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Acetaminophen poisoning: An update for the intensivist

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Abstract

Acetaminophen overdose is common and can result from deliberate/nonstaggered or accidental/staggered ingestion. Patients presenting within 24 h of an acetaminophen overdose can safely be managed on medical wards. Early management of nonstaggered overdose is guided by the plasma acetaminophen concentration, whereas management of accidental/staggered ingestion is guided by ingested dose. Ingested dose and time from ingestion to presentation are important prognostic factors in accidental/staggered ingestion. Acetaminophen-induced acute liver failure (ALF) requires meticulous supportive care in an intensive care unit (ICU), with early identification and transfer of patients who are likely to require liver transplantation to a specialist liver centre. The modified King's College Hospital criteria (incorporating lactate into the traditional criteria) represent the best tool for identifying patients who require transplantation.

Keywords

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Commentary

Acetaminophen poisoning: an update for the intensivist

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Abstract

Acetaminophen overdose is common and can result from deliberate/nonstaggered or accidental/staggered ingestion. Patients presenting within 24 h of an acetaminophen overdose can safely be managed on medical wards. Early management of nonstaggered overdose is guided by the plasma acetaminophen concentration, whereas management of accidental/staggered ingestion is guided by ingested dose. Ingested dose and time from ingestion to presentation are important prognostic factors in accidental/staggered ingestion. Acetaminophen-induced acute liver failure (ALF) requires meticulous supportive care in an intensive care unit (ICU), with early identification and transfer of patients who are likely to require liver transplantation to a specialist liver centre. The modified King's College Hospital criteria (incorporating lactate into the traditional criteria) represent the best tool for identifying patients who require transplantation.

Keywords accidental poisoning, acetaminophen, acute liver failure, overdose, transplantation

Acetaminophen poisoning is common. In the UK 50% of poisoning admissions involve acetaminophen; this figure is nearer 10% in the USA [1,2]. Acetaminophen poisoning can result from deliberate or accidental/staggered ingestion. The present commentary discusses the differences in management of these two presentations, and management of patients with established hepatotoxicity who require ICU admission.

Management of early, nonstaggered acetaminophen poisoning

The antidote for acetaminophen poisoning is N-acetylcysteine (NAC). It provides complete protection against hepatotoxicity if given within 12 h of nonstaggered overdose [3]. Management of patients presenting within 24 h of nonstaggered overdose is guided by the plasma acetaminophen concentration, plotted against time since ingestion on a treatment nomogram [3,4]. A number of treatment nomograms are in use worldwide. All of these are based on the Prescott nomogram, in which a line is drawn that joins an acetaminophen concentration of 200 mg/l at 4 h and one of 30 mg/l at 15 h (the '200-line') [3]. The nomograms are less reliable in patients who present late (more than 15 h after ingestion), and patients with an acetaminophen concentration just below the line should also receive treatment [4,5].

The hepatotoxic dose of acetaminophen is generally accepted to be 150 mg/kg [4,5], although the evidence for this is far from strong [5]. We recommend that, regardless of ingested dose, all patients presenting within 24 h of nonstaggered acetaminophen overdose should have their plasma acetaminophen concentration determined.

A lower treatment line (the '100-line'), which joins an acetaminophen concentration of 100 mg/l at 4 h with one of 15 mg/l at 15 h, is widely used for patients in one of two high-risk groups [4,5]: conditions that lead to decreased hepatic glutathione (e.g. malnutrition and anorexia nervosa); and circumstances that increase cytochrome p450 microenzyme activity (particularly cytochrome p450 isoforms 2E1, 1A2 and 3A4), such as regular use of enzyme-inducing drugs (e.g. phenytoin and carbamazepine) and possibly chronic ethanol excess. However, a critical review of the

ALF = acute liver failure; ICU = intensive care unit; NAC = N-acetylcysteine PT = prothrombin time.

literature [6] did not support the view that chronic ethanol excess increases the risk for hepatotoxicity after acetaminophen overdose. The evidence for the 100-line is largely based on case reports, and is best described as a 'best guess' [5]. Until further evidence becomes available, however, we support the use of the 100-line in the categories of patients described above because it provides a safety margin in patients who may provide an unreliable history or who may present late.

