THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the Sri Lanka Medical Association
Volume 60, No.3, September 2015
Quarterly ISSN 0009–0875

Paracetamol overdose: Relevance of recent evidence for managing patients in Sri Lanka

Paracetamol poisoning is the commonest overdose recorded in high income countries [1-4]. In Sri Lanka paracetamol overdose has exponentially increased in urban and rural areas [5, 6]. It is responsible for 50% of admissions due to overdose in the National Hospital of Sri Lanka (National Poisons Information Center data), and on average two patients are admitted every day with paracetamol overdose [7]. In the Kurunegala district primary hospitals, paracetamol was responsible for 18% of overdose admissions in 2012 (South Asian Clinical Toxicology Research Collaboration cohort data).

Paracetamol toxicity is mostly due to the toxic intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI) produced by cyctochrome P450 enzymes. This normally binds to sulfhydral groups in gluthathione to form non toxic metabolites. In overdose, gluthathione stores can become depleted and NAPQI binds to sulfhydral groups in other proteins causing hepatic and renal damage. Early administration of sulfhydral donor antidotes such as methionine or N-acetylcysteine (NAC) significantly reduces the risk of death or hepatic injury [8-10]. Risk factors for death includes late presentations (>8 hours), staggered overdoses or unintentional therapeutic excesses [3,11-14]. In 2012 Sri Lanka spent Rs 41 million on methionine and Rs 126 million for NAC, distributed to both urban and rural areas (Medical Supplies Division data).

The international standard for risk assessment following a single ingestion of paracetamol is to plot the paracetamol concentration on a risk nomogram. As a small percentage of patients with paracetamol levels below the nomogram threshold develop some hepatic injury, current research seeks to define optimal treatment thresholds and dose and duration of antidotes [15, 16]. This article focuses on some recent developments and discusses the relevance of the new evidence for managing patients in Sri Lanka.

Antidote treatment thresholds in different countries

A strong risk benefit ratio favouring treatment and a desire to simplify the decision process have led to different treatment thresholds internationally, but the lower thresholds are not supported by evidence from randomized controlled trials [17, 18]. In Denmark, all patients with suspected paracetamol overdose receive antidote [19]. In the UK from 1995-2012, the treatment threshold was based upon a paracetamol concentration measured between 4-16 hours [20]. Two lines were used, the line starting at 200 mg/l at 4 hours ('200 mg/l line'), the usual threshold line for treatment and the line starting at 100mg/l at 4 hours ('100mg/l, line) for those considered to be at high risk of

hepatotoxicity such as patients on concomitant enzyme inducing medications, starvation, chronic ethanol misuse, and dehydration [10]. In North America a treatment line starting at 150mg/l ('150mg/l line') was mandated by the FDA to provide an added margin of safety [15]. In New Zealand and Australia a single150 mg/l line was adopted to simplify management.

In 2012, following the death of a patient with a concentration below the treatment line, the UK Chief Medical Officer mandated a reduction in the treatment threshold [21]. The key changes included using a single '100 mg/l treatment line' for all cases, ceasing risk assessment; treating all staggered/uncertain ingestions; and increasing the duration of the initial NAC infusion from 15 to 60 minutes. Evaluation of effect of changes have shown that there is no evidence for improved clinical outcomes but there is a significant increase in costs and adverse reactions to treatment [22].

Although a low cost paracetamol assay has been developed and validated in Sri Lanka, it is not available in routine patient care [23]. Thus treatment decisions are normally based upon the history of ingested dose [7, 24, 25]. This approach is consistent with international guidelines which use the ingested dose when paracetamol concentration is not available, easily interpreted or appropriate. However using the commonly recommended ingested dose threshold of 200 mg/kg would result in 41% of patients receiving antidote unnecessarily [23]. In this situation there is a strong case for providing effective lower risk and cheaper treatment. This is addressed by the 2012 NPIC guidelines and flow charts for management of paracetamol overdose [26]. For patients who have taken a potentially toxic dose, intravenous NAC over 20.25 hours is recommended for admissions more than 8 hours after acute overdose, staggered overdoses and those having vomiting and abdominal pain [24]. Oral methionine is recommended for patients presenting within 8 hours and not having vomiting or history of liver disease as it is a more cost effective alternative in the absence of studies proving superiority of NAC [17, 18, 27, 28].

