AN EVALUATION ON THE PRACTICE, PERCEPTIONS AND KNOWLEDGE ON THE USE OF ACETAMINOPHEN (PARACETAMOL) AMONG THE LOCAL CONSUMERS IN PENANG, MALAYSIA

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BY

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LIST OF ABBREVIATIONS

AC	Activated charcoal
ALF	Acute liver failure
ALT	Alanine aminotransferase
AMDI	Advance Medical and Dental Institute
AOR	Adjusted odd ratio
AP	Alkaline phosphate
APAP	Acetaminophen
AST	Aspartate aminotransferase
ATN	Acute tubular necrosis
BM	Bahasa Malaysia (National language of Malaysia)
BUN	Blood urea nitrogen
CI	Confidence interval
Cr	Creatinine
CYP2E1	Cytochrome P450 2E1
CMV	Cytomegalovirus
CF	Cystic Fibrosis
EBV	Epstein-Barr Virus
FDA	Food and Drug Administration
FHF	Fulminant hepatic failure
GIT	Gastrointestinal tract
HINTs	Health Information National Trend Survey
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IV NAC	Intravenous N-acetylcysteine
INR	International normalized ratio
KCHC	King's College Hospital criteria
LDH	Lactic acid dehydrogenase
MOH	Ministry of Health Malaysia
MRI	Magnetic resonance imaging
NAC	N-acetylcysteine
NAPQI	N-acetyl-p-benzoquinone imine

NPDs	Non-prescription drugs
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OA	Osteoarthritis
OR	Odd ratio
OTC	Over-the-counter
PT	Prothrombin time
PTT	Partial thromboplastin time
RA	Rheumatoid arthritis
RR	Relative Risk
RSTI	Repeated supra-therapeutic ingestion
SAC	Superactivated charcoal
SAF-M	Severe acute liver failure related to therapeutic misadventure
SAF-O	Severe acute liver failure in drug overdose
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIRS	Systematic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
UK	United Kingdom
URTI	Upper respiratory tract infection
USM	Universiti Sains Malaysia
US	United State of America

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PENILAIAN AMALAN, PERSEPSI DAN PENGETAHUAN TENTANG PENGGUNAAN ACETAMINOPHEN (PARACETAMOL) DALAM KALANGAN PENGGUNA TEMPATAN DI PULAU PINANG, MALAYSIA

ABSTRAK

Acetaminophen (paracetamol) adalah ubat yang boleh dibeli di kaunter yang biasa digunakan oleh pengguna-pengguna Malaysia sebagai swa-pengubatan untuk demam panas dan sakit. Memandangkan peningkatan dalam kos perubatan adalah salah satu cabaran kepada rakyat Malaysia, amalan swa-pengubatan dijangka akan terus meningkat. Namun demikian, amalan swa-pengubatan tanpa maklumat dan pengetahuan yang mencukupi boleh meningkatkan risiko keracunan acetaminophen. Sesungguhnya, keracunan acetaminophen merupakan salah satu masalah sosial dalam kalangan pengguna di Malaysia. Oleh itu, kajian ini dijalankan untuk menilai penggunaan produk-produk acetaminophen dalam kalangan pengguna tempatan di Pulau Pinang, Malaysia dari segi isu-isu berkaitan amalan, persepsi dan pengetahuan mereka mengenai produk-produk tersebut. Kajian ini dibahagikan kepada dua bahagian. Di bahagian pertama kajian ini, satu kaji selidik melalui penggunaan borang soal selidik telah dijalankan di antara 400 orang pengguna di Pulau Pinang melalui persampelan mudah. Bahagian kedua kajian ini adalah satu temu bual kualitatif berstruktur separa yang dijalankan antara empat belas pengguna yang berumur antara 24 hingga 82 tahun dan tinggal di Pulau Pinang. Bahagian pertama kajian ini menunjukkan bahawa produk-produk acetaminophen adalah popular dalam kalangan pengguna. Semasa menilai jumlah pengambilan harian acetaminophen, 24.8 % dan 11.8 % daripada pengguna-pengguna tersebut masing-masing didapati telah terlebih guna tablet acetaminophen 500 mg dan 650 mg. Majoriti pengguna memandang acetaminophen sebagai satu ubat yang selamat untuk diguna (69.1 %) dan sangat

berkesan untuk kesakitan yang ringan dan sederhana (81.8 %). Namun demikian, kebanyakan daripada pengguna-pengguna tersebut didapati kurang berpengetahuan terhadap dos, langkah berjaga-jaga semasa menggunakan acetaminophen, kesan-kesan dan tanda-tanda bagi penggunaan acetaminophen secara berlebihan. Bahagian kedua kajian ini menunjukkan bahawa pengguna-pengguna mempunyai sikap yang positif terhadap acetaminophen dari segi populariti, keselamatan dan keberkesanan. Namun demikian, mereka mempunyai kesukaran dalam membezakan antara produk-produk generik yang terdapat di pasaran. Sesetengah pengguna menyatakan bahawa mereka akan menggandakan dos atau mengambil dengan lebih kerap jika keadaan atau gejala mereka berterusan selepas mengambil acetaminophen. Selain itu, label bagi sesetengah produk acetaminophen didapati tidak menarik hati dan tidak mengandungi maklumat yang mencukupi bagi pengguna-pengguna. Pengguna-pengguna tersebut mencadangkan bahawa Kementerian Kesihatan Malaysia perlu menghasilkan kaedah pendidikan yang berkenaan dengan penggunaan acetaminophen yang betul. Sebagai kesimpulan, amalan, persepsi dan pengetahuan pengguna-pengguna mengenai penggunaan acetaminophen perlu diperbaiki untuk memastikan penggunaan secara berkualiti bagi produk-produk yang mengandungi acetaminophen.

