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Review Article

Pharmacology Section

Ten Challenges Associated with Management of Paracetamol Overdose: An Update on Current Practice and Relevant Evidence from Epidemiological and Clinical Studies

AHMED IBRAHIM FATHELRAHMAN

ABSTRACT

Paracetamol is a commonly used medication all over the world. Although it is relatively safe, it results in serious toxicities requiring emergency department visits and hospitalisations, and may cause death. Toxicity can be predicted from drug blood concentration using Rumack-Matthew nomogram or from the ingested amount per body weight. Patients with expected toxicities are treated with activated charcoal if presented within two hours and N-acetylcysteine besides symptomatic and supportive measures. The present review represents a compilation of ten common challenging situations associated with management of paracetamol overdose. They include high risk patients, hypersensitivity reactions to the antidote, massive ingestions, late presentations, multiple ingestions of immediate release formulations, modified release ingestions, repeated supratherapeutic ingestions for therapeutic purposes, paediatric exposures, toxicity during pregnancy, and co-administered medications. Medical practitioners, who treat the patients presenting with paracetamol overdose and pharmacists working with drug or poison information centers, would benefit from having all ten challenging scenarios presented together in one place.

Keywords: Acetaminophen, Activated charcoal, N-Acetylcysteine, Pregnancy, Toxicity

INTRODUCTION

Paracetamol, also known as acetaminophen in the American literature, is one of the most-used medications worldwide. It is an over-the-counter product and the most commonly available medication in the market, sold everywhere even in ordinary shops and sales outlets. This wide availability and ease of accessibility are because it is considered relatively a safe medication. Despite this, it represents a serious source of toxicity that is responsible for significant rates of emergency department visits, hospitalisations, and deaths [1-5].

Overdose exposures are likely associated with deliberate self-poisoning and suicidal attempts specially among adolescents and young adults. A recent epidemiologic data from UK estimated that paracetamol alone represents the third causative agent responsible for emergency department visits accounting annually for 50,000 exposures during 2011-2014 [1]. Accounting for co-administration of paracetamol with other medications would further raise such statistics by about 8000 exposures. In US, each year, there are about 80,000 paracetamol-related emergency visits and about 30,000 patients are admitted to hospitals because of paracetamol overdose [2]. In Australia, the annual paracetamol overdose-related admissions have increased by 44.3% from 8,147 cases in the year 2007-2008 to 11,754 cases in the year 2016-2017 [3]. Whereas, the annual number of intentional exposures in the same report have increased by 77% from 1,263 cases in the year 2004 to 2,235 cases in the year 2017.

Paracetamol is a significant cause of acute liver failure. According to Lee WM, it was responsible for approximately half of all acute liver failure reported over the past 40 years in the US and Europe including the UK [4]. According to a study conducted in 52 liver transplant centers across seven countries including Ireland, UK, France, the Netherlands, Greece, Portugal and Italy; paracetamol was responsible for 20% of acute liver failures leading to registration for transplantation [5]. When it comes to mortality, statistics reveal relatively low rates of deaths due to paracetamol overdoses. However, in reality because of the paracetamol high rates of exposures worldwide such mortality rates reflect a significant health problem. In this regard, Blieden M et al., from the US reported 1% deaths among patients admitted to the hospitals after paracetamol exposures and 8.6% deaths among patients who develop acute liver injury due to paracetamol overdose [2].

Rationale and Objectives of the Current Review

The present review represents a compilation of ten common challenging situations associated with management of paracetamol overdose. To the best of our knowledge, they have been described in the literature scattered in various places. Medical practitioners who deal with treating such overdoses in the emergency departments and the pharmacists who work with drug or poison information centers would benefit from having all ten challenging scenarios presented together at one place. Another objective of the review was to highlight the current updates in practice regarding the management of paracetamol overdose based on recently published guidelines and experts' reviews supported with relevant evidence from epidemiological and clinical studies. This review was intended to raise the attention of the practitioners to the important aspects to consider while assessing and managing a paracetamol toxicity associated with anyone of the ten described challenges. However, this review is not intended to act as a clinical practice guideline and it is advised that the practitioners develop their own clinical practice guidelines based on the available resources. In addition, there is a need to make a consensus on some details such as when a case is presented with more than single challenging scenario.

