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Understanding lactic acidosis in paracetamol (acetaminophen) poisoning

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Paracetamol (acetaminophen) is one of the most commonly taken drugs in overdose in many areas of the world, and the most common cause of acute liver failure in both the UK and USA. Paracetamol poisoning can result in lactic acidosis in two different scenarios. First, early in the course of poisoning and before the onset of hepatotoxicity in patients with massive ingestion; a lactic acidosis is usually associated with coma. Experimental evidence from studies in whole animals, perfused liver slices and cell cultures has shown that the toxic metabolite of paracetamol, N-acetyl-p-benzo-quinone imine, inhibits electron transfer in the mitochondrial respiratory chain and thus inhibits aerobic respiration. This occurs only at very high concentrations of paracetamol, and precedes cellular injury by several hours. The second scenario in which lactic acidosis can occur is later in the course of paracetamol poisoning as a consequence of established liver failure. In these patients lactate is elevated primarily because of reduced hepatic clearance, but in shocked patients there may also be a contribution of peripheral anaerobic respiration because of tissue hypoperfusion. In patients admitted to a liver unit with paracetamol hepatotoxicity, the post-resuscitation arterial lactate concentration has been shown to be a strong predictor of mortality, and is included in the modified King's College criteria for consideration of liver transplantation. We would therefore recommend that post-resuscitation lactate is measured in all patients with a severe paracetamol overdose resulting in either reduced conscious level or hepatic failure.

Introduction

Paracetamol (acetaminophen) is the most commonly taken drug in overdose in the UK and is a common cause of overdose morbidity and mortality [1, 2]. Death is most commonly due to hepatotoxicity and it is the most common cause of acute liver failure (ALF) in the UK [3]. Paracetamol poisoning is also common in other developed countries [4]. In the USA it is involved in more than 50 000 Emergency Department visits and 400 deaths each year [5].

Paracetamol poisoning has complex effects on cellular metabolism, and may cause lactic acidosis in two different scenarios. First, there are numerous reports of severe early lactic acidosis, often with coma, occurring prior to the onset of hepatotoxicity. These occurred in patients with very large paracetamol overdoses (usually more than 40 g, with peak plasma paracetamol concentrations typically over 800 mg l^{-1}). Many of these patients did not develop liver damage after treatment with N-acetylcysteine [6, 7]. The second scenario occurs later in the course of paracetamol poisoning, in patients with established paracetamol-related hepatotoxicity. In this group, an elevated arterial lactate concentration has been shown to be a strong predictor of death [8, 9].

A healthy volunteer study using a single supra-therapeutic (4 g) dose of paracetamol was not associated with hepatotoxicity, but caused two peaks of lactate at 6 and 72 h post-ingestion [10]. These changes in metabolite concentrations are likely to be exaggerated in patients with paracetamol poisoning. This review will explore the circumstances and clinical significance of lactic acidosis in patients with paracetamol poisoning.

Methods

We searched MEDLINE (PubMed®) from 1970 to February 2010 for articles containing the terms '(acidaemia OR acidemia OR acidosis OR hyperlactatemia OR hyperlactataemia OR lactic OR lactate) AND (paracetamol OR acetaminophen)' in the title, abstract or keywords. This search returned 324 entries. We reviewed the titles and abstracts of these entries and retrieved the full text of relevant articles. We identified a further 43 relevant articles by hand searching reference lists of papers retrieved.

Mechanism of mitochondrial inhibition by paracetamol

In vitro and *in vivo* studies in perfused liver, liver slices and kidney cells have demonstrated that high concentrations of paracetamol can cause early mitochondrial inhibition after glutathione depletion but prior to cellular damage [11–14].

Experiments on perfused rat livers showed that paracetamol concentrations of 0.2 to 5 g l^{-1} in the perfusate caused hepatotoxicity and a dose-dependent reduction in oxygen consumption [12]. However, oral administration of high dose paracetamol to rats (5 g kg^{-1}, with peak plasma concentration 800 mg l^{-1}) did not reduce hepatic oxygen consumption despite hepatotoxicity, suggesting that direct inhibition of cellular respiration occurs only at extremely high paracetamol concentrations [12].