AN EVALUATION ON THE PRACTICE, PERCEPTIONS AND KNOWLEDGE ON THE USE OF ACETAMINOPHEN (PARACETAMOL) AMONG THE LOCAL CONSUMERS IN PENANG, MALAYSIA

ABSTRACT

Acetaminophen (paracetamol) is an over-the-counter medicine commonly used by the Malaysian consumers for self-medication of fever and pain. As increasing healthcare costs is one of the challenge to Malaysians, the self-medication practice is expected to increase. However, self-medication without proper information and knowledge could increase risk of acetaminophen poisoning. Indeed, acetaminophen poisoning is one of the social problems among the consumers in Malaysia. Hence, this study was conducted to evaluate the use of acetaminophen products among the consumers in Penang, Malaysia on the issues around their practices, perceptions and knowledge about such products. This study was divided into two parts. In part I of the study, a qualitative structured survey using a questionnaire was conducted among 400 consumers in Penang via convenient sampling. The second part of the study was a qualitative semi-structured interview conducted among fourteen consumers aged between 24 to 82 years old and living in Penang. Part I of the study revealed that acetaminophen products were popular and usually used for fever and common pain among consumers. About 24.8 % and 11.8 % of the consumers found to have over-consumed the recommended maximum daily dose of acetaminophen 500 mg and 650 mg tablets respectively. The majority of consumers perceived acetaminophen as a safe drug to use (69.1 %) and very effective for mild and moderate pain (81.8 %). Nevertheless, most of the consumers had lack of knowledge regarding dosage and precautions when consuming acetaminophen, and effects and signs of acetaminophen over-consumption. The part II study showed that the consumers had a positive attitude

towards the popularity, safety and efficacy of acetaminophen. However, they had difficulty in recognizing generic acetaminophen-containing products available in the market. Some consumers claimed that they will double the acetaminophen dose or take it more frequently if their conditions persisted. Besides, the product package label for certain acetaminophen products were not attractive and informative enough for the consumers. The consumers suggested that the Ministry of Health Malaysia should established educational tools on the proper use of acetaminophen. In conclusion, the consumers' practices, perceptions and knowledge about use of acetaminophen need to be improved in order to ensure the quality use of acetaminophen containing products.

CHAPTER 1
GENERAL INTRODUCTION

1.1 Introduction

Acetaminophen is a common constituent of over-the-counter (OTC) analgesic and non-prescription medicine used to reduce fever and relieve general pain such as headache, backache, toothache and menstrual pain. Besides, acetaminophen combination products can use to treat cold and flu. In Malaysia, the OTC products can be obtained easily from the supermarket, pharmacy, sundry shop, government hospitals and clinics. Meanwhile, use of OTC products is popular among Malaysian consumers (Ali et al., 2010). However, special attention is needed on the target population included parents, caregivers, the elderly, pregnant women, students, chronic alcohol drinkers, the adolescents and school-aged children who are at higher risk of involve in drug poisoning (Gilbertson et al., 1996; Ecklund et al., 2001; Fawole et al., 2001; Amoako et al., 2003; Bortolon et al., 2008; Crocetti et al., 2009; Du et al., 2009; Ali et al., 2010; Dawood et al., 2010; Jensen et al., 2010; Klemenc-Ketis et al., 2010; Albsoul-Younes et al., 2011; Almasdy et al., 2011; Dawood et al., 2011; El-Ezz et al., 2011; Himmelstein et al., 2011; Chang et al., 2012; Chowdhury et al., 2012; Corrêa Da Silva et al., 2012; Du et al., 2012; Fouladbakhsh et al., 2012; Anjan et al., 2013; Baghianimoghadam et al.,2013; Garvey et al., 2013; Manchanda et al., 2013; Abubakar et al., 2014; Almalak et al., 2014; Eldalo et al., 2014; Jensen et al., 2014; Ayad et al., 2015; Gualano et al., 2015; Italia et al., 2015; Bohio et al., 2016). The proper recommended dose of acetaminophen for adults is 500 mg to 1,000 mg every 4 to 6 hours, up to a total daily dose of 4000 mg and for infant or children is 15 mg/kg every 4 to 6 hours, up to a total daily dose of 2400 mg (Madlen, 2010). An acute single ingestion of acetaminophen greater than 10 g or 200 mg/kg (whichever is lower) in

adults or 200 mg/kg in children is considered hepatotoxic (Madlen, 2010). However, acetaminophen toxicity can also occurred after repeated ingestion of supra-therapeutic doses over a period of more than 8 hours (Madlen, 2010). These may lead to the symptoms such as confusion, loss of appetite, stomach pain, nausea or vomiting. Liver injury becomes evident when levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) begin to increase within 24 to 48 hours. This may eventually lead to death (Schiødt et al., 1997; Dart et al., 2006a).

Currently, activated charcoal (AC) and N-acetylcysteine (NAC) is the antidote for acetaminophen poisoning. AC helps to prevent absorption of drug in bloodstream (Blakely and McDonald, 1995; Sato et al., 2003; Wananukul et al., 2010). Meanwhile, NAC provides L-cysteine which is important to stimulate glutathione synthesis (Waring et al., 2008a). Nevertheless, early initiation of AC and NAC therapy respectively is essential as it is most effective for patients who are admitted to the hospital within 1 to 2 hours (Brent, 1993; Lystbaek et al., 1995; Zed and Krenzelok, 1999; Christophersen et al., 2002; Wallace et al., 2002; Dart et al., 2006a; GlaxoSmithKline, 2007; Daly et al., 2008; Thomason, 2012) and 8 to 10 hours (Yang et al., 2009) of the acetaminophen ingestion. Besides, gastric lavage is effective at reducing the absorption and increasing elimination of acetaminophen after the overdoses and thus reducing the risks of liver injury (Dart et al., 2006a). Wendon et al. suggested that gastric lavage is effective for patients who present within 1 to 6 hours post ingestion (Wendon et al., 1995) while Lystbaek et al. recommended it to be given between 2 to 4 hours after acetaminophen overdose (Lystbaek et al., 1995).