ASSESSMENT OF TOXICITY

Assessing the toxicity is a critical step in toxicity management. A decision to treat a patient of paracetamol overdose with antidote is undertaken when a toxic exposure is expected. Paracetamol toxicity occurs due to the accumulation of the hepatotoxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) in the liver, after the depletion of the glutathione stores that is needed for its elimination [6-8]. In normal situations, minor amount of paracetamol (5%) is excreted

unchanged in the urine and the bulk amount is metabolised in the liver through glucuronidation and sulfation [6]. Another minor amount is metabolised by cytochrome P450 producing the hepatotoxic metabolite NAPQI. Glutathione in the liver conjugates with NAPQI producing a non-toxic metabolite that can be eliminated without producing any harm to the liver. In the case of an overdose, all metabolic pathways are saturated and all extra amount of drug is shifted towards cytochrome P450 pathway and once glutathione stores in the liver get depleted, NAPQI is accumulated and causes liver injury [6].

A patient exposed to a toxic dose of paracetamol progresses through four phases, starting with a first asymptomatic phase extending 12 to 24 hours after ingestion [6]. If a patient develops symptoms during the first phase he would show mild nausea, vomiting and malaise. Hepatotoxicity can be detected within 24 hours of exposure and in some cases as early as 12 hours during which the hepatic enzymes start to elevate. This represents the second phase of toxicity, and hepatotoxicity is defined as an elevation in the transaminase concentration greater than 1000 IU/L [6]. During the third phase occurring 72 to 96 hours postingestion, the patient progresses into fulminant hepatic failure. This is evident from hepatic encephalopathy, coma and sometimes haemorrhage. Hepatic transaminases are elevated dramatically reaching more than 10000 IU/L [6].

Other common signs of hepatic failure includes prolonged prothrombin time, hypoglycaemia and lactic acidosis. The third phase in toxicity may end with multisystem organ failure such as respiratory failure, haemorrhage and cerebral oedema leading to death. A lucky patient goes into phase four, which represents complete hepatic recovery, with most laboratory readings returning to normal within seven days. However, transaminases and serum creatinine may require several weeks to return normal [6].

Ideally, toxicity should be assessed by measuring drug level in blood and checking it against time lag between exposure and sampling using Rumack-Matthew nomogram. The nomogram is a graphical presentation of paracetamol blood concentrations expected to be toxic, starting from 4 hours to 24 hours postingestion and it includes three lines [6-8]. The first one is a probable toxicity line which represents the treatment line that extends from 200 mcg/mL at four hours postexposure and goes down linearly up to 24 hours. The second line is a possible toxicity line that extends from 150 mcg/mL at four hours postexposure and it can be considered for treatment to allow for correcting possible errors in measurement or history taking. The third line is a line for high-risk patients and it extends from 100 mcg/mL at four hours postexposure.

Toxicity can be also predicted from the ingested amount if it can be accurately estimated, where 150 mg/kg ingestions of normal formulations are expected to be toxic. Toxicity may occur with half of such dose in high-risk groups. Measurements of the liver enzymes {i.e., Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)}, the prothrombin time/INR, blood urea and creatinine levels, blood glucose levels, and the arterial blood gas concentration are required to monitor the patient's prognosis. Deliberate overdose exposures are likely associated with large and sometimes with massive ingestions and they should be handled seriously. According to a US report, although accidental exposures are more likely to cause liver injury than intentional ones, the latter are more likely associated with deaths [2].

A Summary of Standard Treatment

Potentially toxic exposures are primarily treated by trying to reduce the gut absorption. This is made using a single-dose of activated charcoal ideally if presentation occurs within two hours from an ingestion and up to four hours in certain situations. In case of an expected toxicity, the antidote N-acetylcysteine must be provided as an oral or intravenous form, although the latter form is more commonly used in practice. The standard treatment with activated charcoal for adults is 50 gm and 1 g/kg for children [7]. The activated charcoal reduces the chance of drug absorption and the toxicity and in turn the need for antidote [8]. Such practice has not changed up to date. The standard treatment with N-acetylcysteine for both adults and children was a 21 hours three-bags regimen that is started with 150 mg/kg loading dose over one hour, followed by 50 mg/kg over four hours, followed by 100 mg/kg over 16 hours [6,7]. However, this has been modified into 20 hours two-bags regimen provided as 200 mg/kg over four hours followed by 100 mg/kg over 16 hours [6,10].

