Paracetamol: Safety versus Toxicity

John Stephen Forte BPharm (Hons), MSc (Lond.)

Paracetamol is an effective analgesic-antipyretic that can be administered safely to children and adults at the appropriate therapeutic doses. The drug is readily metabolised by the liver and toxic metabolites are removed by conjugation with endogenous glutathione. Accidental or deliberate overdosage can lead to hepatic toxicity that can be fatal if not treated urgently with antidotes that replenish depleted glutathione. Pharmacists have an important role to play in patient education to help reduce the incidence of paracetamol poisoning.

Keywords: paracetamol, metabolism, toxicity, poisoning

Introduction

Paracetamol (N-acetyl-p-aminophenol) is a safe and effective agent that is widely used for its analgesic and antipyretic properties. It was first used in medicine in 1893 but only became popular in the second half of the last century.[1]

As the principal para-aminophenol derivative in use, paracetamol replaced its predecessors in the same therapeutic class, acetanilide and phenacetin, as the analgesic-antipyretic of choice for patients in whom salicylates and other nonsteroidal anti-inflammatory drugs are contraindicated.[2] Due to its weak inhibition of cyclo-oxygenase, paracetamol is not indicated as an anti-inflammatory drug.[3]

The conventional adult oral dose of paracetamol is 0.5g to 1g every 4 to 6 hours with a maximum daily dose of 4g. Rectal doses for persons over 12 years of age are 0.5g to 1g administered up to four times daily. In children, oral and rectal doses depend on age and body weight, with a maximum of four doses in a 24-hour period.[2]

Absorption of paracetamol from the gastro-intestinal tract is rapid. The peak plasma concentration is attained within 30 to 60 minutes and the elimination half-life in plasma is about 2 hours following administration of a therapeutic dose.[1] Paracetamol is distributed into most body tissues and plasma protein binding is negligible at therapeutic doses, but increases with increasing plasma concentrations.[2] The drug readily crosses the placenta although there is no published evidence of teratogenic effects.[4]

Metabolism of paracetamol

The metabolic reactions by which drugs are biotransformed in the body are divided into two phases. Phase I reactions prepare a drug for the subsequent phase II reactions. The latter are the true detoxification pathways which result in products that are generally water-soluble and easily excreted in urine or bile.[5]

The metabolic biotransformation of paracetamol predominantly proceeds through phase II pathways in the liver (Figure I). The main reaction is hepatic conjugation with glucuronic acid, which accounts for about 60% of renally excreted metabolites. Conjugation with sulphate contributes a further 35% to urinary metabolites. A small amount, about 3%, is excreted as mercapturic acid, the N-acetylcysteine conjugate.[1] Less than 5% of paracetamol is excreted unchanged in urine.[2]

The conjugates are not chemically reactive and therefore not likely to cause any organ damage. However mercapturic acid is formed via the conjugation reaction between a potentially hepatotoxic reactive intermediate and sulphydryl groups in glutathione. This reactive intermediate is probably N-acetyl-p-benzoquinoneimine (NAPQI), a cytotoxic electrophile that binds to cellular proteins.[6] Compared with

Drug interactions

- Exposure to drugs that are inducers of hepatic drug-metabolising enzymes, e.g. phenobarbital, increases susceptibility to hepatotoxic effects of paracetamol.[6]

- Inhibition of glucuronidation of both paracetamol and zidovudine may occur when the drugs are administered concurrently resulting in increased toxicity of both drugs.[4]

- Resistance to the hepatotoxic effects of paracetamol is seen in the presence of drugs that are inhibitors of microsomal enzymes.[6] Cimetidine, an inhibitor of cytochrome P-450, decreases the toxicity of paracetamol by preventing formation of hepatotoxic metabolites while having no effect on conjugation reactions that yield non-toxic metabolites.[16]

Alcohol

- Acute exposure to alcohol (ethanol) decreases metabolism of paracetamol by Phase II pathways so that the drug exhibits a longer elimination half-life.[5]

- Chronic exposure to alcohol with no hepatocellular changes leads to induction of Phase I and Phase II metabolism. Induction of cytochrome P450 2E1 increases Phase I metabolic oxidation of paracetamol with enhanced toxicity due to increased formation of toxic metabolite.[5]

- When the extent of alcoholic liver disease becomes extensive there is a reduction in the metabolism of paracetamol as seen in cirrhosis.[5]

Diet

- Animal studies have shown that hepatotoxicity of paracetamol increases after a low-protein diet. This may be due to reduced levels of intracellular glutathione that offsets the reduced amount of cytochrome P450 caused by protein deficiency.[6]