Studies on rat liver slices showed that paracetamol exposure was followed by an early decrease in the mitochondrial membrane potential [11] and fall in the adenosine triphosphate concentration [15]. These changes preceded cellular damage as assessed by a change in the plasma membrane potential or release of hepatic enzymes, and were independent of cytochrome-P450 activity [11]. The non-hepatotoxic meta-isomer of paracetamol, 3-hydroxyacetanilide, inhibited respiration in perfused rat liver and rat mitochondrial preparations in a similar dose-dependent manner to paracetamol. These findings imply that paracetamol elicits a direct effect on mitochondrial function which precedes cellular injury, and is independent of its hepatotoxic effect [16]. Similar results were found using mouse hepatocytes [17].

Paracetamol causes a similar reversible, concentration-dependent inhibition of respiration in rat isolated kidney tubules as in the liver [13]. Paracetamol inhibited respiration when glutamine or lactate were supplied as fuel, but not with succinate, implying that succinate dehydrogenase (complex II of the mitochondrial transport chain) was not affected. Spectrophotometric studies showed that paracetamol affected the aerobic reduction level of cytochrome b (part of complex III) more than other cytochromes. NADH dehydrogenase (complex I) worked normally in the presence of paracetamol if it was isolated from the rest of the mitochondrial electron transport chain. This suggests that paracetamol affects not complex I itself, but electron transport from complex I to complex III [13].

Investigation of cultured mouse hepatocytes revealed mitochondrial depolarization and inner membrane permeabilization 4.5 h after paracetamol administration [18]. Paracetamol also causes mitochondrial oxidant stress, as shown by an increase in intra-mitochondrial glutathione disulphide [19]. The toxic effects of paracetamol can be directly reproduced by its toxic metabolite NAPQI (N-acetyl-p-benzo-quinone-imine) in isolated mitochondria, and it is thought that NAPQI may covalently bind to mitochondrial proteins [20]. Paracetamol itself also covalently binds to mitochondrial proteins such as aldehyde dehydrogenase [21] and causes down-regulation of mitochondrial genes [10].

Apart from its effect on the mitochondria, NAPQI causes damage to multiple intracellular proteins by arylation and nitration, activating multiple pathways leading to cell necrosis [20]. Oxidant stress precedes the onset of cell injury [14].

Paracetamol toxicity

Paracetamol is a widely used analgesic and antipyretic and is safe at therapeutic dosages [22]. In normal therapeutic use, the majority of paracetamol is conjugated by glucuronyltransferases or sulphotransferases to form safe excretable products [20]. A small fraction of paracetamol is metabolized by cytochrome-P450 isoenzymes (particularly CYP2E1 and CYP3A4 [23]) to form NAPQI. Following a therapeutic dose, this highly reactive metabolite is detoxified by conjugation with glutathione. However in overdosage, a greater proportion of the paracetamol is metabolized to NAPQI and there may be insufficient glutathione for conjugation [24]. Early administration of substrates which can be converted to glutathione (e.g. cysteine in animal experiments [25], or N-acetylcysteine (NAC) in clinical use [26]) protects the liver from damage.

The majority of patients presenting early in the course of paracetamol poisoning without evidence of hepatic damage have a normal blood lactate concentration [27]. A prospective study of 53 patients admitted with paracetamol poisoning showed a significant correlation between admission plasma lactate and paracetamol concentration [28]. A retrospective review of patients with ALF due to paracetamol or other causes found that blood lactate, pyruvate and acetoacetate were significantly higher than in a control group of healthy volunteers [29]. Three patients who presented 48 h after paracetamol ingestion had severe metabolic acidosis (pH 7.14–7.27) accompanied by hypotension, peripheral vasoconstriction and dehydration. The acidosis was present before the onset of clinical hepatic failure, and was associated with hyperlactataemia (up to 20.2 mmol l^{-1}) in two patients [29].

Early lactic acidosis and paracetamol poisoning

The blood lactate concentration in unstressed healthy individuals is usually 0.5 to 1.0 mmol l^{-1}, and the upper limit of the reference range is often quoted as 2 mmol l^{-1} [30]. However, such limits are somewhat arbitrary, as there is a continuous relationship between increasing lactate concentration and mortality in critically ill patients [31]. Clinical thresholds for elevated lactate include 4 mmol l^{-1}

as one of the criteria for severe sepsis [32], and 3 mmol l^{-1} in the revised King's College criteria for liver transplantation in patients with acute liver failure due to paracetamol [8].