TEN CHALLENGES ASSOCIATED WITH MANAGEMENT OF PARACETAMOL OVERDOSE

Ten categories of patients constitutes real challenging scenarios, associated with management of paracetamol overdose. These necessitate special considerations for assessment and/or treatment of toxicity and may require some deviation from standard therapeutic regimen. The categories include high risk patients, hypersensitivity reactions to the antidote, massive ingestions, late presentations, multiple ingestions of immediate release formulations, modified release ingestions, repeated supratherapeutic ingestions, paediatric exposures, toxicity during pregnancy, and co-administered medications [Table/Fig-1].

1. Patients at High Risk of Toxicity

High risk groups, such as persons with malnutrition and chronic alcohol users, are vulnerable to hepatotoxicity at doses that are lower than the normal toxic dose. In UK, it was estimated that about half of paracetamol overdoses were associated with alcohol ingestions [1]. Chronic (long term) alcohol ingestion has been found to be associated with an increased risk of liver toxicity in animal studies [9,11]. This effect in human was debatable [9]. Whereas, while some reports claimed no significant effect [11], another provided an evidence of a significant effect [12]. On the other hand, acute (short term) alcohol ingestion has been proved to be protective against liver damage in both animal and human studies [11]. However, Schmidt LE et al., reported that such protection is only for the chronic alcohol users who have had acute alcohol ingestions prior to or during paracetamol exposures [12]. A lower line for treatment with antidote has been suggested for long term alcohol users [9]. In current practice, chronic alcohol users and abstinent alcohol patients are treated as one of the high risk groups and a line starting at 100 mcg/mL at four hours has been adopted to guide the treatment with the antidote [6]. Other high risk groups include those receiving enzyme-inducing medications such as isoniazid and carbamazepine and those who are fasting or suffering from malnutrition [9,10].

2. Hypersensitivity Reaction to the Antidote

A hypersensitivity like anaphylaxis reaction is a common adverse effect experienced by patient receiving N-acetylcysteine particularly when administered intravenously. It is believed to be a histamine-related mechanism and the symptoms range from mild skin rash, pruritus, angioedema, bronchospasm, and hypotension [13]. The probability of its occurrence reached up to 23% of cases in retrospective studies and 48% in prospective studies and few fatalities have been reported [13]. The chance of reaction increases when the antidote is administered in high rate and when the amount of paracetamol ingestion is small. This requires reducing the antidote dosing rate and carefully assessing the need for it based on estimating the amount ingested from paracetamol. For this reason, updated clinical practice guidelines shifted from the 21 hour three bags regimen to 20 hour two bags regimen [6,10]. Given that reactions are likely to occur at the beginning of therapy, the two bags regimen skipped the first loading dose of 150 mg/kg over 1 hour