Acetaminophen poisoning is a common phenomenon around the globe. In the United Kingdom, acetaminophen poisoning accounted for 48 % of hospital admission and lead to 100 to 200 deaths yearly (Gunnell et al., 2000; Hawkins et al., 2007). The data from the United States Poison Control Centres showed that there were 91 deaths out of 98,578 of all acetaminophen overdose cases in 2008 (Burda and Sigg, 2012) where the government spend US$87 million yearly to treat acetaminophen poisoned patients (Mehrpour and Ballali-Mood, 2011). A study conducted at a general hospital in Northern Malaysia found that acetaminophen poisoning accounted for around 29 % of all drug poisoning incidents with 60 % of the cases were due to suicidal and 33.3 % cases involved accidental ingestions. The majority (73.3 %) of the acetaminophen poisoning cases involved patients aged between 16 to 30 years and 38 % of the cases involved ingestion dose of more than 10 gram (Mohd Zain et al., 2006). Lack of health literacy is the main reason for poor knowledge and potential unsafe use of acetaminophen-containing products (Shone et al., 2011). Besides, self-medication without consultation of healthcare providers, which is a common practice among consumers in Malaysia, could increase the risk of misuse and over-consumption of acetaminophen (Almasdy and Sharrif, 2011). To overcome this problem, proper labeling, educational interventions and public health activities may help to promote proper use of acetaminophen (Shone et al., 2011).

1.2 Problem statement

In Malaysia, consumers are able to treat minor illness themselves due to easy accessibility to over-the-counter (OTC) drugs including acetaminophen. However, self-medication using acetaminophen without proper information and knowledge is dangerous as this might leads to acetaminophen overdose and poisoning.

Acetaminophen poisoning is becoming an increasingly common social problem in Malaysia and it involves consumers from various age groups. The poisoning requires immediate emergency department visits and hospital admission and this places a significant burden on healthcare costs. Indeed, the poisoning could leads to severe liver injury and even death. Currently, little is known about the reasons behind the acetaminophen poisoning among the Malaysian consumers. The consumers might be unaware about the safe use of acetaminophen. However, currently there is no study been carried out to evaluate the Malaysian consumers' practices, perception and knowledge of acetaminophen about its uses, dosage and toxicities.

1.3 Rational for the study

Currently, to the best of our knowledge, there are limited educational tools in Malaysia to promote rational use of acetaminophen. Besides, little is known about the Malaysian consumers' practices, perceptions and knowledge of acetaminophen. An understanding of consumers' practices, perceptions and knowledge about use of acetaminophen is important to the overall planning of educational interventions to address the misuse of acetaminophen and subsequent poisoning. Therefore, this study will provide baseline data to help in the development of educational tools on the proper use of acetaminophen. Besides, the study findings will help the government agency or private health institutions in designing educational interventions or programs for the consumers with regards to the proper use of acetaminophen. This in return will enhance the quality of acetaminophen use in achieving optimum health outcome for the public.

1.4 General objectives

This study aimed to evaluate the practices, perceptions and knowledge of acetaminophen among the consumers in Penang, Malaysia.

1.5 Specific objectives

1. To evaluate the differences in the consumers' practices, perceptions and knowledge of acetaminophen according to demographic characteristics.
2. To assess the risk factors for acetaminophen poisoning among the consumers according to demographic characteristics.
3. To assess the consumers' ability in differentiate between originator and generic acetaminophen products.

The first and second specific objectives were achieved through both the phase I (quantitative) and phase II (qualitative) study. Meanwhile, the third objective was achieved by the phase II study.

1.6 Overview of thesis

Chapter 2, the literature review, starts with trends of acetaminophen use, epidemiology of acetaminophen poisoning in Malaysia and overseas and also recommended and toxic dose of acetaminophen in both adults and children.

The chapter continues with the prognosis, risk factors and clinical presentations of acetaminophen poisoning. It is followed by the review of acetaminophen induced fulminant hepatic failure (FHF), acetaminophen induced nephrotoxicity, King's College Hospital criteria versus Modified King's College Hospital criteria for determining mortality or requirement of liver transplantation, severe acute liver failure

related to therapeutic use of acetaminophen (SAF-M) versus severe acute liver failure related to acetaminophen overdose (SAF-O) and accidental staggered overdose versus single time point overdose. A review of previous case reports and case series of acetaminophen poisoning cases in infants, children, pregnant women, alcoholic patients, teenagers, young adults, middle aged and elderly people and fatal cases were also included.

The chapter continues with the regulations to control sale and label of acetaminophen. A review of the previous studies on consumers' practices, perception and knowledge about acetaminophen in overseas and Malaysia were also included in this chapter.

The methodology, results and discussion of the study are presented in chapter 3, 4 and 5 respectively. In chapter 6, conclusions and a set of recommendations to improve the quality use of acetaminophen are provided.

CHAPTER 2
LITERATURE REVIEW

2.1 The use of over-the-counter (OTC) medicinal products among the consumers

OTC medicinal products are widely used among the consumers around the globe. A study in India showed that prevalence of self-medication using OTC drugs for fever was observed among the University students (74 %) (Kumar et al., 2013). Besides, the studies in Pakistan and Poland noticed that use of these drugs for headache were found among the pregnant women (60 %) (Bohio at al., 2016) and secondary school students (52 %) respectively (Pisarska et al., 2011).

