CLINICAL AND TOXICOLOGICAL ASPECTS ASSOCIATED WITH PARACETAMOL POISONING, AND PREDICTORS OF ITS OUTCOMES

by

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DEDICATION

I would like to dedicate this thesis to my wonderful family. Particularly, to the woman in my life, my understanding and patient wife “Samah”, who has put up with these many years of research, to our precious daughter “Sima”, who is the joy of our lives, and to my family.

To the loving memory of all those who have devoted themselves to the scholarship of teaching, research, learning, science, and helping humanity

Allah says in the Holy Quran

“And say: "Work (righteousness): Soon will Allah observe your work, and His Messenger, and the Believers”

Surat-at-Tawbah (9), ayah 105

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LIST OF ABBREVIATIONS

ADRs	Adverse drug reactions
ABC	Airway, breathing, circulation
AED	Accident and emergency department
ALT	Alanine aminotransferase
APAP	*N*-acetyl-para-aminophenol
AST	Serum Aspartate aminotransferase
AT	Aminotransferases
AUC	Area under the concentration time curve
CI	Confidence interval
CNS	Central nervous system
COX	Cyclooxygenase
CYP	Cytochrome
df	Degrees of freedom
DNA	Deoxyribonucleic acid
DSP	Deliberate self-poisoning
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetate
FDA	Food and Drug Administration
FHF	Fulminant hepatic failure
GI	Gastrointestinal
GSH	Glutathione
HPP	Hospital Pulau Pinang
ICD-10	International Classification of Diseases tenth revision
IL-6	Interleukin-6
INR	International Normalized Ratio

IV	Intravenous
IV-NAC	Intravenous N-acetylcysteine
KCHC	King’s College Hospital Criteria
LOS	length of hospital stay
LS	Long hospital stay
NAC	N-acetylcysteine
NADP	Nicotinamide adenine dinucleotide phosphate
NAPQI	N-acetyl-p-benzoquinoneimine
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PG	Prostaglandin
PGH	Penang General Hospital
PT	Prothrombin time
Q1-Q3	lower quartile - upper quartile
S.E	Standard error
SD	Standard deviation
SPSS	Statistical Package for Social Sciences
SS	Short hospital stay
SSRI	selective serotonin reuptake inhibitor
TDM	Therapeutic drug monitoring
TX	Thromboxane
UDP	Uridine diphosphate
UK	United Kingdom
USA	United States of America
vWF	von Willebrand factor

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ASPEK KLINIKAL DAN TOKSIKOLOGI BERKAITAN KERACUNAN PARASETAMOL, DAN PREDIKTOR - PREDIKTOR KESUDAHANNYA

ABSTRAK

Parasetamol merupakan satu sumber keracunan yang lumrah; dan pengenalpastian awal pesakit-pesakit yang mengalami keracunan yang lebih teruk adalah kunci kepada memperbaiki kesudahan. Banyak aspek toksisiti parasetamol dan rawatannya masih kurang difahami. Untuk meningkatkan pengetahuan mengenai keracunan parasetamol, kajian 5 tahun berasaskan-hospital ini telah dilaksanakan dengan objektif-objektif utama seperti berikut: (1) untuk menentukan corak keracunan parasetamol dalam kalangan pesakit yang dimasukkan ke Hospital Pulau Pinang (HPP); dan (2) untuk mengenalpasti indikator-indikator prognosis buruk semasa presentasi awal di hospital bagi meningkatkan penjagaan klinikal dan menentukan sasaran-sasaran intervensi untuk pencegahan, pengesanan awal, diagnosis dan rawatan. Ini adalah satu kajian pemerhatian kohort retrospektif mengenai kemasukan ke hospital bagi kes keracunan parasetamol akut antara 1 Januari 2004 dan 31 Disember 2008.

Secara keseluruhannya, 305 orang pesakit telah memenuhi kriteria penyertaan. Manifestasi gastrousus (GI) lazimnya berlaku dalam kalangan pesakit yang dilaporkan menelan ≥ 8 grams parasetamol, di mana masa latensi adalah melebihi 8 jam; dan kedua-dua faktor ini telah dikenalpasti sebagai prediktor yang bebas dan kukuh untuk kehadiran manifestasi GI, terutamanya loya/muntah. Kehadiran gejala-gejala GI merupakan satu penanda penting bagi kesudahan yang buruk dan peningkatan jangka masa pesakit tinggal di hospital. Selain itu, hipokalemia mempunyai kaitan yang tinggi dengan keracunan parasetamol. Ciri-ciri klinikal yang spesifik semasa presentasi awal di hospital, seperti muntah, penyakit psikiatrik, dan dos parasetamol yang dilaporkan ditelan, boleh digunakan untuk mengenalpasti pesakit yang mempunyai risiko tinggi untuk mendapat

hipokalemia. Yang penting, jangka masa lama tinggal di hospital berkurang dengan ketara apabila terapi IV-NAC diberikan dalam tempoh 8 jam selepas pengambilan parasetamol ($p = 0.006$). Tindakbalas advers drug (ADR) terhadap terapi IV-NAC biasa berlaku dalam kalangan pesakit keracunan parasetamol, tetapi kebanyakannya adalah kes ringan dan mudah dirawat: tiada kematian dilaporkan. Kepekatan parasetamol yang rendah dalam serum mempunyai kaitan yang ketara dengan gejala kulit kemerah-merahan atau *flushing* ($p < 0.001$), ruam ($p < 0.001$) dan gatal-gatal ($p < 0.001$). Tambahan pula, infusi NAC yang lambat diberikan mempunyai kaitan yang ketara dengan tindakbalas anafilaktoid kutaneus, apabila dibandingkan dengan pesakit yang tidak mengalami ADR jenis ini ($p < 0.001$). Akhir sekali, dalam kebanyakan keracunan diri yang disengajakan (DSP), pesakit mengalami pelbagi tekanan hidup dan penyakit psikiatri, yang boleh dikaitkan dengan niat membunuh diri yang berbeza-beza tingkatnya. Masalah alkohol merupakan satu-satunya kategori tekanan hidup yang ketara berbeza antara jantina. Tambahan pula, dalam kajian semasa, pesakit DSP lelaki mengambil parasetamol dalam dos yang lebih banyak, dan oleh itu, pesakit lelaki mungkin terdedah kepada risiko yang lebih tinggi.