- An increase in hepatotoxicity of paracetamol has also been seen in animals after overnight fasting due to depletion of glutathione levels.[6]

Genetics

- Genetic control of drug metabolism is exemplified by the appearance of racial differences in glucuronidation of paracetamol between Caucasians and Chinese.[5]

- Variability in rates of metabolic oxidation of paracetamol by cytochrome P450 in human populations has been identified. Where the rate of oxidation is highest there is increased susceptibility to hepatotoxicity of paracetamol. At the lowest rate, about 25% of the highest, there is relative resistance to hepatotoxicity.[5]

- CYP2D6, one of the pharmacogenetically important cytochrome P450 isoforms that exhibits polymorphism, may contribute significantly to the formation of the toxic metabolite at toxic doses of paracetamol especially in CYP2D6 ultra-rapid and extensive metabolisers.[8]
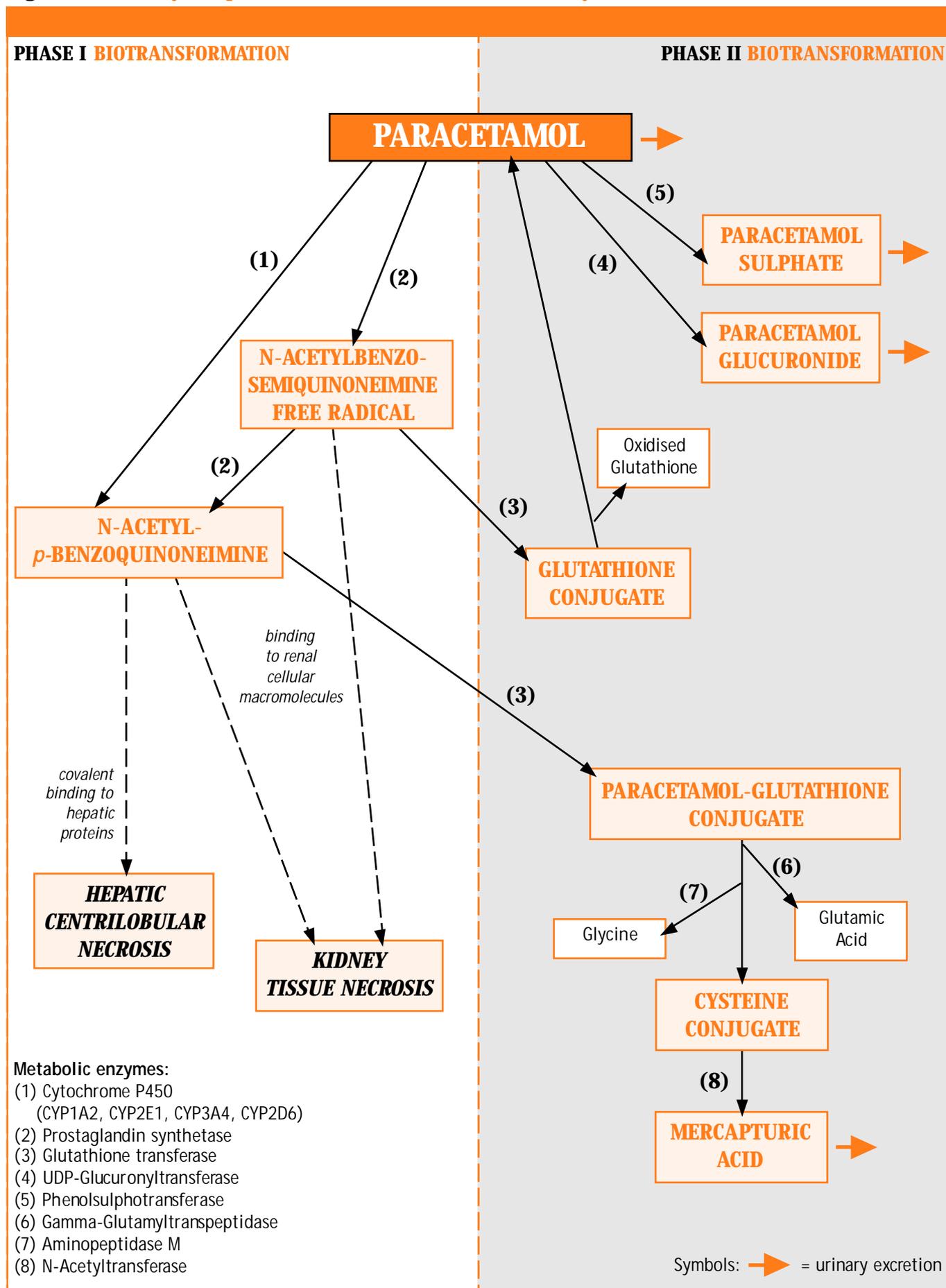
glucuronidation and sulphation, conjugation with glutathione is a minor pathway of paracetamol biotransformation, even though the liver contains high levels of both glutathione and glutathione transferases. The relatively low rate of glutathione conjugation reflects the slow rate of formation of NAPQI by the dehydrogenation of paracetamol, a reaction catalysed by the hepatic and renal phase I mixed-function oxidases, the cytochrome P450 isozymes namely CYP2E1, CYP1A2, CYP3A4[7] and CYP2D6.[8]