We found 24 case reports of patients presenting with an early lactic acidosis (or metabolic acidosis with no other apparent cause) after massive paracetamol ingestion (summarized in Table 1) [6, 7, 33–46]. These patients typically presented with a reduced conscious level early after paracetamol ingestion (median 5 h), with a very high plasma paracetamol concentration (maximum 1614 mg l^{-1}, median 844 mg l^{-1}) and a metabolic acidosis with high arterial or venous lactate on presentation. Other substances such as ethanol [47] and propylene glycol [48] may cause lactic acidosis in large doses, but paracetamol was the sole drug ingested in just over half of the cases listed in Table 1, as confirmed by toxicology analysis [6, 7, 33, 36–38, 46]. Three patients experienced hypoglycaemia [37, 39], which may have been due to inhibition of gluconeogenesis by paracetamol. Eight patients (33%) were treated with intravenous bicarbonate (100 to 400 mmol) and more than half required intubation and ventilation for significant respiratory depression. Only six patients (25%) developed hepatotoxicity with peak AST (aspartate aminotransferase) or ALT (alanine aminotransferase) over 1000 IU l^{-1}. Five patients died; in four of these cases the time of ingestion was not known. Only two of the five deaths were as a result of hepatic failure, but these patients presented late and had already developed ALF on admission to hospital [37].

We found another case in the literature of a young child who had a similar presentation to the cases in Table 1, but was found to have a normal lactate [49]. The patient was an 18-month-old girl who presented with altered mental status and respiratory failure 2 h after ingesting 10 g of paracetamol. She had a high 4 h plasma paracetamol concentration (1010 mg l^{-1}) and metabolic acidosis (pH 7.14, base excess −17 mmol l^{-1}) but normal lactate (0.6 mmol l^{-1}) and anion gap (17 mEq l^{-1}). She was treated with intravenous NAC (commenced at 4 h post-ingestion) and sodium bicarbonate. Renal and hepatic function were normal throughout the child's hospital stay. The authors suggested that despite the normal lactate, the acidosis may still have been due to inhibition of mitochondrial respiration by NAPQI. An alternative explanation that has been suggested for such cases is the occurrence of transient acquired pyroglutamic acidaemia (or 5-oxoprolinuria) [50]. Pyroglutamic acidaemia can cause depressed conscious level and metabolic acidosis with a relatively normal lactate [51]. It typically occurs in unwell hospital patients given therapeutic doses of paracetamol over a number of days [52–58]. A case has also been reported in a healthy 44-year-old woman taking paracetamol for 1 month for back pain [59]. Some patients may be more susceptible because of defects of enzymes involved in the gamma glutamyl cycle or other metabolic pathways [60]. Pyroglutamic acidosis should be considered in the differential diagnosis of a high anion gap metabolic acidosis, and it can be detected by measurement of 5-oxoproline in the urine.

Management of early lactic acidosis in paracetamol poisoning

The majority of patients with early lactic acidosis due to paracetamol toxicity, summarized in Table 1, were given the UK standard treatment regimen of N-acetylcysteine (NAC), which prevents hepatic injury primarily by restoring hepatic glutathione [25, 26]. As well as preventing hepatocyte necrosis, NAC may protect cellular metabolic enzymes, and has shown some benefit in early septic shock [61]. *In vitro* studies [14] have shown that NAC treatment attenuates the decrease in cellular respiration due to paracetamol toxicity. NAC has been used for over 30 years and almost eliminates the risk of hepatic damage when given within 8 h in paracetamol overdose [62]. In patients who have taken very large overdoses, the half-life of paracetamol may be prolonged [46, 63], so an extended course of NAC may be required.

In addition, nine of the 24 cases were treated with haemofiltration, haemodialysis or haemoperfusion to aid the removal of paracetamol or for treatment of renal failure [33–39, 43, 46]. Paracetamol and its metabolites have a large volume of distribution, so extracorporeal methods do not significantly increase overall total body clearance [64]. We would therefore not recommend the use of haemofiltration or haemodialysis solely to remove paracetamol and its metabolites, but it may be indicated in the management of severe metabolic disturbances.