Where should patients with early acetaminophen poisoning be managed?

Regardless of the ingested dose, within the first 24 h of ingestion patients with acetaminophen poisoning do not exhibit significant symptoms or signs other than vomiting. Gyamlani and Parikh [7] recommended that patients with deliberate acetaminophen poisoning be managed on medical floors, but that patients with accidental ingestion and chronic alcoholic persons require ICU admission. We would go one step further and advise that all patients presenting within 24 h of acetaminophen overdose, without concomitant poisoning, can safely be managed on medical wards or emergency department observation wards; this is current routine practice in the UK [8]. Conversely, patients with acetaminophen-induced ALF require meticulous supportive care in an ICU.

Accidental versus deliberate acetaminophen overdose

In the series reported by Gyamlani and Parikh [7], 14% of ingestions were accidental and 86% were deliberate. These findings differ from those reported in other US series (65% accidental/35% deliberate, reported from poisons centre data [2]; 60% accidental/40% deliberate, reported from liver unit data [9]), but are similar to findings reported in the UK (16% accidental/84% deliberate [8]) and Denmark (15% accidental/85% deliberate [9]).

The plasma acetaminophen concentration is not interpretable in patients with staggered ingestion, and management is guided by the dose ingested [5]. Ingestion of more than 150 mg/kg over 24 h (75 mg/kg over 24 h in high-risk patients) requires treatment with NAC [4,5].

There are few published data on outcome and prognosis in accidental/staggered poisoning. Gyamlani and Parikh [7] reported that peak aminotransferase and International Normalized Ratio were greater in patients with accidental/staggered ingestion, and the two patients who developed ALF presented after accidental/staggered ingestion. However, no data are provided regarding relative times of presentation or ingested dose in the accidental and deliberate ingestion groups. Those findings are in contrast to those of two recent UK series [8,10]. In the first ($n = 160$) [8], 26 patients (16%) presented with staggered ingestion (20 presented within 24 h of ingestion). Nine received NAC and only three developed hepatotoxicity (all three presented more than 24 h after ingestion). Of those three patients, one died after developing ALF and the other two were discharged with normal liver function within 72 h. In the second series ($n = 280$) [10], 19 patients (6.8%) presented with staggered ingestion (mean dose 240 mg/kg over 24 h, range 112–464 mg/kg over 24 h). A total of 17 received NAC and five developed hepatotoxicity (four of these presented more than 24 h after ingestion, and one at 18 h). All aminotransferase/International Normalized Ratio abnormalities resolved within 48 h, and none of the patients developed ALF.

On the basis of these, albeit limited, data, the most important prognostic factors in accidental/staggered ingestion are the ingested dose and time to presentation. Presentation beyond 24 h is associated with increased risk for hepatotoxicity. This is because by this time the active N-acetylbenzoquinoneimine metabolite has formed, and once hepatic glutathione has been depleted hepatocellular damage occurs.

Acute liver failure in acetaminophen poisoning

Considering the number of acetaminophen overdoses that occur, hepatotoxicity is uncommon; ALF occurs in only 0.6% of UK hospital episodes [9]. The most sensitive prognostic marker is prothrombin time (PT). Approximately 50% of patients with a PT of 36 s at 36 h after ingestion will develop ALF [11]. In our clinical experience, when PT starts to improve, full recovery follows.

If hepatic damage is extensive, ALF ensues on days 4–5 [5,12]. Acetaminophen-induced ALF is a multisystem disorder, with acute renal failure, hypotension, sepsis, coagulopathy, encephalopathy and cerebral oedema [5,12]. Decisions about management and prognosis must be made quickly in order to allow transfer of patients to liver transplantation centres before they deteriorate (Table 1) [13,14].

The role of NAC in late acetaminophen poisoning is controversial. There are many theories regarding its potential mechanisms (e.g. free radical scavenging, oxygen kinetics), and clinical studies have yielded conflicting findings on its efficacy [5]. Routine UK practice is to continue NAC infusion at 150 mg/kg over 24 h until either PT improves or the patient receives a liver transplant [4,14].