Glutathione plays an essential role in protecting hepatocytes from injury by chemically reactive metabolites. When low doses of paracetamol are administered, NAPQI preferentially combines with glutathione. As the dose is increased, the availability of glutathione in tissues is decreased until, at a certain threshold dose, accumulation of NAPQI results in a sharp increase in binding to sulphydryl groups in hepatocytes with formation of adducts, arylation of hepatic cellular macromolecules and ensuing centrilobular necrosis. Thus, at therapeutic doses of paracetamol, glutathione provides the cell with a means of preventing the reactive metabolite from attaining a critical, effective concentration.[9]

The paracetamol-glutathione conjugate that is formed in the liver is converted to mercapturic acid in the kidneys and excreted in urine.

Glutathione is a tripeptide consisting of the amino acids cysteine, glutamic acid and glycine. Thus the formation of mercapturic acid involves the sequential cleavage of glutamic acid and glycine from the glutathione moiety in the conjugate to give the cysteine conjugate which is, in turn, N-acetylated to the mercapturic acid.[7]

Besides hepatic damage, paracetamol can also induce damage to the kidney medulla. Prostaglandin synthetase, which is more predominant than cytochrome P450 in the kidneys, is involved in the formation of NAPQI via an intermediate free radical, N-acetylbenzosemiquinoneimine, that can bind to renal proteins.[7] This free radical may undergo reduction with glutathione to reform paracetamol.[5] Therefore the biotransformation of the free radical is adversely affected by depletion of glutathione.

Paracetamol toxicity and treatment

When administered in the recommended therapeutic doses, paracetamol is usually well tolerated. Hypersensitivity reactions including skin and other allergic reactions may occur occasionally. Haematological reactions have also been reported. Prolonged use of the drug may cause nephropathy and animal studies have indicated the possibility of tumour-inducing effects.[4]

The major toxic effects of paracetamol are by far associated with acute overdosage, which is primarily manifested as a dose-dependent hepatocellular necrosis unless treated promptly. Renal tubular necrosis occurs less commonly and may be seen in the absence of liver damage.[4] Myocardial abnormalities and pancreatitis are also non-hepatic symptoms of overdosage.[2]

The early symptoms of overdosage are not alarming and in the first 12 hours could include nausea, vomiting, lethargy and sweating.[2,10] While damage to the liver starts to take place within hours of ingestion, clinical manifestations such as abdominal pain and tenderness followed by jaundice may only be apparent after 24 to 48 hours and may be delayed by 4 to 6 days after ingestion.[2,4] Abnormal liver function tests with increases in

Figure 1: Pathways of paracetamol metabolism and toxicity

PHASE I BIOTRANSFORMATION

PHASE II BIOTRANSFORMATION

PARACETAMOL

(1)

(2)

(5)

(4)

N-ACETYLBENZO-SEMIQUINONEIMINE FREE RADICAL

PARACETAMOL SULPHATE

PARACETAMOL GLUCURONIDE

(2)

(3)

Oxidised Glutathione

N-ACETYL-*p*-BENZOQUINONEIMINE

GLUTATHIONE CONJUGATE

binding to renal cellular macromolecules

(3)

covalent binding to hepatic proteins

PARACETAMOL-GLUTATHIONE CONJUGATE

(7)

(6)

HEPATIC CENTRILOBULAR NECROSIS

Glycine

Glutamic Acid

KIDNEY TISSUE NECROSIS

CYSTEINE CONJUGATE

(8)

Metabolic enzymes:
(1) Cytochrome P450
    (CYP1A2, CYP2E1, CYP3A4, CYP2D6)
(2) Prostaglandin synthetase
(3) Glutathione transferase
(4) UDP-Glucuronyltransferase
(5) Phenolsulphotransferase
(6) Gamma-Glutamyltranspeptidase
(7) Aminopeptidase M
(8) N-Acetyltransferase