Sodium bicarbonate was given to eight of the 24 of the patients [34, 35, 37, 38, 40, 44]. There are no controlled data on the use of sodium bicarbonate in this situation, but it has been found to be ineffective in other situations of metabolic acidosis (e.g. sepsis, diabetic ketoacidosis) in both animal and clinical studies [65] and should probably not be recommended for paracetamol-induced lactic acidosis. There are potential adverse consequences of sodium bicarbonate infusion, including the stimulation of lactate production and generation of carbon dioxide, and cellular and whole animal studies have shown varying effects of sodium bicarbonate on intracellular acidosis [66]. A human healthy volunteer study showed that sodium bicarbonate infusion lowered the intracellular pH in the brain [67].

Dichloroacetate, which stimulates the oxidation of lactate to acetyl-coenzyme A and carbon dioxide, has been investigated as a possible therapy in lactic acidosis. Although it caused an improvement in arterial pH and lactate concentration in clinical trials, it had no effect on haemodynamic parameters or survival [68].

Table 1

Characteristics of reported cases of paracetamol poisoning with early lactic acidosis or early metabolic acidosis of uncertain cause

Case number	Author, year and reference	Age (years)	Sex	Amount ingested (g)	Time before presentation (h)	Other drugs taken	Peak paracetamol (mg l^{-1})	Initial presentation
1	Vale & Meredith, 1982 [33]	43	F	>26	–	None detected	1150	Grade 4 coma, hypotension
2	Williams *et al.*, 1982 [34]	15	F	40	16	Temazepam	238	Not described
3	Zezulka & Wright, 1982 [35]	56	F	75	11	Unknown	959	Unconscious, diminished reflexes
4	Lieh-Lai *et al.*, 1984 [36]	1½	M	10	6	None detected	863	Unconscious, hypothermic
5	Zabrodski & Schnurr, 1984 [37]	29	F	36	–	None detected	24.2	GCS 10, lethargic and confused
6	Zabrodski & Schnurr, 1984 [37]	48	F	–	–	None detected	45.4	Confused, abdominal pain
7	Flanagan & Mant, 1986 [38]	45	F	–	4	None detected	1100	Grade 4 coma, hypotension
8	Flanagan & Mant, 1986 [38]	59	F	–	3	Unknown	950	Unconscious, drowsy
9	Flanagan & Mant, 1986 [38]	50	F	–	<21	Salicylate	900	Grade 3 coma, hypotensive
10	Flanagan & Mant, 1986 [38]	80	F	–	–	None detected	1400	Grade 4 coma, vomiting
11	Flanagan & Mant, 1986 [38]	17	M	100	4	None detected	950	Grade 4 coma, hyper-ventilation
12	Kritharides *et al.*, 1988 [39]	30	F	12	–	Codeine	190	Unrousable, hypothermic
13	Dunn, 1998 [40]	26	M	50	12	Sulphasalazine	844	Unconscious, hypothermic, seizures
14	Koulouris *et al.*, 1999 [41]	29	F	75	–	Aspirin, pine oil, isopropyl alcohol	1072	GCS 8, hypothermic
15	Roth *et al.*, 1999 [6]	32	F	100	1	None detected	500	Confused, lethargic
16	Roth *et al.*, 1999 [6]	32	F	150	31	None detected	850	GCS 3
17	Roth *et al.*, 1999 [6]	17	F	–	9	None detected	143	Comatose
18	Roth *et al.*, 1999 [6]	47	F	–	2	None detected	388	Comatose
19	Ashtekar & Vyas, 2003 [42]	14	M	>32		Dextropro-poxyphene	320	Seizures, coma GCS 3
20	Ala *et al.*, 2004 [43]	34	F	150	5	Unknown	817	GCS 9, wandering, confused.
21	Mendoza *et al.*, 2006 [7]	2¼	F	–	–	None detected	804	Vomiting, somnolent
22	Ryan, 2006 [44]	34	M	48	–	Dextropro-poxyphene	–	Asystolic cardiac arrest
23	Bourdeaux & Bewley, 2007 [45]	55	M	50	2	Aspirin, cinnarizine	524	Agitated, confused
24	Wiegand *et al.*, 2010 [46]	23	F	200	1½	None detected	1614	Unresponsive