Kesimpulannya, kajian ini adalah yang pertama seumpamanya untuk menilai hubungan di antara ciri-ciri klinikal pesakit keracunan parasetamol semasa dimasukkan ke hospital, dan semasa berada di hospital. Pengetahuan mengenai ciri klinikal dan kaitannya dengan kesudahan mungkin menyumbang kepada pengurangan kadar komplikasi dengan meningkatkan penjagaan klinikal dan menentukan sasaran-sasaran untuk intervensi. Hasil kajian ini akan membolehkan pakar perubatan dan pakar toksikologi klinikal mengenalpasti pesakit yang mempunyai risiko tinggi untuk mendapat toksisiti parasetamol dan kebarangkalian berlakunya hepatotoksisiti kemudiannya supaya rawatan dapat dimulakan.

CLINICAL AND TOXICOLOGICAL ASPECTS ASSOCIATED WITH PARACETAMOL POISONING, AND PREDICTORS OF ITS OUTCOMES

ABSTRACT

Paracetamol is a common source of poisoning, and early identification of patients with more severe poisoning is the key to improving outcomes. Many aspects of paracetamol toxicity and treatment remain poorly understood. To improve knowledge about paracetamol poisoning, the current 5-year, hospital-based study was carried out with the following primary objectives (1) to determine the pattern of paracetamol poisoning among patients who were admitted to Hospital Pulau Pinang (HPP); and (2) to identify indicators of poor prognosis at first hospital presentation for improving clinical care and determining intervention targets for prevention, early detection, diagnosis and treatment. This is an observational retrospective cohort study of hospital admissions for acute paracetamol poisoning between 1 January 2004 and 31 December 2008.

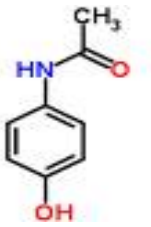
Overall, 305 patients met the inclusion criteria. Gastrointestinal (GI) manifestations were common in patients who reported ingestion of ≥ 8 g of paracetamol, and whose latency was longer than 8 hours; and both of these factors were identified as strong independent predictors of the presence of GI manifestations, especially nausea/vomiting. The presence of GI symptoms was a significant marker of poor outcomes and increased hospital stays. Additionally, hypokalaemia is highly associated with paracetamol poisoning. Specific clinical characteristics upon first presentation to the hospital, such as vomiting, psychiatric illness, and reported paracetamol dose ingested, can be used to identify patients at increased risk for hypokalaemia. Importantly, long hospital stays were significantly less frequent when IV-NAC therapy was administered within 8 hours of paracetamol ingestion ($p = 0.006$). Adverse Drug Reactions (ADRs) to IV-NAC therapy

are common in paracetamol poisoning patients, but are mostly minor and easily managed; no fatalities were observed. Low serum paracetamol concentrations are significantly associated with flushing ($p < 0.001$), rash ($p < 0.001$) and pruritus ($p < 0.001$). Furthermore, delayed NAC infusions were significantly associated with cutaneous anaphylactoid reactions, when compared to patients without this type of ADR ($p < 0.001$). Finally, most paracetamol deliberate self-poisoning (DSP) patients suffer from different life stressors and psychiatric illnesses, which may be associated with varying degrees of suicidal intentions. Alcohol problems were the only life stressor category which was significantly different between genders. Moreover, in the current study, male DSP patients ingested higher amounts of paracetamol, and therefore male patients might be at a higher risk.

In conclusion, this is the first study of its kind to evaluate the relationship between the clinical characteristics of paracetamol poisoned patients upon hospital admission, and during hospitalization. Knowledge of clinical characteristic and their relation to outcome might contribute to reduced complication rates by improving clinical care and determining targets for intervention. The results from this study will allow physicians or clinical toxicologists to identify patients who are at increased risk of paracetamol toxicity and the probability of subsequent hepatotoxicity so as to initiate treatment.

CHAPTER 1

GENERAL INTRODUCTION AND LITERATURE REVIEW OF PARACETAMOL



N-(4-hydroxyphenyl) acetamide: Paracetamol

1.1 INTRODUCTION

The terms *acetaminophen* (used in the United States, Canada, other Latin American countries, Hong Kong, Iran, and Colombia) and *paracetamol* (used elsewhere) (Bradley, 1996) both derive from chemical names for the compound: *para*-**acet**yl**aminophen**ol and ***para***-**acet**yl**am**inophen**ol**. In some situations, it is simply abbreviated as **APAP**, for *N*-**a**cetyl-**p**ara-**a**mino**p**henol (Hoffman *et al.,* 2007).

Paracetamol was synthesised by Morse in Germany in 1878, and subsequently produced by numerous methods. Paracetamol was introduced into clinical practice by Von Mering in 1893 (Haas, 1983). Shortly after, it was replaced in Germany by phenacetin, since phenacetin was assumed to be safer than paracetamol. Paracetamol was found in the urine of patients who had taken phenacetin and was recognised as a metabolite of another analogue of phenacetin, acetanilide (Bateman and Dear, 2010). A key development in the history of paracetamol occurred in 1948, when Brodie and Axelrod, evaluating the effects of phenacetin, identified paracetamol as the major active hepatic metabolite of phenacetin (Brodie and Axelrod, 1948). By this time phenacetin was documented to have kidney toxicity, and the use of paracetamol as an analgesic was promoted in its place (Brodie and Axelrod, 1949).

Paracetamol (Tylenol®) was first marketed in the United States of America (USA) in 1955 by McNeil Laboratories, as an analgesic and antipyretic for children. In 1956, the United Kingdom (UK) Company Frederick Stearns & Co. marketed paracetamol as Panadol®, in a 500 mg tablet, and in 1958 they produced a paracetamol containing children's elixir as a prescribed pain killer and antipyretic (Bateman and Dear, 2010). It is now the best-selling analgesic in the USA (Woodcock *et al.,* 2011).

Although the British medical establishment was initially cautious, in 1963 paracetamol was added to the British National Formulary (List, 1963), and as such became more commonly used as an analgesic, especially when phenacetin was banned from the market in the 1970s (Bateman and Dear, 2010).

Paracetamol has since proven to be a remarkably safe drug at appropriate dosages, making it the antipyretic-analgesic of choice for various conditions (Hoffman *et al.*, 2007).