Scenarios	Description	Outline of current practice
Standard treatment	Ordinary paracetamol ingestions	Treatment is required when paracetamol blood concentration is at or above the line of 200 mcg/ mL at 4 hours postexposure using Rumack-Matthew nomogram or the ingestion is more than 150 mg/kg. Reducing absorption by providing a 50 g single of dose activated charcoal, ideally if presentation occurred within two hours. Providing 21 hours three-bags regimen N-acetylcysteine starting with 150 mg/kg loading dose over one hour, followed by 50 mg/kg over four hours, followed by 100 mg/kg over 16 hours.
Patients at high risk of toxicity	Chronic alcohol users Patients receiving enzyme-inducing medications Patients who are fasting or suffering from malnutrition	Treatment is required when paracetamol blood concentration is at or above the line of 100 mcg/mL at four hours postexposure using Rumack-Matthew nomogram. Reducing absorption by providing a 50 g single dose of activated charcoal ideally if presentation occurred within two hours. Providing 21 hours three-bags regimen N-acetylcysteine starting with 150 mg/kg loading dose over one hour, followed by 50 mg/kg over four hours, followed by 100 mg/kg over 16 hours.
Hypersensitivity reaction to the antidote	A hypersensitivity like-anaphylaxis reaction is a common adverse effect experienced by patient receiving N-acetylcysteine particularly when administered intravenously	Treatment is required based on scenario 0 or one. Reducing absorption by providing single dose of activated charcoal, ideally if presentation occurred within two hours. Reducing the chance of reactions by using the 20 hours two-bags regimen N-acetylcysteine provided as 200 mg/kg over four hours followed by 100 mg/kg over 16 hours. Administration of antihistamines after development of symptoms or providing antihistamines prior to antidotal treatment as prophylaxis in patients susceptible to hypersensitivity based on history.
Late presentations	Presentation to the hospital more than 24 hours postexposure	Treatment cannot be guided appropriately by Rumack-Matthew nomogram as drug level is not predictive of toxicity. Diagnosis and treatment can be made based on clinical symptoms, history and laboratory findings. If toxicity is evident it is advised to provide N-acetylcysteine in all situations. Patient may need haemodialysis if acidosis occurred.
Massive ingestions	Ingestion of about 30-50 tablets paracetamol (15-25 g) or more	The development of a severe lactic acidosis and altered mental status should be expected which may require haemodialysis. Reducing absorption by providing a 50 g single dose of activated charcoal, ideally up to four hours postexposure. Haemodialysis requires increasing the dose of antidote by about two-fold because significant. Proportions of the administered dose are eliminated by dialysis.
Multiple dose ingestions of immediate release formulations	A patient ingests multiple ingestions of a drug for an intentional self-harm purpose. The patient takes the amount divided over more than two hours	Both times of the first and the last ingested amounts are considered to guide assessment of toxicity based on Rumack-Matthew nomogram. It is recommended to start treatment with antidote whenever more than eight hours passed from first ingestion till assessing paracetamol level and evaluating ALT for presence of liver injury. Whenever paracetamol concentration measurement is made within two hours of the last ingested amount, another blood sample should be taken after two hours (i.e., being sure that at least four hours passed post last ingestion) to exclude risk of further ongoing absorption which may change drug level in blood from nontoxic to toxic. If either concentration is above treatment level start or continue the antidotal treatment.
Repeated supratherapeutic ingestions for therapeutic purposes	A patient ingests an excessive amount of paracetamol unintentionally for treatment purposes over a period of 24 hours or more. It may occur due to prescribing paracetamol by more than one prescriber to the patient. Sometimes, a patient takes paracetamol as an OTC medication to treat a symptom and gets it again prescribed as a combination with other medication	According to a guideline from Australia and New Zealand [10], there are three scenarios for possible toxicity: a) ingestion of ≥10 g or ≥200 mg/kg over a single 24 hours period; b) ingestion of ≥12 g or ≥300 mg/kg over a single 48 hours period; and c) ≥ ingestion of a daily therapeutic dose per day for more than 48 hours in patients who also have abdominal pain or nausea or vomiting. The guideline says, "if the paracetamol concentration is greater than 20 mg/L (132 µmol/L) or ALT is greater than 50 U/L, then acetylcysteine is commenced, and pathology repeated eight hours after the initial sampling". The guideline also says, "all patients with an initial ALT greater than 1000 U/L should receive at least a full 20 hours course of intravenous acetylcysteine".
Modified release ingestions	An ingestion of a modified release paracetamol formulation	According to a guideline from Australia and New Zealand [10], not relay on paracetamol blood concentration to assess the toxicity. Assessment of toxicity should be based on the amount of ingested drug where an ingestion of 10 g (i.e., 20 tablets) or more than 200 mg/kg requires a provision of activated charcoal if presented within upto four hours from exposure and initiating the antidotal treatment. Patients may need more doses of N-acetylcysteine and the measurement of drug level in blood can be used to assess the need for extra dose. Activated charcoal can be provided beyond four hours of exposure if ingestion is both due to a modified release formulation and massive because absorption may continue up to 24 hours.
Paediatric exposures	Paediatric exposures are likely to be accidental	The risk factors such as refusing to take food for more than a day while being febrile, a viral infection, or the coadministration of an enzyme inducer medication might be responsible for the liver toxicity occurs among some children in accidental exposures. To avoid toxicity, it is generally recommended to not prescribe more than 75 mg/kg/day of paracetamol to young febrile children. Toxicity should not be overlooked. When toxicity is expected treat as usual.
Toxic exposures during pregnancy	Ingestion of a toxic dose by a pregnant woman	The presence of pregnancy may complicate the diagnosis of an overdose if the patient history is not clearly indicating an ingestion of a toxic dose Limited evidence suggests absence of specific risk on pregnant women or foetuses due to paracetamol overdose during pregnancy There is no reported risk on the pregnant women or foetuses from being treated with N-acetylcysteine The clinical practice is to treat pregnant women who present with paracetamol overdose as ordinary cases Rumack-Matthew nomogram can be used to assess the toxicity as any other ordinary case The dose of the antidote is calculated using the patient's actual pregnant weight up to a maximum of 110 kg
Co-administered medication/drug combinations	A presence of co-administered medications	The presence of other medications may increase the toxicity of paracetamol and may complicate the clinical picture of the toxicity by exhibiting a variety of signs and symptoms