Case number	Initial blood values (mmol l^{-1}) Lactate	Glucose	Anion gap	Bicarbonate	Base excess	Initial pH	Treatment NAC	Intubated	Other treatment	Peak AST (ALT) (IU l^{-1})	Peak INR (PT) (s)	Outcome
1	–	–	–	6	–	7.1	•	•	Charcoal haemoperfusion	372	1.7	Died of intra-cerebral infarcts and bleed
2	–	–	–	–	–	7.2	•	○	HCO_3 (100 mmol), charcoal haemoperfusion	>3000	(PT 60)	Recovered, liver function normal after 7 days
3	12.9	–	34	5.1	–25.2	6.9	•	?	Gastric lavage, HCO_3 (300 mmol bolus then slow infusion), charcoal haemoperfusion	258	(PT 19)	Recovered; fully alert at 24 h
4	–	–	–	13	–	7.34	•	•	Haemodialysis	5500	(PT 20)	Recovered; home after 2 weeks
5	25.8	2.2	39	–	–	6.98	○	?	Activated charcoal, HCO_3 (200 mmol), haemodialysis	>1800	(PT > 50)	Died of hepatic and renal failure after 4 days
6	16.4	<1	23	–	–	6.92	•	?	Activated charcoal, HCO_3 (150 mmol)	4080	(PT > 50)	Died of hepatic failure after 3 days
7	–	10.9	–	12.9	–16	7.06	○	•	HCO_3, neomycin, magnesium sulphate	123	–	Paralytic ileus, pneumonia; recovered
8	–	16.6	–	17	–9	7.32	○	○	Gastric lavage, methionine, cimetidine	243	(PT 27)	Full recovery; normal liver function on day 6
9	–	–	–	15	–6	7.45	•	○	Intensive care, haemodialysis	–	(PT 19)	Hepatorenal failure, recovery
10	–	16.4	–	14.7	–9	7.34	•	?	Supportive care	–	(PT 16)	Hypotensive, died after 36 h
11	–	–	–	3.7	–24.8	7.07	•	?	HCO_3	–	(PT 22)	Pneumonia, recovered, home on day 5
12	–	2	–	4.8	–	6.85	•	?	Inotropes, haemofiltration	(ALT 4240)	(PT 51)	Anuric for 10 days, recovered
13	21.3	14.4	–	2	–	6.91	•	•	Methylene blue, HCO_3 (250 mmol), activated charcoal, insulin	(ALT 172)	1.5	Recovered; ITU stay 2 days, home on day 10
14	14	–	30	6	–	7.09	•	•	Activated charcoal	–	–	Recovered, extubated after 3 days
15	2.3	19.4	21	–	–18	7.21	•	○	Activated charcoal	42	1.3	Discharged after 4 days
16	>11	13.1	24	–	–24	7.03	•	•	Activated charcoal	4680	5.3	Liver and renal failure, pancytopaenia, recovered
17	–	6.4	17	–	–14	7.4	•	•	Activated charcoal	283	1.1	Discharged after 3 days
18	–	7.3	12	–	–12	7.4	•	○	Activated charcoal	4	0.9	Discharged after 3 days
19	7.3	19.5	15	–	–	–	•	•	Intensive care	–	–	Extubated after 9 days
20	–	–	–	7	–19	7.27	•	•	Haemofiltration	67	(PT > 50)	Full recovery after 10 days
21	4.6	–	–	17.3	–	7.32	•	•	36 h NAC infusion	27	–	Recovered, liver function normal
22	31.8	–	–	–	–26.4	6.61	○	•	HCO_3 (400 mmol), inotropes	–	–	Recovered, home on day 14
23	15.5	20.6	–	11	–13.5	7.35	•	•	Vasopressors	(ALT 138)	2.5	Developed ARDS and died at 84 h
24	25.1	12.6	–	12	–	7.17	•	•	Activated charcoal, haemodiafiltration	420	3.3	Alert from day 3, full recovery

–, unknown; •, yes; ○, no; ?, implied but not stated explicitly; NAC, N-acetylcysteine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; PT, prothrombin time.

Lactic acidosis and prognosis of paracetamol-related acute liver failure (ALF)

As discussed earlier, the second scenario in which lactic acidosis occurs in patients with paracetamol poisoning is in patients with established hepatotoxicity. This is more likely in those presenting late or in whom treatment is delayed [69]. In a series of 23 patients presenting more than 15 h after a paracetamol overdose, the median plasma lactate concentration was 3.6 mmol l^{-1}, and 11 (48%) were acidotic. Twenty patients (87%) developed hepatotoxicity and four died of hepatic failure [28]. Hyperlactataemia in patients with established ALF due to paracetamol reflects predominantly reduced hepatic clearance [70]. This may be exacerbated by increased production, particularly in those who are systemically unwell with significant hypotension or poor peripheral perfusion [71].