Paracetamol (Panadol®) was introduced in Malaysia in 1957, and by 1962, Sterling Drug Malaysia began business in Malaysia, marketing Panadol® to hospitals initially, thereby gaining acceptance from the medical community. By the 1970s, Panadol® had gained enormous popularity, and could be found almost everywhere, from pharmacies to supermarkets and clinics. In fact, Panadol® has become the foremost over-the-counter pain reliever in Malaysia (GlaxoSmithKline, 2007a; GlaxoSmithKline, 2007b). Paracetamol has since proven to be a remarkably safe drug at appropriate dosages, making it the antipyretic-analgesic of choice for various conditions (Hoffman *et al.*, 2007). Paracetamol in Malaysia is available alone, in numerous single-agent dose formulations and delivery systems, and in a wide variety of combinations with antihistamines, other analgesics, decongestants, expectorants, opioids, and sedatives. Common brand names for paracetamol include Panadol®, Arfen®, Avadol ®, Axcel Paracetamol®, Hoemal®, Panadol Actifast®, Panadol Extend®, Panadol Soluble®, Parafizz®, Paratamol®, Poro®, Rapidol®, Remedol®, Tempol®, and Uphamol® (MIMS Malaysia, 2011).

The main topics under investigation in this thesis are: i) early prediction of paracetamol poisoning/overdose outcomes; ii) evaluation of management patterns for acute paracetamol poisoned patients and hospital stay; iii) the adverse reactions caused by intravenous infusion of N-acetylcysteine (NAC); and iv) risk factors and life stressors contributing to paracetamol poisoning. This introductory chapter includes four separate parts. In part 1, pharmacology and toxicology of paracetamol are discussed. In part 2, outcomes and prognostic indicators following paracetamol poisoning are reviewed. In part 3, the management of paracetamol poisoning is reviewed. Finally, in part 4, NAC treatment of paracetamol poisoning and its associated adverse reactions are discussed.

1.2 PHARMACOLOGY AND TOXICOLOGY OF PARACETAMOL

1.2.1 Pharmacology

Paracetamol is an antipyretic and analgesic with weak peripheral anti-inflammatory properties. Antipyretic activity is reported at serum paracetamol concentrations between 4-18 mcg/mL, and analgesic activity at 10-20 mcg/mL (Wilson, 1985; Stocker and Montgomery, 2001; Hoffman *et al.*, 2007).

In spite of its popularity, the mechanism(s) by which paracetamol achieves its antipyretic and analgesic effects is still being debated (Anderson, 2008; Toussaint *et al.*, 2010). Antipyretic activity is mediated by central nervous system (CNS) inhibition of prostaglandin E_2 (PGE_2) synthesis, via either inhibition of membrane-associated PGE synthase or direct inhibition of cyclooxygenase (COX)-2 (Aronoff and Neilson, 2001; Graham and Scott, 2005). PGE synthase inhibition may be a result of local reductions of glutathione (GSH) concentrations, initiated by metabolic processing of paracetamol to reactive metabolites via the hepatic cytochrome P450 enzyme system (Graham and

Scott, 2005; Toussaint *et al.*, 2010). Furthermore, binding and inhibition of COX-3 by paracetamol may have an antipyretic effect (Botting, 2000; Chandrasekharan *et al.*, 2002; Botting and Ayoub, 2005); although the idea that paracetamol acts directly through COX-3 has been rejected (Kis *et al.*, 2005; Williams *et al.*, 2011).

The analgesic effect of paracetamol is also mediated by central inhibition of PG synthase and COX-2, and probably via indirect modulation of serotonergic pathways (Graham and Scott, 2005; Anderson, 2008). Additional effects may be related to indirect stimulation of endogenous opioid pathways (Raffa *et al.*, 2000; Raffa *et al.*, 2004) .

Some studies have also suggested that paracetamol may have mild anti-inflammatory effects (Graham and Scott, 2005; Aronoff *et al.*, 2006; Hinz *et al.*, 2008; Flood, 2010). A German study on healthy volunteers orally administered 1000 mg paracetamol found substantial and selective inhibition of COX-2 (>80%), similar to the effects reported for non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors (Hinz *et al.*, 2008). This study also demonstrated that COX-1 inhibition, as measured by thromboxane B2 (TXB2) synthesis, was minor (56%), and not sufficient for the inhibition of platelet function (Hinz *et al.*, 2008). These data support an anti-inflammatory action by paracetamol, and explain why it has a better overall gastrointestinal (GI) safety profile than NSAIDs (Bannwarth, 2004; Gonzalez-Perez and Rodriguez, 2006; Hinz *et al.*, 2008).

1.2.2 Pharmacokinetics

Following oral ingestion, therapeutic doses of paracetamol are rapidly absorbed, and peak blood levels are reached within approximately 1 hour (Prescott, 1981), while liquid paracetamol levels peak in 30 minutes (Ameer *et al.,* 1983). Extended-release paracetamol has a time to peak of 1-2 hours, but is almost completely absorbed by 4 hours (Tan and Graudins, 2006). Even when taken in toxic doses, absorption of paracetamol is approximately complete within 4 hours, with no additional rise in blood levels after this time (Prescott *et al.,* 1971). However, in an Australian study, Roberts and Buckley (2008) reported a case of acute poisoning from extended-release paracetamol presented 14.5 hours post-ingestion. The paracetamol absorption phase and elimination half-life appeared prolonged, with peak blood concentrations occurring at 20 hours post-ingestion (Roberts and Buckley, 2008). Time to peak can be delayed by anticholinergic agents or coingestion of opioids (Halcomb *et al.,* 2005) and food (Divoll *et al.,* 1982).

The oral bioavailability of paracetamol is 60-98% following administration of therapeutic dose, ranging between 8-32 mcg/mL (Hoffman *et al.,* 2007). Paracetamol has a total protein binding of 10-30%, which does not change with toxic doses (Milligan *et al.,* 1994). Paracetamol crosses both the blood brain barrier (van der Marel *et al.,* 2003; Kumpulainen *et al.,* 2007) and placenta (Levy *et al.,* 1975; Wilkes *et al.,* 2005).

After ingestion of therapeutic doses of paracetamol in adults, first-pass metabolism eliminates 25% of the therapeutic dose (Hoffman *et al.,* 2007). Once absorbed, approximately 90% of the ingested paracetamol is metabolised to phenolic glucuronide (40-67%) and sulphate (20-46%) in the liver, by uridine diphosphate (UDP)-glucuronosyltransferases and sulfotransferases, forming inactive metabolites which are subsequently excreted in the urine (Schenker *et al.,* 2001; Hoffman *et al.,* 2007; Larson, 2007; Chun *et al.,* 2009; Klein-Schwartz and Doyon, 2011); (Figure 1.1). Although a small portion of un-metabolised paracetamol (<5%) and other minor metabolites reaches the urine, these are not considered to be clinically significant (Prescott, 1996b; Schenker *et al.,* 2001; Rumack, 2002; Larson, 2007). The residual fraction, which usually ranges between 5-15%, is metabolised by the hepatic cytochrome P450 enzyme system (cytochrome 2E1: CYP2E1, and, to a lesser extent, cytochrome 1A2: CYP1A2, cytochrome 2A6: CYP2A6, and cytochrome 3A4: CYP3A4 isoenzymes); (Manyike *et al.,* 2000; Hazai *et al.,* 2002; Hoffman *et al.,* 2007), resulting in the formation of N-acetyl-p-benzoquinoneimine (NAPQI), a highly toxic metabolite. GSH quickly combines with this intermediate metabolite, and the resulting complex is converted into nontoxic cysteine or mercaptate conjugates which are eliminated in the urine (Mitchell *et al.,* 1974; Prescott, 1996b). The elimination half-life of paracetamol is approximately 2-3 hours after a nontoxic dose, but may become extended in patients who develop hepatotoxicity (Prescott *et al.,* 1971).

