefully in high risk patients</p> |
| Lansoprazole (an acid proton inhibitor used in the treatment of ulcers) | <p>This report is about a pharmacokinetic interaction between lansoprazole and acetaminophen in which the peak plasma concentrations of acetaminophen were significantly higher than in controls, and the time to peak was significantly shorter³⁶.</p> | <p>Mechanism unknown. Clinical significance unknown.</p> |
| Thyroxine | <p>A 17-year-old woman taking 100 micrograms/day of L-thyroxin for nontoxic goiter developed elevated transaminase levels and centrolobular hepatic necrosis after taking 1.5 to 2 grams of acetaminophen daily for 12 days. Viral and autoimmune hepatitis were excluded as etiologies of her hepatic injury³⁷.</p> | <p>Mechanism unknown</p> |
| Mercury | <p>The authors reported a potentiation of acetaminophen hepatotoxicity in a 9-year-old girl with mercury poisoning. The authors speculated that mercury deposition in the liver impaired the biochemical pathways necessary for acetaminophen degradation³⁸.</p> | <p>Mechanism unknown</p> |
| Total Parenteral Nutrition (TPN) | <p>A fatal chronic acetaminophen toxicity was reported in a 18-month-old male (born 14 weeks premature), who received less than the toxic dose of 1 household teaspoonful of acetaminophen elixir (160 milligrams (mg)/5 millimeters (mL), approximately 19.5 mg per kilogram (kg) per dose) every 4 hours for 4 days. Concurrent medication taken by the patient included ranitidine, cisapride, amoxicillin, and cefprozil. He was admitted for vomiting, fever, listlessness, and decreased urine, elevated liver enzymes and the acetaminophen level was 46 micrograms per mL approximately 36 hours after the last dose was received. Oral N-acetylcysteine was started with 140 mg/kg loading dose followed by 70 mg/kg for 17 doses. Patient subsequently developed respiratory and renal failures and died on hospital day</p> | <p>The patient may have residual hepatic dysfunction (fatty liver) from receiving several months of TPN that made him more susceptible to acetaminophen toxicity. Persistent vomiting may indicate hepatic inflammation from acetaminophen overdose. Caution should be taken when dosing patients with underlying risk factors for hepatotoxicity.</p> <p>Total parenteral nutrition (TPN)</p> |

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| | 12. Autopsy revealed centrilobular necrosis and macrovesicular fatty changes of the liver, acute tubular necrosis in the kidney, and cerebral ischemic injury. (Pershad et al, 1999) ³⁹ . | may diminish patients' hepatic reserve, particularly infants and toddlers, making them more susceptible to hepatotoxicity from chronic acetaminophen usage |
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B. Disease states and and Nutritional Status

| Drug | Case Report or Study Design | Probable Mechanism of Action |
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| Gilberts' Syndrome (Benign, mild, chronic unconjugated hyperbilirubinemia) - | Biotransformation of 1.5 grams of oral acetaminophen was studied in 6 patients with Gilbert's disease and 32 healthy volunteers. Two of the subjects with Gilbert's disease excreted less of the glucuronide conjugate (47.6% and 30.8%) compared with healthy volunteers (64.7%) and the other 4 subjects with Gilbert's (56.2%). These two subjects also excreted more of the cysteine and mercapturic acid conjugates (20.5% and 28.8%) than did healthy volunteers (4.9%) and the other 4 subjects with Gilbert's (7.5%) ⁴⁰ . | Suggests some patients with Gilbert's disease may be predisposed to develop acetaminophen-induced hepatotoxicity. Need to study more subjects to determine clinical significance. |
| Chronic renal, cardiac and pulmonary disease | A 67-year-old man with chronic congestive heart failure, COPD, and mild renal insufficiency developed hepatic injury (AST 3,500 IU/L, PT 20.4 seconds, zone 3 necrosis on liver biopsy) and worsening renal insufficiency after ingesting 1 to 3 grams a day of acetaminophen for 3 days. His acetaminophen level was 27.5 mcg/ml 72 hours after his last dose. There was no history of alcohol abuse or malnutrition. He was treated with NAC and recovered. Subsequent testing 5 months after recovery revealed reduced hepatic glutathione stores, prolonged acetaminophen half-life (more than 24 hours), and acetaminophen-dependent reduction in renal function (creatinine clearance 82 ml/min prior to 650 mg of acetaminophen reduced to 49 ml/min the following day) ⁴¹ . | Chronic renal, cardiac and pulmonary disease appeared to predispose this patient to acetaminophen toxicity. |
| Starvation and Excessive Alcohol Intake | Cases of two patients with fulminant hepatic failure after intake of 4-8g of paracetamol was described. In both patients starvation due to abdominal pain, nausea and vomiting or diarrhea was probably contributing to APAP hepatotoxicity. One of the patients also had excessive alcohol intake ⁴² . | Low food intake and alcohol appeared to predispose the patients to APAP hepatotoxicity |
| Diabetes mellitus | Cyp2E1 was measured in peripheral lymphocytes of 14 patients with insulin-dependent diabetes-mellitus who were in poor metabolic control (as evidenced by elevated Hb A1 levels) levels of CYP2E1 was very low to undetectable in human lymphocytes from 7 normal subjects. However, levels of CYP2E1 were elevated in lymphocytes from patients with insulin-dependent diabetes mellitus ⁴³ . | Increased activity of CYP2E1 |
| Obesity | Disposition profiles of chlorzoxazone (a putative probe of CYP2E1 activity) were obtained in 6 healthy white men (after an overnight fast and on a separate occasion a 38-hour fast) and, nine obese women and nine age-matched women. Serious to morbid obesity was associated with increased 6-hydroxylation of chlorzoxazone, consistent with induction of CYP2E1 ⁴⁴ . | Obese individuals may be at increased risk of CYP2E1 – mediated toxicities, such as APAP hepatotoxicity. |

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