MERCAPTURIC ACID

Symbols: ➤ = urinary excretion

seen as early as 8 hours from ingestion although they may result later within the first 24 hours.[10] Liver damage reaches a maximum in 72 to 96 hours after ingestion and may progress to hepatic failure with ensuing complications.[2] Acute renal tubular damage may occur concurrently with liver damage.[1,2]

The metabolism and consequently the toxicity of paracetamol are influenced by a number of factors (Table I). The adult minimum toxic dose of about 12g may be lowered to 6 g in high-risk patients because of increased susceptibility.[4] Thus there may be a relatively narrow margin between the recommended adult daily dose of 4 g and the minimum toxic dose. Paracetamol doses of 20 to 25 g are potentially fatal.[1]

The relatively mild symptoms that are seen in the first hours after ingestion and the delay in clinical manifestations of hepatic damage may deter patients from seeking prompt treatment at a hospital even in the absence of symptoms. Gastric lavage is usually performed if ingestion was within 2 to 4 hours of admission[1,2] and full supportive measures are instituted.

Although peak plasma paracetamol concentration is best measured at least 4 hours after ingestion and not later than 16 hours from ingestion,[2] therapy should not be delayed if significant overdosage is suspected.[1,2] Plasma paracetamol concentrations are compared against a standard nomogram reference line that relates plasma concentration to time after ingestion. When the plasma concentration of the patient is above the normal reference line treatment must be instituted. For patients who are at increased risk of toxicity a lower high-risk treatment line is employed.[2]

Methionine and N-acetylcysteine are the two antidotes that are used to treat paracetamol toxicity. The former is available as an oral preparation and the latter as oral and intravenous formulations. Oral administration is the preferred treatment route in the United States.[10] However, in the United Kingdom, intravenous N-acetylcysteine is preferred because the unpleasant taste and odour of the oral form of the antidote may exacerbate the early symptoms of nausea and vomiting.[2,10]

N-Acetylcysteine is a well-tolerated source of intracellular cysteine, the rate-limiting amino acid in glutathione synthesis.[11] There are four mechanisms by which the antidote may act:[6]

- promotion of the synthesis of glutathione which is necessary for the detoxication of the reactive metabolite, NAPQI, by conjugation;
- stimulation of the synthesis of glutathione used in the protection of protein thiols;
- relief of the saturation of sulphate conjugation which occurs during paracetamol overdose; and
- direct involvement in the reduction of NAPQI.

N-Acetylcysteine may be effective when administered 15 hours or more after an overdose[6] and may even be of benefit 24 hours after paracetamol ingestion.[11,12] Since by this time most of the metabolite NAPQI would have reacted with cellular proteins, the antidote may, at a late stage, afford protection against subsequent cellular changes.[6]

Methionine is not as effective when administration is delayed. This may possibly be due to inhibition of glutathione synthesis by thiol-containing enzymes involved in the synthetic pathway.[6]

Pharmacy practice points

The relative ease with which paracetamol can be obtained as a non-prescription medicine is believed to be a major factor that accounts for the relatively high incidence of accidental and deliberate overdosage in the United Kingdom and the United States.[10]

Several measures have been taken to reduce incidents of paracetamol poisoning. In the United States, standards for product labelling were revised to clarify dosing instructions and introduce a more specific warning

---

Table II: Pharmacy Practice Points: Preparations containing Paracetamol

- Paracetamol-containing products are generally classified as over-the-counter preparations to be dispensed at the discretion of the pharmacist unless compounded with active ingredients that have prescription status. **Avoid dispensing large quantities unless justified.**

- Paracetamol is considered to be a safe and effective drug only if taken for its intended use and at the recommended therapeutic doses for children and adults. **Advise patients never to exceed the stated doses unless under the supervision of a physician.**

- There are several multi-ingredient preparations, such as cold and flu products and compound analgesics, that contain paracetamol. **Advise patients not to take more than one product containing paracetamol at any time to avoid the risk of exceeding the recommended daily dose.**

- Paracetamol is also known by the name acetaminophen. This terminology is primarily used in products originating from the United States and Canada. **Always inform patients that acetaminophen is the same as paracetamol when dispensing such products.**

- The liver and the kidneys are the major organs in the body that are susceptible to the toxic effects of paracetamol. **Products containing paracetamol should be used with caution in patients with impaired hepatic or renal function, dependent on alcohol, or taking medicines that are potentially hepatotoxic.**