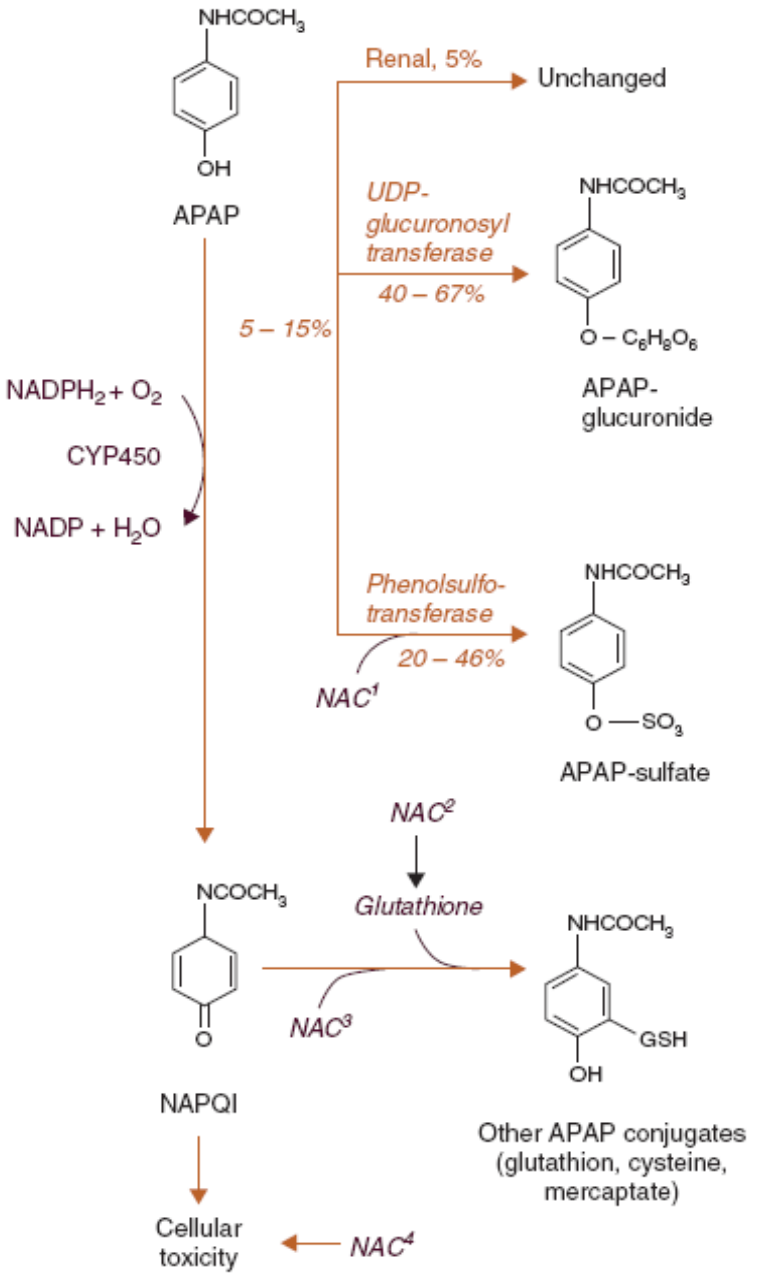


Figure 1.1. Important routes of paracetamol metabolism in humans, and mechanisms of N-acetylcysteine (NAC) hepatoprotection; Adapted from Hoffman *et al.*, 2007; Reproduced with permission of the McGraw-Hill Companies.

APAP: N-acetyl-p-aminophenol=paracetamol; NADP=nicotinamide adenine dinucleotide phosphate; CYP=Cytochrome; UDP=uridine diphosphate; NAC^1: augments sulfation; NAC^2 is a glutathione (GSH) precursor; NAC^3 is a GSH substitute; and NAC^4 improves multiorgan function during hepatic failure and possibly limits the extent of hepatocyte injury; NAPQI = *N*-acetyl-*p*-benzoquinoneimine.

1.2.3 Toxicology

In general, paracetamol is a safe drug when taken at therapeutic dosages. Even after poisoning, the majority of paracetamol absorption takes place within 2 hours. Peak plasma concentrations are normally reached within 4 hours, while later peaks are rarely predictable in paraceta (Tighe and Walter, 1994; Prescott, 1996b). The lowest oral/ingested dose of paracetamol which is generally considered to be able to cause toxicity is 7.5 g in adults and 150 mg/kg in children (Hoffman *et al.*, 2007; Saccomano and Deluca, 2008). In addition, it is believed that toxicity in general occurs at doses above 150 mg/kg (Hoffman *et al.*, 2007).

1.2.3.1 Mechanism of toxicity

Following a clinically significant overdose of paracetamol, hepatic GSH becomes depleted and the formation of reactive intermediate metabolites (i.e. NAPQI) exceeds detoxification rates; saturation of the normal nontoxic routes (i.e. sulfation) of metabolism then becomes significant as toxicity progresses enabling NAPQI to bind covalently to hepatocellular proteins, leading liver cell damage and eventually resulting in cell death and liver failure (Prescott, 1980). The quantity of NAPQI produced is increased out of proportion to the paracetamol dose, because maximal rates of sulfation are exceeded (Davis *et al.*, 1976). Although glucuronidation was initially believed to be saturable, it is probable only saturated in severely poisoned patients. In addition to an increase in the formation of toxic metabolites, general elimination is prolonged as normal metabolic systems become saturated (Hoffman *et al.*, 2007); (see Figure 1.1).