Reducing adverse effects from intravenous NAC

With the initial loading dose of NAC in the 20.25 hour regimen, up to 60% of patients may experience dose-related vomiting and/or anaphylactoid reactions, particularly patients with lower paracetamol concentrations. While these are easily managed, it leads to treatment interruption and refusal in 20% of patients [29, 30].

Aiming to reduce adverse events, a clinical trial published in 2014 evaluated the efficacy and safety of a shorter 12 hour NAC regimen compared to the standard 20.25 regimen in UK [31]. The trial randomly allocated patients with acute paracetamol overdose to four arms, either the standard intravenous NAC regimen or a shorter 12 hour modified protocol, with or without 4 mg of ondansetron IV given as pretreatment. The trial protocol administered 100 mg/kg NAC in 200 ml, over 2 hours followed by 200 mg/kg in 1l, over 10 hours, giving the same total amount of NAC as the standard regimen.

The 12 hour modified NAC regimen resulted in less vomiting, fewer anaphylactoid reactions, and reduced need for treatment interruption. Although there was no significant difference in hepatotoxicity, as the study was not powered to detect non inferiority and had significant clinical exclusions, further research is required to establish efficacy of the 12 hour modified NAC regimen over the standard approach. As there was an unexpected small increase in aminotransferases, ondansetron probably should not be used as an antiemetic. In Sri Lanka the issue of anaphylactoid reactions are important when intravenous NAC is used but not in situations where methionine is given orally.

Unintentional and staggered paracetamol overdoses

Staggered paracetamol overdoses are defined as ingestion of potentially toxic amounts of paracetamol (>4 g day) within 7 days of presentation [12]. About one third of staggered overdoses are taken deliberately as a suicide attempt. Other causes for staggered overdose are accidental overdose during non-specific systemic illness, iatrogenic overdose due to medication errors and cognitive impairment. Staggered overdose is strongly associated with reduced survival compared with single time point overdose [12]. Unintentional paracetamol over-dose (frequently staggered or associated with intoxication) is also independently associated with reduced survival compared with intentional overdose [32]. These studies highlight the need for unintentional and staggered paracetamol overdoses to be treated as high-risk for development of multi-organ failure, and to be considered for antidote treatment irrespective of serum paracetamol concentration at admission. Sri Lankan guidelines reflect this approach. There is some evidence that oral NAC is as effective as intravenous NAC [33]. If this can be confirmed it would provide additional options for earlier initiation of treatment in primary care and rural hospitals.

Medication errors in administration of paracetamol and acute liver failure

Retrospective analysis of paracetamol-associated paediatric acute liver failure cases during a 10 year period in Australia and New Zealand, has shown that medication errors in administration of paracetamol, as the leading cause of paediatric acute liver failure [34]. Vast majority of children were under the age of 5 years. Seven children had received doses in excess of 120 mg/kg/day. Many of the other children had received either a double dose, or too frequent administration. The study suggested a review of regional safety practices surrounding paracetamol use in children and dosing based on lean body mass.

Sensitive markers of hepatotoxicity

Most patients present to the hospital soon after drug ingestion, before acute liver injury (ALI) can be diagnosed, or confidently excluded, using the current biomarkers such as alanine transaminase (ALT) or International Normalising Ratio (INR). Thus a need for new biomarkers to identify paracetamol-induced ALI early is emphasized [35, 36]. A recent study investigated the potential of a panel of novel biomarkers, plasma micro RNA-122 (miR-122; having high liver specificity), high mobility group box-1 (HMGB1; a marker of necrosis), keratin-18 (K18; a marker of necrosis and apoptosis), and glutamate dehydrogenase (GLDH; a marker of mitochondrial dysfunction) at first presentation to the hospital [34, 36]. Within 8 hours, miR-122, HMGB1, and K18 identified the development of liver injury with a high degree of accuracy and may be used in risk stratification of patients in future [37]. ALT alone or in combination with new markers is a good negative predictor of adverse outcome [38].