[Table/Fig-1]: A summary of standard treatment and the ten challenging scenarios associated with paracetamol overdose.

that used to be followed by 50 mg/kg over four hours and replaced them by a dosing of 200 mg/kg over four hours (i.e., beginning with lower rate while maintaining the total amount offered). The last bag remained as it is as 100 mg/kg over 16 hours.

Other possible interventions that have been reported to manage N-acetylcysteine hypersensitivity includes- withholding the administration of antidote for short period (i.e., temporary cessation of infusion for less than one hour) and then continuing it after controlling

symptoms of hypersensitivity reaction [13]. Among interventions also, the administration of antihistamines after development of symptoms or providing antihistamines prior to antidotal treatment as prophylaxis in patients susceptible to hypersensitivity based on history. Corticosteroids and inhaled beta-agonists have been also used as symptomatic treatment. However, it seems that adopting the 20 hours two bags regimen is safer and provides the same effectiveness as the 21 hours three bags regimen [6,10,14].

3. Late Presentations

An important factor affecting management of paracetamol overdose is latency period (i.e., time from exposure to presentation at hospital). The latency period determines whether activated charcoal use would be effective or not and determines the effectiveness of antidote use. While evidence indicates that N-acetylcysteine provides full protection, if it has been administered within 8 to 12 hours [6,7], some evidence indicates that it is still useful if administered later [15-17]. Late presentation of paracetamol overdose is associated with poor prognosis specially when the exposure history is not clear and not diagnosed correctly or is made late. Treatment cannot be guided appropriately by Rumack-Matthew nomogram as drug level is not predictive of toxicity beyond 24 hours [18]. Diagnosis can be made and the treatment can be provided based on clinical symptoms, history and laboratory findings. Naz S et al., reported a case of late diagnosis of paracetamol overdose who was referred after five days of stay at other hospital without being diagnosed properly [19]. The patient developed acute fulminant hepatic failure that was progressed to multisystem organ failure, ascites and neurological symptoms and ended with death. The laboratory analyses, which have been performed late, indicated high toxic level of paracetamol.

On the other hand, the provision of antidote to the late presenting paracetamol overdose cases has been found to be effective in saving lives even after developing acute liver injury. Els JR et al., reported a case of 22-year-old female who presented to the hospital after three days from exposure with symptoms of liver injury (i.e., jaundice and right upper quadrant tenderness) that has been confirmed by laboratory results [15]. The antidotal treatment was provided beside symptomatic and supportive therapy for three days till the patient's clinical and laboratory results improved. Later on, the patient was discharged on day 14 without any symptom. Another case report by Serjeant L et al., documented a development of lactic acidosis associated with a late presentation of 23-year-old women, that presented to the emergency department with suicidal ingestion of paracetamol [20]. The exact quantity and timing of exposure were unknown and there were concomitant ingestions of codeine, ibuprofen and alcohol within the same 24 hours. Despite supportive treatment and administration of antidote the acidosis persisted. The patient underwent haemodialysis and accordingly all markers of acidosis improved and later on the patient made a full recovery without the need for transplantation.