As the plasma lactate concentration seems to correlate with increased risk of mortality [28], it has been investigated as a prognostic marker particularly for making decisions about liver transplantation. It is important to make the correct decision in these cases, because although transplantation can be potentially life-saving, it is a major operation and donor organs are scarce. O'Grady *et al*. published a series of liver transplants for paracetamol overdose from the King's College Hospital (London) liver unit in 1991 [72]. Patients were selected for transplantation based on a prognostic model derived from a retrospective review of 588 previous cases admitted between 1973 and 1985. The 'King's College criteria' for selection of patients for liver transplantation in paracetamol related ALF thus derived were: (i) arterial pH < 7.3 at 24 h or more following overdose after correction of hypovolaemia or (ii) concurrent presence of serum creatinine >300 μmol l^{-1}, grade 3 or 4 encephalopathy and prothrombin time >100 s. The criteria were tested for accuracy in predicting death in a second cohort of 121 patients with paracetamol-induced ALF admitted between 1986 and 1987. The positive predictive value (PPV) was 84% and the negative predictive value (NPV) was 86% [73]. Among children with paracetamol-induced ALF, similar clinical parameters (pH < 7.3, renal impairment, encephalopathy; but not hepatic transaminase concentrations) predicted death or the need for transplantation [74].

The King's College criteria have been tested in a number of cohorts around the world, and found to have varying performance [69, 75]. Although they have been of use in selection of patients for liver transplantation [69], some patients with poor prognosis who may potentially benefit from transplantation are not detected early enough, because of the poor sensitivity and negative predictive value, and the time for some of the clinical parameters to develop [76]. In a retrospective review of 120 patients with paracetamol-related ALF admitted to the Birmingham liver unit, 1990–1994, who did not receive a liver transplant, 48 patients died. The King's criteria yielded a PPV of 88% and NPV of 65%, which was worse than in the original cohort [77]. Amongst 18 patients with paracetamol-induced ALF in Pittsburgh, USA who did not undergo transplantation, the sensitivity of the pH criterion was 90% but specificity was only 50% [78]. However, in this cohort the criteria based on prothrombin time, serum creatinine and encephalopathy were 73% sensitive and 100% specific.

As noted earlier, blood lactate concentration is commonly raised in those with severe paracetamol-related ALF [28]. Bernal *et al*. proposed a modification of the standard King's College criteria based on a retrospective sample of 103 patients with severe paracetamol-related ALF admitted to King's College Hospital liver unit between 1998–1999. Of the 103 patients in the initial cohort, 10 were transplanted and excluded from analysis, 57 survived and 36 died. Early arterial blood lactate concentration was significantly greater in non-survivors (median 8.5 mmol l^{-1}) than survivors (median 1.4 mmol l^{-1}), $P < 0.0001$. On multivariate logistic analysis, pH and lactate were the only independent predictors of mortality. Receiver operator characteristic curve analysis identified that lactate cut-offs of 3.5 mmol l^{-1} on admission (before fluid resuscitation) and 3.0 mmol l^{-1} post-resuscitation gave the greatest sensitivity and specificity [8].

The modified King's criteria for selection of patients with paracetamol-related ALF for liver transplantation, based on this study, are: (i) to strongly consider listing for transplantation if the arterial lactate is >3.5 mmol l^{-1} after early fluid resuscitation, and to list for transplantation if (ii) arterial pH < 7.3 or arterial blood lactate >3.0 mmol l^{-1} after adequate fluid resuscitation or (iii) concurrent presence of serum creatinine >300 μmol l^{-1}, grade 3 or 4 encephalopathy and international normalized ratio > 6.5 [8].

The prospective validation cohort for the modified criteria consisted of 107 patients admitted in 1999–2000, of whom 21 died, 78 survived and eight were transplanted and excluded from analysis. The median time between paracetamol ingestion and transfer to the liver unit was 51 h (range 18–98 h). Patients received a median of 1.5 l colloid and 3.3 l crystalloid for resuscitation. The original King's College criteria yielded a sensitivity of 76% and specificity of 95%, and criteria were fulfilled at a median of 10 h from admission. The initial lactate criterion was 67% sensitive and 95% specific, and post-resuscitation lactate was 76% sensitive and 97% specific. The new combined criteria had a sensitivity of 95% and specificity of 91%, and were met within a median time of 4 h, a significant improvement over the standard King's criteria [8]. The PPV was 74% and NPV 99% [79]. Results were similar when transplanted patients were included as non-survivors [8].