A previous cross-sectional survey involved 481 female University students in Malaysia revealed that the most common non-prescription drugs used by them were pain killers & fever reducers (30.2 %), otolaryngology (ear, nose & throat) medicines (10.8 %), health supplements (10.8 %), gastrointestinal disorders medications (8.5 %), anti-infective agents (7.3 %) and traditional drugs (3.5 %) (Ali et al., 2010). Another survey study in Malaysia involved 197 parents noticed that use of OTC drugs without seeing a doctor were common among them in treating their children's ailments included pharyngitis (sore throat), pyrexia, cough and diarrhoea (Dawood et al., 2010).

2.2 The use of acetaminophen products among the consumers

Acetaminophen is one of the most popular OTC medicinal products among the consumers in both developing and developed countries. Most consumers and healthcare professionals had taken either acetaminophen-alone or acetaminophen-combination products to treat menstrual pain (Tangchai et al., 2004; Chuamoor et al.,

2012; Tanmahasamut and Chawengsettakul, 2012), headache (Boardman et al., 2004; Martínez Eizaguirre et al., 2006; Cuvellier et al., 2009), fever (Murphy, 1992; Linder et al., 1999; Walsh et al., 2005; Walsh et al., 2007; Jensen et al., 2010; Trajanovska et al., 2010; Oziegbe et al., 2011; Demir and Sekreter, 2012; Lava et al., 2012), dental pain (Vogel et al., 2011) and common pain (Lucas et al., 2007; Trajanovska et al., 2010; Kassaw and Wabe, 2012; Bello and Bello, 2013; Gonçalves et al., 2013).

Acetaminophen products were common among Nigerian secondary students due to its efficacy, availability and affordability (Onohwosafe and Olaseha, 2004) whilst Palestinian consumers were likely to purchase many strips of acetaminophen per transaction and keep them in the house (Sweileh et al., 2004). In United States, acetaminophen was the most common over-the-counter medications used among children aged below 12 years old (Vernacchio et al., 2009) whilst the middle aged and elderly people preferred to use combination of acetaminophen with hydrocodone and propoxyphene to treat common pain (Blazer and Wu, 2009). Meanwhile, the children in Switzerland were preferred to consume acetaminophen disintegrating tablets (Ceschi et al., 2011). However, acetaminophen is less popular in some European countries such as Finland since consumers preferred to use NSAIDs to treat chronic pain (Pitkala et al., 2002; Breivik et al., 2006). A study in Bahrain showed that acetaminophen products was the most common non-prescription pain killers used by the consumers to treat headache, fever and pain due to the flu-like symptoms (Mahmood Al-Qallaf, 2015).

Currently, there is lack of data on the use of acetaminophen among the Malaysian consumers. Hence, surveys are needed to evaluate the issues around the use of acetaminophen in both the public and private healthcare settings in Malaysia.

2.3 Epidemiology of acetaminophen poisoning in overseas

In United States, most acetaminophen poisoning cases were due to accidental or staggered overdoses (70.4%) (Schiødt et al., 1997). Similar trend was observed in Singapore where staggered overdose accounted for 68% of the acetaminophen poisoning cases (Ng, K.C., 2003). However, staggered overdose only accounted for 24.3% and 15% of acetaminophen poisoning cases in the United Kingdom (Craig et al., 2012) and Australia respectively (Sood et al., 2013). Acute acetaminophen poisoning occurred mostly in younger adults (Hegazy et al., 2012; Schmidt, 2004; Schmidt, 2005; Siddique and Patel, 2012) and females (Aakvik and Jacobsen, 2006; Angalakuditi et al., 2008; Hegazy et al., 2012; Simkin et al., 2012; Sood et al., 2013), with minimal involvement of children (Hegazy et al., 2012; Sood et al., 2013). The average age group of the patients involved in acetaminophen poisoning were found to be within the range of 15 to 24 years (Schmidt, 2005) and 15 to 50 years (Sood et al., 2013) according to findings from previous studies. Children and infants are at risk of consuming acetaminophen accidentally while teenagers and adults are more prone to suicidal poisoning (Amar and Schiff, 2007; Noshad et al., 2010; Olguín et al., 2011).

Acetaminophen poisoning accounted for 21 % in Norway (Aakvik and Jacobsen, 2006), 40 % in the United Kingdom (Gunnell et al., 2000; Vale, 2003; Hawkins et al., 2007; Hewett et al., 2013) and 33 % in Singapore (Ponampalam et al., 2009) of all hospital admissions due to poisoning. In United Kingdom, acetaminophen poisoning

accounts for more than 70,000 emergency hospital attendances and there were around 18 deaths per million populations yearly (Waring et al., 2008a). However, withdrawal of co-poxamol (combination of acetaminophen and dextropropoxyphene) from the market in United Kingdom has led to reduction in poisoning deaths in recent years (Sandilands and Bateman, 2008; Hawton et al., 2009; Hawton et al., 2011; Hawton et al., 2012; Thomason, 2012). Acetaminophen was responsible for over half of deliberate self-poisoning cases among children and adolescents below 15 years who were admitted to United Kingdom general hospitals (Hawton and Harriss, 2008). Meanwhile, England and Wales had four times higher in mortality rate from acetaminophen toxicities as compared to France (Gunnell et al., 1997; Morgan and Majeed, 2005). In Oxford, acetaminophen was responsible for 50 % of acute kidney injury cases (Lee, 2004; Amar and Schiff, 2007) and it caused 47 % of drug overdoses (Mehrpour and Ballali-Mood, 2011).