The mechanisms of liver injury are not yet fully understood but recent reports had suggested that NAPQI could directly interact with macromolecules in the liver cell

causing lipid peroxidation, protein dysfunction, damage of deoxyribonucleic acid (DNA), oxidative stress and peroxynitrite formation in the mitochondria (Letelier *et al.*, 2011; Loguidice and Boelsterli, 2011; Mitchell *et al.*, 2011; Ramachandran *et al.*, 2011b). A more recent study by Ramachandran *et al.* (2011a) showed that the oxidative stress and peroxynitrite formation are responsible for mitochondrial DNA damage and opening of the mitochondrial membrane permeability transition pore, which generates the collapse of the mitochondrial membrane potential and stops ATP formation. Furthermore, another recent study reported that the consequential of mitochondrial swelling lead to the burst of the outer membrane with the release of intermembrane proteins and subsequent nuclear DNA fragmentation and necrotic cell death (Jaeschke *et al.*, 2011). Dysfunction of mitochondria possibly will thereby result in disrupting energy production, interrupting ionic gradients and intracellular calcium stores resulting in cell death and liver damage (Holt and Ju, 2006; Larson, 2007; Ferner *et al.*, 2011; Mitchell *et al.*, 2011). A more recent study by Li *et al.* (2011) suggested that initial changes of hepatocyte injury included basal membrane disruption and loss of mitochondrial membrane potential leading to irreversible paracetamol-induced hepatocyte injury.

1.2.3.2 Factors affecting toxicity

The toxicity of paracetamol is amplified by several factors that cause GSH depletion, such as increased production of the toxic metabolite NAPQI, or reduced antioxidative capacity of the liver (Thomas, 1993). Furthermore, low protein diets caused GSH depletion, and thus enhanced paracetamol toxicity (McLean and Day, 1975). A number of drugs, such as carbamazepine, phenytoin, phenobarbital, phenytoin, primidone, and

rifampicin induce cytochrome P450 enzymes, and thus increase subsequent formation of the toxic metabolite NAPQI (Miners *et al.*, 1984).

The effects of ethanol ingestion on paracetamol toxicity are complex, and the role of ethanol in acute poisoning remains controversial (Hoffman *et al.*, 2007). Acute ethanol ingestion presumably reduces toxic metabolic activation, because ethanol competitively inhibits CYP2E1, preventing metabolism of paracetamol to NAPQI. Therefore, co-administration of ethanol with paracetamol may be somewhat hepatoprotective (Schmidt *et al.*, 2002a; Waring *et al.*, 2008b). In contrast, chronic excessive alcohol ingestion can induce CYP2E1, consequently increasing the potential toxicity of paracetamol (Schmidt *et al.*, 2002a; Gomez-Moreno *et al.*, 2008; Ansari, 2010; Megwas and Izuawuba, 2010).

Vitamin E reduction also increases paracetamol toxicity, possibly by impairing the hepatic response to oxidative stress (Sener *et al.*, 2003). On the other hand, paracetamol toxicity is reduced by GSH production induced by hepatic enzyme inhibitors, such as cimetidine (Prescott, 1996b; Sajedianfard *et al.*, 2009). Paracetamol toxicity is also reduced by antioxidants (Oz *et al.*, 2004). Reducing agents, such as ascorbic acid, enhance the conversion of NAPQI back to paracetamol and inhibit the covalent binding of paracetamol metabolites to liver microsomal protein (Mitra *et al.*, 1991; Abraham, 2005). Also, the toxicity of paracetamol is increased in patients with a negative nitrogen balance, such as those with cancer (Barker *et al.*, 1977).

1.2.3.3 Clinical features of poisoning

1.2.3.3.1 Diagnosis

Early detection and treatment of patients with paracetamol poisoning is essential for preventing morbidity and mortality. However, this recognition is complicated by the lack of predictive clinical findings early in the course of paracetamol poisoning, and clinicians should not be reassured by a lack of clinical symptoms shortly after paracetamol ingestion. In fact, the first symptoms of paracetamol poisoning may be related to hepatic injury, and may develop many hours after ingestion, when antidotal therapy will have diminished efficacy.

1.2.3.3.2 Early signs

The first 24 hours are considered to be the first phase of paracetamol poisoning. Early clinical symptoms of paracetamol poisoning are usually non-specific, and include nausea and vomiting, malaise, pallor, and diaphoresis; while laboratory indices of liver function are typically normal (Hoffman *et al.,* 2007). In very rare cases of massive overdose, decreased consciousness and metabolic acidosis may also occur during the first phase; although still without any signs or symptoms of hepatotoxicity (Roth *et al.*, 1999; Wiegand *et al.,* 2010). Hepatic tenderness may first appear after about 12 hours and may persist for 18-72 hours (Prescott, 1983). However, these clinical findings should never be assumed to be due to paracetamol poisoning alone without a thorough assessment of other probable causes.

1.2.3.3.3 Hepatic toxicity

In the second phase of paracetamol poisoning, the patient begins to develop clinical and laboratory evidence of hepatotoxicity. Although healthcare practitioners are usually taught that paracetamol-induced liver dysfunction takes place only after a latency of 24 to 48 hours (Rowden *et al.,* 2006); several studies have demonstrated that liver enzymes often become elevated during the first 24 hours (Singer *et al.,* 1995; James *et al.,* 2002; Green *et al.,* 2010).

Signs and symptoms during the second phase vary with the severity of liver injury, but are often similar to those of other causes of hepatocellular injury, such as hepatitis A. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are the most sensitive, readily available marker for identification or prediction of the onset of hepatotoxicity, and AST/ALT abnormalities always precede evidence of definite liver dysfunction, such as prolonged prothrombin time (PT), elevated bilirubin concentrations, metabolic acidosis and hypoglycemia (Hoffman *et al.,* 2007; Hinson *et al.,* 2010). Although uncommon, elevated AST/ALT concentrations may be detectable as early as 8-12 hours after paracetamol ingestion (Singer *et al.,* 1995; Rowden *et al.,* 2005; Green *et al.,* 2010). A more recent studies reported asymptomatic ALT elevations in research subjects who were administered therapeutic doses (4 g/day or less) of paracetamol for more than 4 days (Heard, 2011; Sabate *et al.,* 2011). Based on these studies, the authors recommended that toxicologists should consider therapeutic paracetamol use as a cause of ALT elevations (Heard, 2011; Sabate *et al.,* 2011). While the clinical course of these elevations was not completely defined, available evidence suggests that, even in high risk groups, ALT elevations are not accompanied by

evidence of hepatic dysfunction, and are resolved if treatment is discontinued (Heard, 2011).