According to Jones AL and Dargan PI, it is important that patients that present later than 24 hours with paracetamol overdose be offered supportive care, including assessment of acid-base balance prothrombin ratio and creatinine, and they should start treatment with N-acetylcysteine immediately [7].

4. Massive Ingestions

A massive ingestion may involve an exposure to quantities of 50 tablets or more [4]. According to Schult RF and Acquisto NM, an ingestion of 40 g (i.e., 80 tablets of 500 mg strength) or more is considered a massive ingestion [6]. Based on epidemiologic studies, large ingestions are common. In UK, it was estimated that about one quarter of paracetamol overdoses were large ingestions of more than 30 tablets, and it has been reported a massive ingestion as much as 400 tablets [1]. Chiew AL et al., from Australia analysed the clinical characteristics and outcomes of massive paracetamol overdose (ingestions >40 g) [21]. Of 200 cases studied, 14% developed hepatotoxicity. Activated charcoal was offered to 25% of them at median of two hours post-ingestion. Paracetamol concentration was reduced dramatically in those receiving activated charcoal within four hours. The increase in N-acetylcysteine dose within 21 hours for those having high drug levels was associated with a significant reduction in hepatotoxicity.

A common feature among patients presenting with massive paracetamol ingestions is the development of severe lactic acidosis and altered mental status which warrant the use of activated charcoal, supportive treatment and haemodialysis or haemofiltration in addition to the antidotal therapy [6]. Although, it is recommended for any potential toxic paracetamol exposures as a preliminary measure to limit drug absorption if patients presented within two hours of ingestion, activated charcoal use is essential in massive ingestions and it can be offered upto four hours after exposure. On the other hand, the use of haemodialysis requires increasing the dose of antidote by about two-fold because significant proportions of the administered dose are eliminated by dialysis [6].

5. Multiple Dose Ingestions of Immediate Release Formulations

A multiple dose ingestion of an immediate release paracetamol refers to a situation where a patient ingests multiple ingestions of a drug for an intentional self-harm purpose. It has been also described as a staggered ingestion [10]. Instead of ingesting the amount at once as the common situation, the patient takes the amount divided over more than two hours. This is still considered as an acute ingestion, however what makes it a special situation is that it may cause confusion about the time for ingestion required for blood sampling to measure the paracetamol level and identifying the position of drug concentration against time after ingestion in the Rumack-Matthew nomogram to see if level is below or above treatment level. In general, treatment is made according to the normal acute immediate release ingestions [10].

However, both times of the first and the last ingested amounts are considered to guide assessment of toxicity based on Rumack-Matthew nomogram. It is recommended to start the treatment with an antidote whenever more than eight hours have passed from first ingestion till assessing paracetamol level and evaluating ALT for presence of liver injury [10]. Whenever paracetamol concentration measurement is made within two hours of the last ingested amount, another blood sample should be taken after two hours (i.e., being sure that atleast four hours passed post last ingestion) to exclude risk of further ongoing absorption which may change the drug level in blood from non-toxic to toxic and if either concentration is above the treatment level, start or continue the antidotal treatment [10].

6. Repeated Supratherapeutic Ingestions for Therapeutic Purposes

A repeated supratherapeutic ingestion refers to a situation where a patient ingests an excessive amount of paracetamol unintentionally for treatment purposes, over a period of 24 hours or more. Some patients use the medication to treat pain or to relief fever and if symptoms do not get controlled, they ingest additional amount, finally exceeding the daily recommended therapeutic dose. The therapeutic dose is 60 mg/kg over 24 hours, up to a maximum dose of 4 g/day (i.e., 8 tablets of 500 mg strength). In some cases, this occurs when paracetamol is prescribed by more than one prescriber to the patient. Sometimes, a patient may take paracetamol as an OTC medication to treat a symptom and he tends to get it again prescribed as a combination with other medication. This can be worsened further if the patient is one of the high risk groups, such as being fasting for a long time, chronic alcohol user, or receiving an enzyme inducing medication.