There were 91 deaths out of 98,578 of all acetaminophen overdose cases according to data from the United States Poison Control Centres in 2008 (Burda and Sigg, 2012). The United States government spend US$87 million every year to treat acetaminophen poisoned patients (Mehrpour and Ballali-Mood, 2011). Meanwhile, another study from United States reported a reduction in yearly percentage of acetaminophen-related acute liver failure from the year of 1998 to 2003 (Bataller, 2007)

2.4 Epidemiology of acetaminophen poisoning in Malaysia

In Malaysia, approximately half (51.5%) of the acetaminophen poisoning cases were due to suicidal attempts (Fathelrahman et al., 2005). The poisoned cases occurred mostly in females (about 70 %) (Fathelrahman et al., 2005; Mohd Zain et al., 2006;

Kaur et al., 2010), those who self-treatment with acetaminophen (69.7 %) (Kaur et al., 2010) and unmarried people (54.4 %) (Kaur et al., 2010) The average age group of the poisoned patients were found to be relatively young. A study by Kaur et al. found that 55.2% of the poisoned patients were aged between 16 to 25 years old (Kaur et al., 2010). Another retrospective case review conducted in years 2000 to 2002 found almost similar trend whereby 55.2% of the patients who involved in acetaminophen poisoning were in the age group of 15.1 to 30 years old (Fathelrahman et al., 2005). In this retrspective study, acetaminophen overdose accounted for 44.7% of all the 493 drug poisoning cases. For racial differences, Chinese made up 37.7 % of all cases, followed by Indians (31.6 %) and Malays (26.6 %) (Fathelrahman et al., 2005). Another retrospective case review involved 437 drug poisoning cases showed that acetaminophen (44.6 %) was main causative agent of all cases. Besides, Indians patients constituted 41.0 % of all cases, followed by the Malays (31.8 %) and Chinese (20.5 %) (Kaur et al., 2010).

2.5 Recommended dose of acetaminophen in adults and children

The proper recommended dose of acetaminophen for adults is 500 mg to 1,000 mg every 4 to 6 hours, up to a total daily dose of 4000 mg. For infant or children the recommended dose is 15 mg/kg every 4 to 6 hours, up to a total daily dose of 2400 mg (Madlen, 2010).

2.6 Toxic dose of acetaminophen in adults and children

An ingestion of 10 to 15 grams of acetaminophen may increase the risk of hepatotoxicity (Prescott et al., 1974; McLean et al., 1976; Waring et al., 2008a; Tanaka et al., 2000; Mehrpour and Ballali-Mood, 2011) while a 25 grams of acetaminophen

ingestion is considered as fatal (Schueler and Harper, 1995; Clark et al., 1973). However, an ingestion of more than 3.25 grams of acetaminophen daily can increase risk of liver injury among patients with osteoarthritis pain (Altman and Barthel, 2011). A previous study found that an ingestion of 5 gram of acetaminophen had caused 17 % of death cases in Japan whilst the fatal cases in Western countries were due to ingestion of 13 to 25 gram of acetaminophen. The fatal dose of acetaminophen was low in the Japan study due to additional side effects of other active ingredients used in acetaminophen combination products. Meanwhile, the Western countries consumers preferred to use products which contain acetaminophen as the sole active ingredient (Washio and Inoue, 1997).

2.7 Acetaminophen poisoning

2.7.1 Prognosis of acetaminophen poisoning

The overall mortality of acetaminophen toxicity is about 5 %. The international normalized ratio (INR), pH and blood creatinine concentration are important prognostic factors for predicting hepatotoxicity resulting from acetaminophen poisoning (Vale, 2007). Liver injury occurred when prothrombin time (PT) is more than 20 seconds at 24 hours after ingestion of acetaminophen. A peak PT of more than 180 seconds and blood pH of less than 7.3 is associated with survival rate of 8 % and 15 % respectively. Additionally, poor survival found to have related to increase of serum creatinine for more than 300 μmol/litre (Vale, 2003). A study in the United States reported 73 % of overall survival rate for patients with acute liver failure (Bataller, 2007). Another study in United States revealed a 7.7 % of overall mortality rate for 26,961 patients who experienced acetaminophen poisoning. There is also an elevated mortality risk among patients with underlying liver diseases and heavy

drinkers (Kumar et al., 2011). Meanwhile, Mutimer et al. found that cerebral oedema and sepsis were responsible for most of the acetaminophen mortality cases whilst the rest was due to late treatment seeking, prolonged PT, coma, kidney injury and metabolic acidosis (Mutimer et al., 1994).

2.7.2 Risk factors of acetaminophen poisoning

There were a few studies which revealed that repeated supra-therapeutic ingestion of acetaminophen in heavy drinkers will induce CYP2E1 enzyme and deplete glutathione store This in return will increased the accumulation of toxic substance N-acetyl-p-benzoquinone (NAPQI) and thus increase risk of mortality after hepatotoxicity (Lystbaek et al., 1995; Ho and Lam, 1996; Tanaka et al., 2000; Schmidt et al., 2002; Manchanda et al., 2013). Besides, acetaminophen toxicity after massive overdose usually occurred in patient who ingesting P450-inducing drugs such as rifampicin, phenytoin, phenobarbitone and carbamazepine (Blakely and McDonald, 1995; Lane et al., 2002). The use of St John's Wort (Waring, 2012) and prolonged fasting were also the risk factors for acetaminophen toxicity (Dart et al., 2006a). The use of tobacco with acetaminophen will increase the oxidative metabolism of acetaminophen, elevation of ALT and INR and eventually lead to liver injury (Schmidt and Dalhoff, 2003).

2.7.3 Clinical presentations of acetaminophen poisoning

Vomiting, nausea, abdominal pain, loss of appetite and confusion were common signs of acetaminophen toxicity (GlaxoSmithKline, 2007). However, there are four stages of clinical course of acetaminophen poisoning:

Stage I is occurred within 24 hours of acetaminophen ingestion. The patients may experience nausea, vomiting, anorexia (Clark et al., 1973; Pajoumand et al., 2003;

Vale, 2003; Muñiz et al., 2004) abdominal pain (Vale, 2012; Muñiz et al., 2004) and malaise (Pajoumand et al., 2003).