Following the second phase of paracetamol poisoning, patients enter a third phase, which is defined as the time of maximal hepatotoxicity, and most frequently occurs between 3 and 4 days after paracetamol ingestion. The most common clinical manifestations of this phase include fulminant hepatic failure (FHF) (Chun *et al.*, 2009). The clinical characteristics of FHF are progressive jaundice with hepatic encephalopathy, associated with markedly increased patient drowsiness and confusion; in addition, there may be impairment of blood clotting, causing spontaneous bruising and bleeding from needle sites, as well as flapping tremor and hypoglycemia. Cerebral oedema may also develop, resulting in headaches, a reduced level of consciousness and cardiac dysrhythmias (Prescott, 1996b).

Fatalities from FHF commonly occur between 3 and 5 days after acute paracetamol poisoning, resulting from multiple organ failure, either alone or in combination with other complications, including: acute respiratory distress syndrome, haemorrhaging, cerebral oedema and sepsis (Bjornsson *et al.*, 2005; Hoffman *et al.*, 2007). Patients who survive this period (third phase) enter the fourth phase, which is defined as the recovery phase. Hepatic regeneration leads to full recovery in survivors. Although the rate of recovery varies, in most cases, laboratory test results are within the normal range by 5-7 days after an acute paracetamol poisoning (McGregor *et al.*, 2003; Grypioti *et al.*, 2005; Grypioti *et al.*, 2007; Hinson *et al.*, 2010). However, full recovery may require significantly more time in severely poisoned patients, and histological abnormalities may persist for months (McGregor *et al.*, 2003; Hoffman *et al.*, 2007).

1.2.3.3.4 Renal failure

Renal failure is less frequent than liver failure following paracetamol poisoning, and has been reported in less than 2% of all patients (Prescott, 1983). However, the occurrence rate of renal failure is greater in more severely poisoned patients, and is observed in more than 50% of patients with hepatic failure, and in approximately 25% of patients with significant hepatotoxicity (Prescott, 1983). Less commonly, mild renal insufficiency occurs without elevations in aminotransferase levels, or as an isolated manifestation of paracetamol toxicity (Prescott *et al.,* 1982; Kher and Makker, 1987; Boutis and Shannon, 2001).

Renal failure is sometimes preceded by renal tenderness and back pain, accompanied by haematuria and proteinuria (Thomas, 1993). Renal failure is associated with elevations in plasma creatinine levels, beginning on day 2 and usually peaking between days 3 and 6 (Prescott, 1996b; Pakravan *et al.*, 2009; Waring *et al.*, 2010; O' Riordan *et al.*, 2011), although progressive elevations of creatinine have been reported up to day 16 (Davenport and Finn, 1988). In cases of paracetamol-induced FHF, the incidence of acute renal failure is nearly equal to that of patients with hepatic failure from other causes (Wilkinson *et al.,* 1977).

Although renal failure is a known complication of paracetamol toxicity, the causal mechanisms are poorly understood (Mazer and Perrone, 2008; Pakravan *et al.*, 2009). Toxic metabolites of paracetamol are produced by local metabolism in the kidney, and may lead to acute tubular necrosis, mainly in conditions associated with GSH depletion (Mitchell *et al.,* 1977). Even in the absence of acute renal failure, paracetamol poisoning is associated with short-term (<24 h) dose-dependent changes in electrolyte

transport, suggesting a specific renal effect of paracetamol poisoning, perhaps via cyclooxygenase inhibition mediated changes to renal tubular function (Pakravan *et al.*, 2007). Risk factors, such as dehydration at presentation, chronic excessive paracetamol poisoning, concomitant ingestion of nephrotoxic substances, GSH depletion in the kidney, and pre-existing liver and renal insufficiency, may all increase the risk of renal injury following paracetamol poisoning (von Mach *et al.,* 2005).

Whereas GSH depletion is considered to play an important role in predisposing paracetamol poisoned patients to hepatotoxicity, there is a lack of data supporting a similar mechanism in renal failure (Waring *et al.,* 2010). Other mechanisms of renal failure have been suggested, including lipid peroxidation and oxidative stress, through which paracetamol induces tubular epithelial degeneration and cortical interstitial congestion (Isik *et al.,* 2006). In addition, COX inhibition has been proposed to be responsible for renal tubular injury in the presence of very high paracetamol concentrations, which might be present following poisoning (Waring *et al.,* 2008a; Waring *et al.,* 2010).

1.2.3.3.5 Other features

Hypoglycemia may occur between 12 and 72 hr after paracetamol poisoning, due to impairment of hepatic gluconeogenesis (Zabrodski and Schnurr, 1984); while metabolic acidosis with reduced bicarbonate levels may also be an early feature (Zabrodski and Schnurr, 1984; Zein *et al.,* 2010). Metabolic acidosis occurs in approximately half of paracetamol poisoned patients within the first 15 hours, and is caused by inhibition of lactic acid uptake and metabolism by the liver, and subsequently, by worsening hepatic function and impaired hepatic clearance of lactic acid (Gray *et al.,* 1987; Makin and

Williams, 1997; Bourdeaux and Bewley, 2007; Chun *et al.*, 2009; Shah *et al.*, 2011). Hypophosphatemia is commonly observed in conjunction with paracetamol-induced hepatotoxicity, and depends on the severity of liver damage, since it is believed to be caused by pronounced phosphate uptake by the regenerating liver (Schmidt and Dalhoff, 2002).

Clinically noticeable cardiac disturbances are very uncommon following paracetamol poisoning. Electrocardiogram (ECG) abnormalities and myocardial injury, which were first noted in early case reports (Jones and Prescott, 1997), are most often observed in patients with FHF, but never as an isolated problem (Lip and Vale, 1996); however, in some cases these effects may be caused by hypokalemia, which is common in the early stages of paracetamol poisoning (Heaps and Gormley, 2010). Recently, Contractor *et al.* (2011) reported a case with paracetamol poisoning in which the patient developed widespread ST-elevation. An emergency echocardiogram was recorded, revealing global hypokinesia, consistent with a moderate degree of systolic left ventricular impairment. The authors propose that paracetamol poisoning-mediated myocardial injury occurs via a mechanism similar to that responsible for hepatic damage.

Specifically, paracetamol is partially converted to NAPQI, a toxic metabolite which is in normally activated by glutathione reduction; NAPQI then acts as a direct toxin on the myocardium. Furthermore, paracetamol itself has been shown to covalently bind proteins in both cardiac and liver tissues, causing protein structural and functional changes, and potentially precipitating cytokine release and tissue damage (Contractor *et al.*, 2011).

Hyperamylasemia and pancreatitis have been reported in paracetamol poisoning, either alone or in combination with ethanol abuse (Schmidt and Dalhoff, 2004; Hoffman *et al.,* 2007). Acute pancreatitis, which is characterised by acute abdominal pain and paralytic ileus, has been reported in paracetamol poisoning, generally after an interval of 1-5 days (Schmidt and Dalhoff, 2004; Igarashi *et al.*, 2009).