Patients with acetaminophen-induced ALF require ICU admission for meticulous supportive care, and to monitor for and manage further organ system involvement [12]. Hypotension is common and inotropic support with noradrenaline (norepinephrine) or adrenaline (epinephrine) is often required, and should be guided by invasive haemodynamic monitoring after adequate fluid resuscitation [12]. Continuous veno-venous haemofiltration with lactate-free fluid is used in patients with acute renal failure [14].

Table 1

When to contact a specialist liver centre in patients with acetaminophen-induced hepatotoxicity

Progressive coagulopathy: PT in seconds greater than the number of hours since ingestion (or if the INR is >2 at 24 h, >4 at 48 h, and >6 at 72 h)
Renal impairment (creatinine >200 μmol/l)
Hypoglycaemia
Metabolic acidosis (pH <7.35)
Hypotension despite fluid resuscitation
Encephalopathy

INR = International Normalized Ratio; PT = prothrombin time.
Data from Bernal *et al*. [14].

Cerebral oedema due to elevated intracranial pressure is a common cause of death. Intracranial pressure should be monitored in all patients who require mechanical ventilation, particularly those who fulfil criteria for transplantation [12]. Mannitol and thiopentone are used in management of cerebral oedema, to maintain intracranial pressure below 20 mmHg [12].

Liver transplantation and acetaminophen poisoning

There are no standard selection criteria for transplantation that are in use worldwide, but the King's College Hospital criteria (Table 2) are the most widely accepted [15]. Without transplantation, less than 15% of patients who meet these criteria survive [16]. However, up to 50% of patients who meet transplant criteria are either too unwell for transplantation or die before a graft becomes available [13]. The King's College Hospital criteria have good specificity in identifying patients with poor prognosis, but they are of low sensitivity and may fail to identify a proportion of patients who will die [13].

In one study [16], the Acute Physiology and Chronic Health Evaluation II score correlated with mortality. Specialist liver scores may be less familiar to those who work in general ICUs, and the use of the Acute Physiology and Chronic Health Evaluation II score may help in the early identification of patients who require transplantation and may expedite appropriate transfer to a liver center [16].

A recent study [14] suggested that an arterial lactate concentration greater than 3.5 mmol/l early (4 h) after admission to the liver unit, or greater than 3.0 mmol/l after fluid resuscitation (12 h after admission) identifies patients who are likely to die earlier, with predictive ability equivalent to that of the King's College Hospital criteria. The authors of that study proposed modified King's College Hospital criteria (Table 2), in order to increase the sensitivity of the criteria and the speed of identification of patients who require transplantation.

Conclusion

Patients who present within 24 h of an acetaminophen overdose can safely be managed on medical wards. The management of nonstaggered ingestion is guided by the plasma acetaminophen concentration, whereas management of accidental/staggered ingestion is guided by the dose ingested. Prognostic factors in accidental/staggered overdose include dose ingested and time from ingestion to presentation.

Acetaminophen-induced ALF requires meticulous supportive care on an ICU, and rapid identification and transfer to a specialist liver centre is required for those patients who will die without liver transplantation. Recent evidence indicates that the modified King's College Hospital criteria represent the best tool for identifying patients who require transplantation.

Table 2

King's College Hospital criteria for liver transplantation in acetaminophen-induced acute liver failure

Current criteria [11]	Modified criteria [14]
List for transplantation if: Arterial pH <7.3 after adequate fluid resuscitation	**Strongly consider listing for transplantation if:** Arterial blood lactate concentration >3.5 mmol/l after early fluid resuscitation
List for transplantation if all three of the following occur within a 24-h period: • Creatinine >300 μmol/l • PT >100 s (INR >6.5) • Grade III/IV encephalopathy	**List for transplantation if:** Arterial pH <7.3, or arterial blood lactate concentration >3.0 mmol/l after adequate fluid resuscitation **List for transplantation if all three of the following occur within a 24-h period:** • Creatinine >300 μmol/l • PT >100 s (INR >6.5) • Grade III/IV encephalopathy

INR = International Normalized Ratio; PT = prothrombin time.

Competing interests

AJ and PD have acted as scientific advisors to Glaxo Smith Kline and Orphan Drugs (Europe) and have received funding to attend meetings from Glaxo Smith Kline. AJ has acted as a scientific advisor to Cumberland Pharmaceuticals, Oxford Pharmaceuticals and Syngenta, but has received no personal remuneration for this.

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