Stage II is an initial manifestations of liver toxicity which is occurs within 24 to 48 hours post ingestion (Muñiz et al., 2004). The clinical manifestations included abdominal pain, increase of the AST, ALT, PT and bilirubin levels (Mehrpour and Ballali-Mood, 2011; Pajoumand et al., 2003) and jaundice (Mehrpour and Ballali-Mood, 2011).

Stage III is observed in 3 to 4 days after acetaminophen ingestion. The patients may develop right upper quadrant abdominal pain, tenderness and hepatomegaly. Proteinuria and haematuria may occur as well (Muñiz et al., 2004). There are also elevations of PT, AST, ALT, bilirubin, BUN (Okeke and Okeibunor, 2010) and ammonia levels (Vale, 2003; Muñiz et al., 2004). The patients may experience hepatic necrosis (Pajoumand et al., 2003; Mehrpour and Ballali-Mood, 2011) and palpitation (Clark et al., 1973).

Stage IV is taken place in 4 to 14 days after acetaminophen overdoses. The patient may develop hepatic failure (Pajoumand et al., 2003; Vale, 2003; Muñiz et al., 2004) or even fulminant hepatic failure (Clark et al., 1973; Mehrpour and Ballali-Mood, 2011). However, the patient may start to recover from the acetaminophen poisoning in this state (Muñiz et al., 2004; Mehrpour and Ballali-Mood, 2011).

2.7.4 Acetaminophen induced hepatotoxicity and fulminant hepatic failure (FHF)

Acetaminophen induced hepatotoxicity is associated with production of the intermediate NAPQI by liver cytochrome P450 system. It occurred when the production of NAPQI is greater than the capacity to detoxify it, and the excess NAPQI will bind to cellular components to cause the death of hepatocytes (Schiødt et al., 1997; Dart et al., 2006a). This phenomenon of acetaminophen induced hepatotoxicity is also referred as the raise of ALT or AST level greater than 1000 IU/L (Heubi et al., 1998; Tsai et al., 2004; Prescott, 2005, Aakvik and Jacobsen, 2006; Gupta et al., 2009; Craig et al., 2012; Varney et al., 2012) which may cause by history of exposure to multiple dose of acetaminophen and increased risk in patients with hepatitis, cytomegalovirus, Epstein-Barr virus and Wilson's disease (Heubi et al., 1998).

Some patients developed FHF due to consume large amount of acetaminophen, late treatment seeking and higher serum acetaminophen levels (Chan et al., 1996; Kanter, 2006). Regular alcohol consumption in excess of 21 units/week in males and 14 units/week in female, regular use of enzyme-inducing drugs such as rifampicin, phenytoin, phenobarbitone and carbamazepine; conditions causing glutathione depletion such as malnutrition, HIV infection, eating disorders and cystic fibrosis; and ingestion of oral dose of 250 mg/kg to 350 mg/kg acetaminophen will increase the risk of developing FHF in acetaminophen poisoned patients (Schueler and Harper, 1995; Salgia and Kosnik, 1999; Wallace et al., 2002; Daly et al., 2008). The clinical presentations of FHF included mental confusion, nausea, vomiting, anorexia, stomach pain, jaundice, haematuria and metabolic acidosis (Lall and Paul, 1998; Dart et al., 2006a). Prompt treatment is needed in FHF patients to prevent them from succumbing to hepatic coma and death (Artnak and Wilkinson, 1998).

2.7.5 Acetaminophen induced nephrotoxicity

Acetaminophen induced nephrotoxicity is less commonly occurred than acetaminophen induced hepatotoxicity. The overall incidence of acetaminophen induced nephrotoxicity in patients with and without severe hepatic necrosis were 10 to 40 % and less than 2 % respectively. Besides, a previous study found that mild and severe kidney failure among 45 acetaminophen poisoned patients aged 12 to 18 years were 8.9 % and 2.2 % respectively. Acetaminophen induced nephrotoxicity had been reported in patients with no evidence or mild liver injury and also patients who had consumed large doses of acetaminophen with severe liver injury (Loh and Ponampalam, 2006).

2.7.6 King's College Hospital criteria for liver transplantation in patient with FHF

Liver transplantation is required for acetaminophen poisoning patients who developed severe liver failure. Acidosis, kidney failure, coagulopathy and encephalopathy are the better factors in determining mortality or requirement of liver transplantation rather than transaminases levels (Gupta et al., 2009). Additionally, arterial pH less than 7.3 after adequate fluid resuscitation, serum creatinine more than 300 μmol/L, INR more than 6.5 and grade III-IV hepatic encephalopathy are criteria used by King's College Hospital for liver transplantation in the United Kingdom for the patients with FHF (Schmidt and Larsen, 2006).

2.7.7 Modified King's College Hospital criteria for liver transplantation in patient with FHF

This criteria involved measurement of arterial lactate that exceeds 300 mmol/L after adequate fluid resuscitation. Arterial lactate was confirmed as a prognostic marker in acetaminophen-induced FHF. Arterial lactate is also correlated with Sequential Organ Failure Assessment (SOFA) score and Systematic Inflammatory Response Syndrome (SIRS) components. The SOFA scores included the conditions of respiratory failure, thrombocytopenia and hypotension whilst SIRS components included temperature, heart rate and white blood cell count. Death may occur when there is a high SOFA score and high SIRS components (Schmidt and Larsen, 2006).