1.2.3.4 Toxicoepidemiology

1.2.3.4.1 Global toxicoepidemiology

Paracetamol is considered to be one of the most common causes of poisoning worldwide; and is the leading subject of inquiries to poison centres in the UK and USA (Hawton *et al.*, 2009; Bronstein *et al.*, 2010).

Vale in 2003 documented that up to 40% of all hospital admissions for self-poisoning in the UK involved paracetamol (Vale, 2003). Since the mid-1970s, there had been an increase in the number of paracetamol poisoning, such that paracetamol in 2009 had become the substance most commonly used in deliberate self-poisoning (DSP) in the UK (Hawton *et al.*, 2009). In Oxford, UK, the percentage of paracetamol poisoned cases increased from 14.3% in 1976 to 42% in 1990; while in 1993, 47.8% of all poisoned cases involved either paracetamol or paracetamol-containing drugs (Hawton and Fagg, 1992; Hawton *et al.*, 1996). In fact, paracetamol accounts for half of all poisoning admissions to UK hospitals annually, and is involved in an estimated 150 deaths per year (Hawkins *et al.,* 2007).

Nourjah *et al.* (2006) estimated the number of paracetamol-associated poisoning in the USA. The authors found that paracetamol-associated poisoning cases account for

approximately 56,000 emergency room visits and 26,000 hospitalisations yearly. In addition, analysis of national mortality files revealed that 458 deaths occurred each year from paracetamol-associated poisoning; 100 of which are unintentional. The poison surveillance database reported a near-doubling of the number of fatal cases associated with paracetamol: from 98 in 1997 to 173 in 2001 (Nourjah *et al.,* 2006). A more recent USA study, conducted by Manthripragada *et al,* (2011), suggested that both intentional and unintentional paracetamol poisoning remain a significant public health concern. Furthermore, another recent USA study conducted by Li and Martin (2011), found that children less than 5 years of age, adolescents and young adults account for an overwhelming majority of the emergency department visits attributed to paracetamol poisoning.

1.2.3.4.2 Malaysian toxicoepidemiology

Paracetamol poisoning has also become an emerging problem in Malaysia. Fathelrahman *et al.* (2005) determined the pattern of acute drug and chemical poisoning at Penang General Hospital (PGH), in the northern region of Malaysia. In this retrospective study, the authors found that paracetamol was the main causative agent (44.7%) among cases associated with drugs, and was implicated in 33.47% of all poisoning incidents (Fathelrahman *et al.,* 2005).

Another retrospective review of medical records was conducted to determine the pattern of drug and chemical poisoning cases admitted to the Hospital Universiti Sains Malaysia, in the state of Kelantan (Ab Rahman, 2002). In this study, cases of poisoning with medicinal substances were more common than those with traditional medicines. Medicinal substances included therapeutic drugs such as aspirin and paracetamol

(21.9%), as well as salicylate-containing products (6.7%); hypnotics and sedatives (5.3%); and external preparations (2.3%). The author suggested that paracetamol poisoning did not seem to significantly contribute to the overall pattern of poisoning, in contrast with reports that cases of paracetamol poisoning are increasing elsewhere (Ab Rahman, 2002).

Another cross-sectional survey study conducted in Malaysia used a questionnaire to determine the top 10 toxic agents most commonly reported by accident and emergency departments (AED) as responsible for cases of poisoning during the preceding year at their hospital. Among the responding hospitals, paracetamol poisoning ranked first, and was reported by 86.5% of the hospitals (Al-Sohaim *et al.*, 2011).

1.3 DIAGNOSTIC TESTING

1.3.1 Assessing the risk of paracetamol toxicity

A risk assessment, in which the clinician attempts to determine the most effective clinical course and predict potential complications based on a patient's presentation, should occur as soon as possible during the management of all poisoning patients. The key factors to consider in paracetamol poisoning are the history of the ingested dose and the concentration (early predictors), as well as clinical and laboratory features suggesting hepatic damage (late predictors), and any patient history suggesting an increased risk for toxicity (Daly *et al.*, 2008).

Fatalities from paracetamol poisoning are frequent but avoidable, with appropriate diagnosis and treatment. However, at the same time, the overwhelming majority of paracetamol exposures result in no toxicity. Thus an appropriate approach must be taken to avoid costs associated with unnecessary overtreatment, while eliminating patient risk. To balance these apparently disparate goals, clinicians must be aware of the basis for and sensitivity of current toxicity screening methods (Rowden *et al.*, 2006; Hoffman *et al.*, 2007).

To evaluate and assess patient risk for subsequent toxicity, clinicians often only have unreliable ingestion histories, and measurements of paracetamol levels. However, as described above, the quantity and rate of NAPQI formation, the hepatic GSH supply, the equilibrium of NAPQI formation (CYP2E1 activity), and the capacity for non-toxic metabolism, are all major determinants of toxicity (Rumack and Matthew, 1975). Therefore, the best approach for determining patient risk following paracetamol poisoning would involve assessment of each of these factors. Until recently, none of

these toxicity measures was accessible to clinicians (Schilling *et al.*, 2010). In addition, although the profile of urinary paracetamol metabolites may reveal increased NAPQI formation (Davis *et al.*, 1976), there is no indication or suggestion that NAPQI measurements are of any predictive value in any given case. Furthermore, plasma GSH concentration can also be measured, but have a doubtful relationship with hepatic GSH availability (Smith *et al.*, 1996).

1.3.2 Risk determination after acute poisoning

Acute paracetamol poisoning is generally considered to be a single ingestion, although in reality, many patients poisoning incrementally over a brief period of time. For purposes of this discussion, an *acute overdose/ poisoning* is defined as one in which complete ingestion occurs within a single 4-hour period. In fact, ingestion of 7.5 g of paracetamol in an adult, or 150 mg/kg in a child, is widely considered to be the lowest acute dose capable of causing toxicity (Prescott, 1983). While these principles have been widely applied as sensitive markers, they are not based on human data and are quite conservative. Although there is significant variation in patient susceptibility to paracetamol (Prescott, 1996a), animal data suggest that a single dose of at least 15 g is necessary to cause significant GSH depletion in a human adult (Mitchell *et al.*, 1974).