In a recent guideline from Australia and New Zealand, repeated supratherapeutic ingestions are considered among paracetamol dosing that may be associated with acute liver injury [10]. In such guideline, three scenarios for possible toxicity are mentioned which are: a) ingestion of ≥10 g or ≥200 mg/kg (whichever is less) over a single 24 hours period; b) ≥ingestion of 12 g or ≥300 mg/kg (whichever is less) over a single 48 hours period; and c) ≥ingestion of a daily therapeutic dose per day for more than 48 hours in patients who also have abdominal pain or nausea or vomiting. The abdominal pain, nausea and vomiting are early symptoms of toxicity, and a toxicity occurring at a dose lower than the therapeutic one may be because the patient belongs to one of the high risk groups. According to the guideline, any one of the previous three scenarios warrant measuring paracetamol level and ALT [10]. The guideline says, "if the paracetamol concentration is greater than 20 mg/L (132 μmol/L) or ALT is greater than 50 U/L, then acetylcysteine is commenced, and pathology repeated eight hours after the initial sampling". The guideline also says, "all patients with an initial ALT greater than 1000 U/L should receive at least a full 20 hours course of intravenous acetylcysteine".

7. Modified Release Ingestions

Exposures due to extended-release paracetamol formulations may witness a delay in toxicity and in symptoms and a preliminary good prognosis does not indicate absence of toxicity risk. Such occurrences may warrant the use of activated charcoal after up to and beyond four hours. There are updates in the treatment of patients ingesting paracetamol modified release preparations in the recent guideline from Australia and New Zealand [10]. An important recommendation in this guideline is to not rely on paracetamol blood concentration to assess the toxicity. Assessment of toxicity should be based on the amount of ingested drug where an ingestion of 10 g (i.e., 20 tablets) or more than 200 mg/kg requires a provision of activated charcoal, if presented within up to four hours from exposure and initiating the antidotal treatment. Patients with modified release ingestions may need more doses of N-acetylcysteine and the measurement of drug level in blood can be used to assess the need for extra dose. When an ingestion is both due to a modified release formulation and massive in its amount (i.e., ≥30 g or ≥500 mg/kg), it should be treated with extra dose of antidote. In such situation, the activated charcoal can be provided even beyond four hours because absorption may continue up to 24 hours [10].

8. Paediatric Exposures

It has been postulated that children are relatively safe from liver toxicity due to paracetamol [22]. This can be because of the relatively larger liver size compared to their body than adults which secure a larger glutathione store, resulting in a more effective metabolism [22]. For neonates, their hepatic enzymes which are supposed to metabolise the drug are immature whereas, toxicity occurs merely due to the accumulation of the toxic metabolites in the liver in presence of a glutathione store depletion. However, some reports had documented series of paracetamol toxic exposures and even deaths among children [9,23,24].

It is not clear whether liver injury is due to the infection that necessitates the use of the analgesic antipyretic drug or because of the drug itself. A risk factor such as refusing to take food for more than a day while being febrile, a viral infection, or the co-administration of an enzyme inducer medication might be responsible for the liver toxicity that occurs among some children in accidental exposures and in some cases at normal therapeutic doses too [24,25]. There is not enough evidence to throw light in this regard, except some case reports and case series reports. However, it is generally recommended to not prescribe more than 75 mg/kg/day of paracetamol to young febrile children [9].

A case report of paracetamol overdose in a preterm neonate was reported by Isbister GK et al., [26]. It was a 2.2 kg, 55-day-old male infant who was fed 300 mg paracetamol by mistake. Upon discovering the mistake four hours later, the stomach contents were aspirated, activated charcoal was offered and intravenous N-acetylcysteine was administered. The dosing regimen of the antidote was- 150 mg/kg over 15 minutes; 50 mg/kg over four hours; and 100 mg/kg over 16 hours. The antidote was continued for 20 hours. The important features of the case were that the baby was looking well at time of the overdose, the paracetamol level was below treatment line (i.e., it was 121 mg/L and treatment level is 150 mg/L) and the baby tolerated the antidote without any adverse effects.

Recently, Chiew AL et al., reported a case of three-year-old child that had ingested about 150 mL of 24 mg/mL liquid paracetamol (240 mg/kg) [24]. Although, paracetamol blood concentration was below treatment level the child developed hepatotoxicity. The antidotal treatment was provided at 25 hours from exposure as 20 hours two-bag intravenous regimen and it was continued for 64 hours and the child made uneventful recovery.