2.7.8 Severe acute liver failure related to therapeutic use of acetaminophen (SAF-M) versus severe acute liver failure related to acetaminophen overdose (SAF-O)

SAF-M refers to hepatic injury appear after ingestion of more than 6 grams of acetaminophen daily for 4 days and there are always occurred in consumers with high alcohol consumption. Meanwhile, SAF-O refers to liver damage occur after excessive intake of acetaminophen at single time period. Moreover, patients with SAF-M had higher hepatotoxic dose, longer duration of acetaminophen use and increasing risk of developing fulminant hepatic failure (FHF) as compared to those with SAF-O. The SAF-M is as severe as SAF-O (Wartel et al., 2010).

2.7.9 Types of acetaminophen poisoning

2.7.9(a) Repeated supra-therapeutic ingestion (RSTI) or accidental staggered overdose

Repeated supra-therapeutic ingestion (RSTI) is described as taking two or more high dosage of acetaminophen in an interval of more than 8 hours until the total daily dosage exceeded 4 grams in adults (Craig et al., 2012). Meanwhile, RSTI in children below 6 years old is referred as ingestion of 200, 150 or 100 mg/kg of acetaminophen in an interval of over 24, 48 or 72 hours respectively (Dart et al., 2006b). Besides, the ingestion of 200 or 150 mg/kg of acetaminophen in an interval exceed 24 or 48 hours respectively is considered as RSTI in children above 6 years old (Dart et al., 2006b). Acetaminophen toxicity has been reported after daily repeated ingestion of acetaminophen for 2 to 8 days of 2000 mg in heavy alcohol drinkers, 4000 mg in normal healthy adults and 60 to 150 mg/kg/day in children (Schiødt et al., 1997; Dart et al., 2006a).

In United Kingdom, confusion about dosage of acetaminophen in liquid preparation especially 500 mg/ml was common among parents and healthcare providers which may lead to staggered overdose of acetaminophen (Aabideen et al., 2011). The RSTI patients were usually older in age, chronic alcohol consumers, fasting, starving and did not seek immediate treatment. They had increased risk of developing hepatotoxicity, hepatic coma and acute tubular necrosis (Alhelail et al., 2011; Craig et al., 2012; De-Giorgio et al., 2013). These patients normally had higher aminotransferase levels than suicidal individuals and required admission to intensive care unit (ICU) for further monitoring (Dargan and Jones, 2002; Gyamlani and Parikh, 2002). In the United States, a study reported that 23.7 % of these patients were at risk

of developing liver damage (Alhelail et al., 2011). Two other American studies showed that rectal route of acetaminophen administration were more prone to RSTI as compared to oral route (Losek, 2004). Besides, dental pain patient treated by acetaminophen are at increased risk of RSTI (Vogel et al., 2011). An Australian study revealed that for RSTI patients with low acetaminophen level and normal ALT and AST level at any time, there is no risk of liver damage and prolonged NAC treatment is not needed (Daly et al., 2008).

2.7.9(b) Suicidal or single time point overdose

Suicidal or single time point overdose refers to taking more than 4 grams of acetaminophen at one time (up to 1 hour) (Schiødt et al., 1997; Dart et al., 2006a; Waring, 2012). An ingestion of acetaminophen greater than 6 to 7 gram in adults or 200 mg/kg in children at a single time point is considered hepatotoxic (Schiødt et al., 1997; Dart et al., 2006a). The suicidal overdose patient has higher serum acetaminophen levels and they usually can be safely managed at medical wards rather than in an ICU. This in return has helped the U.S government to save a cost of US$500,000 yearly in managing the acetaminophen poisoning cases (Gyamlani et al., 1999; Dargan and Jones, 2002; Gyamlani and Parikh, 2002).

2.8 Case reports and case series of acetaminophen poisoning

2.8.1 Acetaminophen poisoning in infants and children

Acetaminophen is commonly used for relieve pain and fever in infants and children. It has an excellent safety profile in therapeutic doses. However, a study revealed that sick children who aged less than 2 years old and received acetaminophen over 90

mg/kg/day for more than one day are at increased risk for development of liver injury (Muñiz et al., 2004).

In a previous case report, a 58-day-old, 4.9 kg infant was given acetaminophen 80 mg 6 hourly for two days for her fever by her parent. She was subsequently admitted to hospital with clinical presentation of dry mucous membrane, sunken eyes and respiratory depression. The laboratory findings showed an AP level of 352 IU/L, AST of 1070 IU/L, ALT of 490 IU/L, INR of 3.4, PT of 37.6 seconds and serum acetaminophen level was 287 µg/mL. She was intubated due to her decreasing respiratory function and was admitted to paediatric intensive care unit. She was treated with 72 hours oral NAC regime and was discharged after 10 days (Muñiz et al., 2004).

One study demonstrated that younger children have less toxic metabolite (NAPQI) produced by the P-450 system. Additionally, children are able to clear drugs more efficiently because their livers compose a larger percentage of body weight compared to adults (Bryant et al., 2003). Therefore, chronic liver injury found to be seldom occurred in children after acute single accidental overdose of acetaminophen. (Daly et al., 2008). For instance, in a previous case report, a 15 months old girl was presented to hospital after accidental ingestion of 10 to 12500 mg acetaminophen tablets. She was given 8 gram of activated charcoal at 1 hour post ingestion. The serum acetaminophen level at 4 hours post ingestion was 525.9 µg/mL and a 72 hours oral NAC treatment was given to her. She did not develop liver injury and was discharged with stable condition (Bryant et al., 2003).

In another case report, a premature baby born at 25.5 weeks gestation had accidentally received 420 mg of acetaminophen via IV infusion due to medication error. Ninety minutes following the discovery of the acetaminophen overdose, a 20 hours IV NAC treatment was initiated. The serum level at 5 hours post overdose was 180 mg/L and there was no raised in liver enzymes, bilirubin and PT (Porta et al., 2012).