Hoffman *et al.* (2007) suggest that the ingested dose of paracetamol reported by adults may be considered to be less contentious than that reported for children, because variable histories, massive ingestions, and factors that might influence toxicity occur mainly in adults, allowing continued use of 7.5 g as a screening quantity to avoid missing serious toxicity. In any case, the dose history should be used in the estimation of risk only if there is reliable confirmation or evidence of validity. For example, dose

estimates may be useful in assessment of risk in many cases of unintentional or therapeutic paracetamol ingestion. When the history suggests possible risk, however, the reported dose is inadequate evidence on which to base treatment decisions; risk should then be estimated by determining serum paracetamol concentrations (Hoffman *et al.,* 2007).

Interpretation of serum paracetamol concentrations following acute exposure is based on an adaptation of the Rumack-Matthew nomogram (Rumack and Matthew, 1975). A drug nomogram developed in 1975, called the Rumack-Matthew nomogram, estimates toxicity risk based on the serum paracetamol concentration at a given number of hours after ingestion. Serum paracetamol levels at or above a line connecting 200 mcg/mL at 4 hours post-ingestion and 30 mcg/mL at 15 hours post-ingestion were found to consistently predict hepatotoxicity (Rumack and Matthew, 1975); (Figure 1.2).

When the nomogram was introduced in the United States, the US Food and Drug Administration (FDA) required an alteration of the original nomogram as part of the NAC protocol, resulting in a 25% reduction of the NAC treatment threshold. A line connecting 150 mcg/mL at 4 hours and 4.7 mcg/mL at 24 hours, was defined as the 'possible toxicity' treatment line, to allow for possible errors in plasma assays and ingestion times (Rumack *et al.,* 1981); (Figure 1.2). After an acute ingestion, serum paracetamol levels should be measured 4 hours post-ingestion, or at any time up to 24 hours post-ingestion, and plotted on the nomogram. Patients with paracetamol levels above the 'possible toxicity' line should be treated with NAC (Rumack, 2002; Rowden *et al.,* 2005). Paracetamol concentrations measured within the first 4 hours of ingestion may underestimate the amount of drug in the system, because paracetamol may still be

in the process of being absorbed from the GI tract. Therefore, serum concentration measurements within the first 4 hours post-ingestion are not recommended (Dart *et al.*, 2006).

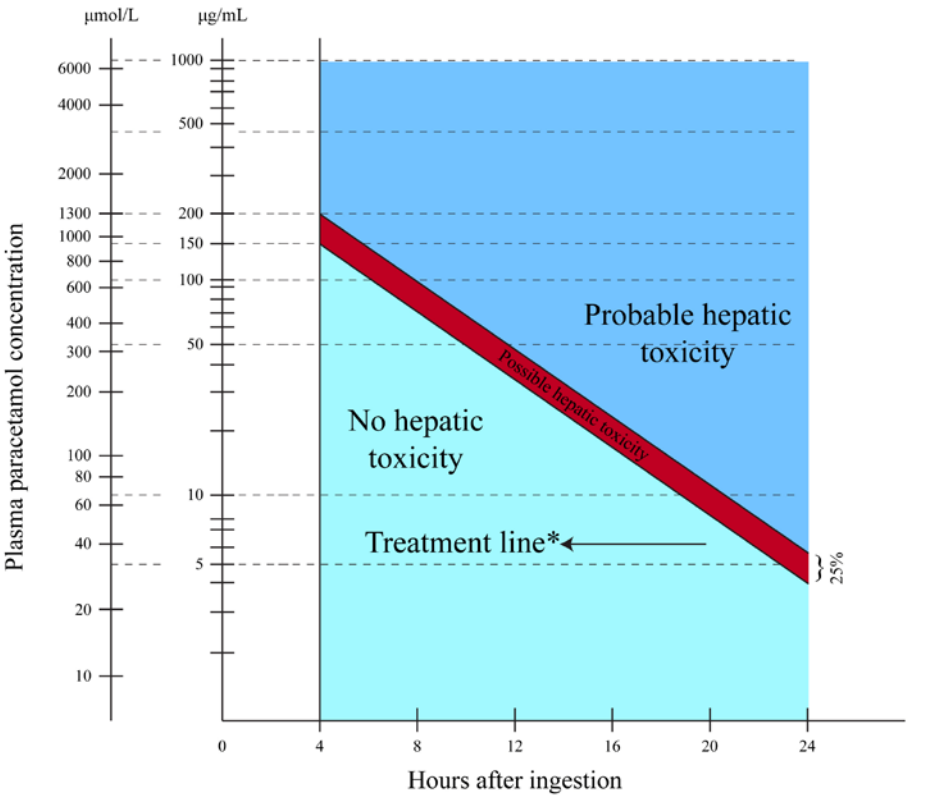


Figure 1.2. Plasma acetaminophen (paracetamol) concentrations versus time post-paracetamol ingestion: Reproduced with permission from pediatrics, vol. 55, page 873, Copyright © 1975 by the American Academy of Pediatrics (AAP).*****The Rumack-Matthew nomogram for determining the risk of paracetamol-induced hepatoxicity following a single acute ingestion. Levels above the treatment line on the nomogram indicate the need for *N*-acetylcysteine (NAC) therapy.

The basic goals of risk assessment should be to determine serum paracetamol concentrations at the earliest point at which they will be significant. Measurement of serum paracetamol concentrations 4 hours post-ingestion, or as soon as possible thereafter, is used to confirm risk of toxicity, and thus the need to initiate NAC. Although it is optimal to start NAC therapy as soon as possible after confirmation of risk, most patients will have good outcomes if therapy is started before 8 hours post-

ingestion (Smilkstein *et al.,* 1988). Although this recommendation is not a permit to delay initiation of NAC treatment until 8 hours post-ingestion, it allows clinicians some flexibility to wait for serum paracetamol concentration laboratory results before deciding to start therapy; especially for patients whose history of paracetamol ingestion suggests that serum paracetamol concentrations will fall under the treatment line. Factors that confuse diagnostic decision making after acute paracetamol poisoning include: circumstances that prevent serum paracetamol concentration measurements prior to 8 hours post-ingestion; unable to determine the time of ingestion; patient brought to the hospital more than 24 hours post-ingestion; and newer formulations of paracetamol (Rumack, 2002; Rumack, 2004) .

Only if serum paracetamol concentration determination results cannot be obtained within 8 hours of poisoning should history alone be used to decide to initiate NAC therapy. In such cases, serum paracetamol concentrations should still be determined as soon as possible. The result, when it does become accessible, should be interpreted in relation to the treatment line on the paracetamol nomogram, and NAC therapy should be either continued or ceased based on this result. In rare circumstances where no determination of serum paracetamol concentrations can ever be obtained, evidence of possible risk by history alone is adequate to initiate and complete a course of NAC therapy (Rumack, 2002; Hoffman *et al.,* 2007).