9. Toxic Exposures during Pregnancy

The limited evidence from research and case report suggests an absence of specific risk on pregnant women or foetuses due to paracetamol overdose during pregnancy [9,27]. In addition, there is no reported risk on the pregnant women or foetuses from being treated with N-acetylcysteine [9]. The clinical practice is to treat pregnant women who present with paracetamol overdose as ordinary cases [16,28]. In addition, Rumack-Matthew nomogram can be used to assess the toxicity as any other ordinary paracetamol overdose exposure as its prediction is not affected by pregnancy [16]. The dose of the antidote is calculated using the patient's actual pregnant weight up to a maximum of 110 kg. This is because, in obese patients, calculations can underestimate the ingested amounts. Thus, according to the National Institute for Health and Care Excellence (NICE) 2019 a weight of 110 kg should be considered as a maximum weight for calculating ingested amount per body weight [18].

However, a presence of pregnancy may complicate the diagnosis of an overdose if the patient history does not clearly indicate an ingestion of a toxic dose. Mills AT et al., reported a paracetamol overdose case of pregnant woman that was diagnosed wrongly as HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome and been on treatment accordingly [17]. After developing clear symptoms of liver injury, supported by laboratory results, a late diagnosis with paracetamol overdose has been made and she was treated with N-acetylcysteine to which she responded successfully. Another case report documented a massive paracetamol ingestion during pregnancy where the patient presented more than 26 hours postexposure [29]. Both mother and infant died (massive ingestion, late presentation and delay in administering the antidote).

10. Co-administered Medication/Drug Combinations

The presence of co-administered medications does not represent an infrequent occurrence in paracetamol overdose. The presence of other medications may increase the toxicity of paracetamol and may complicate the clinical picture of the toxicity by exhibiting a variety of signs and symptoms.

In US, accidental paracetamol overdoses are likely to be due to opioid-paracetamol combinations, where victims look for better relief of symptom (given that about 17% of adults' accidental overdoses go into liver injury) [2]. According to Armstrong TM et al., the most common combinations of paracetamol co-ingested drugs included medications like opioid, NSAID, antidepressant, benzodiazepine, antihistamine, antipsychotic and cardiovascular drugs [30]. Brass EP et al., analysed poison centre exposures due to therapeutic

misuse of non-prescription acetaminophen-containing combination products in the United States, during 2007-2016 [31]. More than one acetaminophen-containing product was involved in 24.8% of exposures. The majority of exposures occurred in 12-19 years of age and 5.4% of exposures required hospitalisation.

Schmidt LE and Dalhoff K, from Denmark conducted study on the effect of regular medication on the outcome of paracetamol poisoning [32]. They found that medications frequently co-ingested with paracetamol included psychotropic medications, analgesics, oral contraceptives, beta-agonists and anticonvulsants. Opioid analgesics were associated with a significantly increased incidence of hepatic injury. In the US, simultaneous ingestion of an enzyme inducing medication such as phenobarbital and phenytoin has been found to be increasing paracetamol toxicity [33]. Case reports also documented the effect of other medications on the outcomes of paracetamol overdose. Being under treatment with carbamazepine and ingesting an amount of paracetamol less than the normal toxic dose had caused fulminant hepatic failure in a 17-year-old adolescent girl [34]. The case was reported as a suicidal attempt; however, the ingested amount was 7800 mg of paracetamol. There were additional risk factors in this case where the patient was having a low body weight and malnutrition.

CONCLUSION(S)

A drug concentration of 200 mcg/mL at four hours postexposure using Rumack-Matthew nomogram is considered toxic. Toxicity can be predicted also from the ingested amount if it can be accurately estimated where 150 mg/kg ingestions are expected to be toxic. Patients with expected toxicities are treated with activated charcoal if presented within two hours and N-acetylcysteine besides symptomatic and supportive measures.

Ten categories of patients that constitute real challenges necessitate special considerations for assessment and/or management of toxicity were discussed in this review.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Clinical Pharmacy, Taif University, Taif, Saudi Arabia.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Ahmed Ibrahim Fathelrahman,
College of Pharmacy, Taif University, P.O. Box 888, Taif, Saudi Arabia.
E-mail: afathelrahman@yahoo.com

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