Although the incorporation of post-resuscitation lactate into the King's College criteria has, in general, been an improvement, the performance of this selection rule has still been inconsistent [9] and needs further validation

in other liver centres [80]. Among 101 paracetamol-related ALF patients in Denmark, the modified King's College criteria applied at the onset of hepatic encephalopathy were 87% sensitive but only 44% specific [81]. In another recent study, nuclear magnetic resonance spectroscopy was used to detect numerous biochemical markers (33 substances including a number of amino acids, creatinine, pyruvate and ketoacids) in 85 patients with paracetamol ALF [82]. The mean plasma lactate was significantly higher in patients who died (4.93 mmol l^{-1}) than in those who survived (2.52 mmol l^{-1}). However a rule based on the novel biomarkers seemed to be superior to the modified King's College Criteria, and could identify patients requiring transplantation at an earlier stage [82].

Clinical and research implications

The clinical implications of these observations are threefold. First, a high lactate concentration on admission in a patient presenting early, within 8 h, after paracetamol overdose may be indicative of direct mitochondrial toxicity and therefore a significant overdose. It has been suggested that such a finding should prompt early administration of N-acetylcysteine, and make clinicians wary of rapid deterioration [45]. They are also likely to have very high plasma paracetamol concentrations (usually above 800 mg l^{-1}) and this, together with the prolonged half-life of paracetamol in these circumstances [46], make it likely that they will require treatment with NAC for longer than the standard 20 h 15 min UK regimen [83]. We would advocate, in these patients, that the plasma paracetamol concentration is measured at the end of the initial course of NAC and repeated every 12 h until it is undetectable. NAC treatment should continue during this period, and until any evidence of hepatotoxicity has started to recover. Secondly, paracetamol poisoning should be considered in the differential diagnosis of metabolic acidosis of unknown aetiology. Thirdly, a high lactate is associated with increased mortality among patients with paracetamol-related ALF, and is part of the revised King's College criteria for considering liver transplantation in these patients.

We recommend that lactate is measured in all patients presenting with reduced conscious level after paracetamol overdose, and in patients with paracetamol-related ALF.

Although the King's College criteria specify that the lactate should be measured in arterial blood, studies in intensive care patients have shown that lactate [84] and pH [85] in central venous blood samples closely correlate with those in arterial blood. Peripheral venous and arterial pH also correlate closely (95% limits of agreement −0.11 to +0.04 units) [86]. However, peripheral venous lactate may deviate somewhat from arterial lactate. A study in Emergency Department patients (n = 74) found that the mean peripheral venous lactate was 0.22 mmol l^{-1} greater than arterial lactate, with 95% limits of agreement for an individual patient −1.3 to 1.7 mmol l^{-1} [87]. Although there have been no such studies specifically in patients with paracetamol poisoning, it seems likely that these relationships will be similar.

Given the risks of arterial or central venous blood sampling (particularly in patients with coagulopathy due to liver failure), we would advocate testing peripheral venous samples in the first instance unless the patient requires central venous access or arterial blood sampling for another reason. If the peripheral lactate is low, arterial sampling will not be necessary. If the peripheral lactate is very high, arterial lactate is also likely to be high and the patient should be treated as if this were the case. Intermediate levels of peripheral lactate may require confirmation with arterial or central venous samples in order to make treatment decisions.

These guidelines are based on the results of small studies. Larger studies of the utility of peripheral venous lactate measurement, including analysis of reclassification based on thresholds, are required to derive more robust recommendations.

Further research is also warranted to investigate other biochemical markers for detection of ALF and aid early listing for transplantation. Larger cohort studies, or individual patient meta-analysis of previous cohorts, could be used to derive more precise estimates of the predictive accuracy of prognostic scores in different populations.

Conclusions

Lactic acidosis may be a marker of severity in paracetamol poisoning, both in those presenting early as a reflection of mitochondrial inhibition by NAPQI, and in those presenting later as a marker of hepatic damage. It is thus important to measure it and act on the results appropriately in severe cases of paracetamol overdose.

Competing interests

Paul Dargan has acted as a scientific advisor to McNeil Pharmaceuticals and the US Food and Drug Administration on paracetamol (acetaminophen).

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