2.8.2 Acetaminophen poisoning during pregnancy

Acetaminophen is a popular and safe drug to be used in pregnancy. However, it is the most commonly reported agents among drug overdose cases during pregnancy. Unintentional acetaminophen poisoning can cause morbidity in pregnant women and there is a need to educate them about the risk of acetaminophen overdose (Thornton and Minns, 2012).

In a previous case report, a 22 years old pregnant woman was admitted to the hospital with stomach pain and signs of liver damage. Before admission, she had taken 8 to 9 grams of acetaminophen daily for 10 to 14 days for her toothache. She developed FHF and a liver transplantation was successfully done. However, intrauterine fetal demise was occurred at two weeks after the liver transplantation. An MRI of the fetus showed extensive peri-cerebral and intraventricular haemorrhage with extensive periventricular leukomalacia (Thornton and Minns, 2012).

In another case report, a 25 years old pregnant woman was admitted to the hospital with 35 grams of acetaminophen overdose and 37 units of alcohol. She had recently split with her partner and this was her first and unplanned pregnancy. The patient was recovered after treated with IV NAC (Shah and Karlapudi, 2009).

2.8.3 Acetaminophen poisoning in alcoholic patients

Repeated supra-therapeutic ingestion of acetaminophen can leads to liver toxicity in chronic alcoholic patient. Alcoholics caused deficient in selenium, vitamin E and zinc and subsequently faster the liver injury process (Schueler and Harper, 1995). There was a case of a 34 year old chronic alcoholic male who ingested 12 extra-strength acetaminophen tablets daily for pain and up to 18 tablets within 3 days. Besides, he was consuming ibuprofen. The patient experienced nausea, vomiting and had dark brown acid urine. His serum acetaminophen level was 34.7 µg/mL and there were elevation of AST, ALT, PT, AP, and bilirubin whereas the albumin level was decreased. He received oral NAC treatment and was discharged after 8 days. (Schueler and Harper, 1995).

2.8.4 Acetaminophen poisoning in teenager and adults

Kavalci et al. reported a 16 years old female who had taken 8 grams of acetaminophen for suicidal attempts. Upon arrival in hospital, she received IV NAC treatment and later discharged with stable condition (Kavalci et al., 2009). Another case report by Kojima et al. showed a 32 years old woman who had ingested 3 gram of acetaminophen daily for several days. She presented to hospital with severe stomach pain. Upon examination, there were increased in liver enzymes, hypokalaemia, hypophosphatemia and low blood urea nitrogen (Okeke and Okeibunor, 2010). The ingestion of acetaminophen was stopped and all the clinical signs and symptoms of poisoning were resolved (Kojima et al., 2006).

Acetaminophen poisoning cases were also found among middle aged adults. Mazer and Perrone reported a 47 years old woman who had ingested 9 grams of

acetaminophen daily for two days. She developed hepatotoxicity and was treated with oral NAC. Her liver function eventually improved after the treatment and she did not need liver transplantation (Mazer and Perrone, 2008).

Zell-Kanter et al. reported a 59 years old female who had serum acetaminophen level of 1141 mg/L upon admission and she was started with IV NAC management. There was an elevation of liver enzymes and creatinine phosphokinase as well. The patient was fully recovery after the IV NAC treatment despite the high serum acetaminophen level (Zell-Kanter et al., 2013).

2.8.5 Fatal cases of acetaminophen poisoning

Fatal cases of acetaminophen poisoning were reported for both high dose acute ingestion and repeated-supra therapeutic dose ingestion. Maclean et al. reported a case of a 40 years old man who ingested 60 tablets of acetaminophen (60 gram). He experienced jaundice, vomiting, dilated pupils, enlarged liver, sinus tachycardia, hypotension, dark brown acid urine and coma for 5 days. Gastric lavage was performed at 7 hours after ingestion. Nevertheless, his clinical condition deteriorated and died at 10 hours after admission due to cerebral oedema and intense gastrointestinal haemorrhage (Maclean et al., 1968).

There was a case report of a 29 years old woman who consumed 36 gram of acetaminophen. The patient had chronically abused alcohol and diazepam, and presented with history of emotional instability. Upon hospital admission, her serum acetaminophen level was 160 μg/mL and she experienced hypotension, hypoglycaemia and metabolic acidosis. Gastric lavage was performed and she was

given activated charcoal to treat the acetaminophen poisoning. Additionally, her serum acetaminophen level at 12 and 36 hours were the same (100 µg/mL). She had experienced impaired acetaminophen liver clearance with a half-life of acetaminophen of more than 16 hours. Furthermore, there were elevation of PT, bilirubin, SGOT and LDH level. The patient subsequently experienced second episode of hypoglycaemia and died due to massive centrizontal liver necrosis, acute tubular necrosis and pulmonary oedema (Zabrodski and Schnurr, 1984).

Zabrodski and Schnurr reported a fatal case which involved a 48 years old woman who ingested 3.25 gram of acetaminophen daily for 3 weeks. The patient was a chronic smoker with bronchitis and peptic ulcer and had 23 years history of chronic back pain with misuse of pain killers. Upon hospital admission, she was presented with slurred speech and complained of both back and stomach pain. Her initial serum acetaminophen level was 300 µg/mL and she experienced hypoglycaemia. Gastric lavage, activated charcoal and NAC were given for her acute acetaminophen poisoning. The patient's acetaminophen level was 220 µmg/mL at 12 hours and 183 µg/mL at 24 hours indicating that these levels were in toxic range. After 36 hours, she had second episode of hypoglycaemia and died due to massive hepatocellular necrosis (Zabrodski and Schnurr, 1984).

2.9 Regulations to control sale and label of acetaminophen

As there is a raise in the cases of acetaminophen poisoning, the US FDA has requested drug companies to control the amount of acetaminophen in prescription products (Martinez et al., 2012). Besides, the policy to control sale of acetaminophen has been implemented by several countries in order to decrease suicide rates and self-poisoning