- Clinical manifestations of paracetamol toxicity are seen several hours after an accidental or intentional overdose but treatment is more successful if the antidote is administered as soon as possible after ingestion. **Always refer a patient with suspected or confirmed paracetamol overdose to hospital for emergency examination and treatment even in the absence of symptoms.**

statement.[13] The regulatory authorities in the United Kingdom subjected some oral paracetamol dosage forms to prescription control with exemptions based on restricted pack sizes, number of packs that could be supplied, and requirements for warning statements.[14]

Restricting the sale of paracetamol preparations solely from pharmacies, as is the case in Malta, or restricting the amount that can be supplied should not be expected to offer sufficient protection against incidents of overdosage. Adults, including parents administering paracetamol to their children, are known to have difficulty measuring and administering a correct dose of a medicine. Of more concern is the fact that many adults fail to associate brand names with the active ingredient in the product, leading to excessive cumulative doses when multiple sources of paracetamol are administered.[15]

Notwithstanding the fact that intentional paracetamol poisoning cannot be prevented without direct intervention, the pharmacist has an important role to play in reducing the incidence of accidental poisoning.

Table II lists several practice points that could contribute to improved patient education on the use of paracetamol.

Conclusion

At therapeutic doses, paracetamol exhibits a good safety profile that makes it a popular drug found in most households. However the ease with which it may be obtained should not be interpreted as a guarantee of absolute safety. Some patients are at an increased risk of poisoning at lower doses than are normal for the rest of the population. In any case, the consequences of overdosage are severe and can lead to death. Thus early and prompt treatment of poisoning is imperative even in the absence of symptoms. Pharmacists advising patients on caution in the use of paracetamol can reassure them that, in using the drug correctly, they can benefit from its therapeutic efficacy in the treatment of mild and moderate symptoms. ✴

References

1. Insel PA. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Goodman Gilman A, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th Edition. New York: McGraw Hill; 1996.

2. Parfitt K, editor. Martindale: The Complete Drug Reference. 32nd Edition. London: Pharmaceutical Press; 1999.

3. Hanel AM, Lands WE. Modification of anti-inflammatory drug effectiveness by ambient lipid peroxides. Biochemical Pharmacology 1982: 31:3307-11.

4. Scott A. Antipyretic analgesics. In: Dukes MNG, editor. Meyler's Side Effects of Drugs. 12th Edition. Amsterdam: Elsevier Science Publishers B.V.; 1992

5. Gibson GG, Skett P. Introduction to Drug Metabolism. 2nd Edition. London: Blackie Academic and Professional; 1994.

6. Timbrell JA. Principles of Biochemical Toxicology. 2nd Edition. London: Taylor & Francis; 1991.

7. Parkinson A. Biotransformation of xenobiotics. In: Klaassen CD, editor. Casarett and Doull's Toxicology: The Basic Science of Poisons. 5th Edition. New York: McGraw-Hill; 1996.

8. Dong H, Haining RL, Thummel KE, Rettie AE, Nelson SD. Involvement of human cytochrome P450 2D6 in the bioactivation of acetaminophen. Drug Metabolism and Disposition 2000: 28:1397-1400.

9. Wallace Hayes A, editor. Principles and Methods of Toxicology. New York: Raven Press; 1989.

10. Routledge P, Vale JA, Bateman DN, Johnston GD, Jones A, Judd A, Thomas S, Volans G, Prescott LF, Proudfoot A. Paracetamol (acetaminophen) poisoning. British Medical Journal 1998: 317:1609-10.

11. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). The New England Journal of Medicine 1988: 319:1557-62.

12. Harrison PM, Keays R, Bray GP, Alexander GJ, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. The Lancet 1990: 335:1572-3.

13. Buck ML. Preventing acetaminophen overdosage. Pediatric Pharmacotherapy 2000, 6(3). (On-line newsletter of the Children's Medical Center, University of Virginia, USA: http://www.hsc.virginia.edu/medicine/clinical/pediatrics/chmedctr/pedpharm/v6n3.htm)

14. Medicines Control Agency. Paracetamol and aspirin: pack size restriction and label warnings to reduce risk from overdose. Current Problems in Pharmacovigilance 1997, 3:9.

15. Simon HK, Weinkle DA. Over-the-counter medications: Do parents give what they intend? Archives of Pediatrics and Adolescent Medicine 1997: 151:43-6.

16. Abernethy DR, Greenblatt DJ, Divoll M, Ameer B, Shader RI. Differential effect of cimetidine on drug oxidation (antipyrine and diazepam) vs conjugation (acetaminophen and lorazepam): prevention of acetaminophen toxicity by cimetidine. Journal of Pharmacology and Experimental Therapeutics