Tools used for prognostication in ALF

A systematic review found that the original King's College Criteria (KCC) without addition of arterial lactate levels remain well-validated with high prognostic accuracy in paracetamol induced ALF [39]. Many alternative prognostic variables to the KCC have subsequently been proposed. Sequential organ failure assessment (SOFA) scores utilise features of extra-hepatic organ injury in an attempt to predict outcome following paracetamol hepatotoxicity [40]. The model for end-stage liver disease (MELD) score, incorporates INR, serum bilirubin and serum creatinine [41]. Although the SOFA score was reported to be superior to MELD score in predicting spontaneous survival, a systematic review of prediction models for poor outcome in patients with acute liver failure concluded that all studies on prognostic models for ALF show methodological and reporting limitations [42, 43].

Influence of Cytocrome P 450 inducing drugs on hepatotoxicity

The only drugs for which there is evidence of the potential for an increased risk of hepatotoxicity in patients with paracetamol overdose are phenobarbital, primidone, and isoniazid [44]. There is no evidence that other drugs often quoted as increasing risk, such as carbamazepine, phenytoin, primidone, rifampicin, and rifabutin, should be considered as risk factors for hepatotoxicity in patients presenting with acute paracetamol overdose.

Impact of pack size reduction on paracetamol overdose in UK and Ireland

In UK, legislation came into effect in September 1998 to restrict pack sizes of paracetamol sold over the counter [45]. Maximum of 32 tablets could be dispensed from pharmacies and 16 from non-pharmacy outlets. In Ireland, similar legislation was introduced in October 2001 with lower tablet numbers; a maximum of 24 tablets from pharmacies and 12 tablets from non-pharmacy outlets [46]. Beneficial effects, seen in England and Wales with reduced sizes of overdoses and numbers of deaths and liver transplantations was not seen in Scotland [47]. In Ireland, changes appeared to have resulted in smaller overdoses (i.e. reduced number of tablets taken) in the first two years after the legislation. However the difference in paracetamol pack size legislation between England and Ireland did not appear to have resulted in a major difference in sizes of overdoses [48]. In Sri Lanka any meaningful changes in pack size would have to reflect the lower body weight of Sri Lankans.

Therapeutic paracetamol dose and acute liver injury

Acute liver failure occurring after administration of paracetamol at the maximum recommended daily dose in adults with lower body weight and chronic medical conditions has been reported [49, 50]. A recent study suggests considering paracetamol in therapeutic dosages in the causality assessment of non-alcoholic patients with liver injury [50].

Hepatotoxicity in Asians

The metabolism of paracetamol in Asians is thought to differ from that of Westerners. Data on over 1000 patients including Malays, Chinese and Indians concluded that paracetamol-induced hepatotoxicity rates in a multi-ethnic Asian population was low at 7.3% and mortality and morbidity were non-existent despite high doses of paracetamol ingestion and delayed presentation [51].

Relevance of recent developments for Sri Lanka

Since vast majority of paracetamol overdoses are managed without using paracetamol levels, which treatment line should be used is not practically important in Sri Lanka. The superiority of the 12 hour NAC regimen over the existing regimen remains to be proven although it is simpler and has less potential for less medication errors. Although incidence of paracetamol overdose has increased in Sri Lanka, since the overall mortality due to poisoning has come down, a campaign to reduce the incidence by reducing pack sizes perhaps may not be justified. Reducing the pack size may not be effectively implemented in Sri Lanka and it may also lead to increased mortality due to a shift towards poisoning with more toxic substances.

As higher mortality in accidental and repeated supra therapeutic ingestions has been repeatedly confirmed and medication errors in administering paracetamol has been

identified as the most common cause of liver failure, education of prescribers, mothers, and public, emphasizing safe use of paracetamol is needed.

We also should be cautious in using maximum doses of paracetamol in adults during febrile illnesses, common during fever epidemics, particularly in patients with lower body weight. It may be appropriate to use paracetamol doses adjusted for weight in such patients.

Conflicts of interest

There are no conflicts of interest.

References

1. Claassen CA, Trivedi MH, Shimizu I, *et al*. Epidemiology of Nonfatal Deliberate Self-Harm in the United States as Described in Three Medical Databases. *Suicide Life Threat Behav* 2006; **36**: 192-212.
2. Gunnell D, Hawton K, Murray V, *et al*. Use of paracetamol for suicide and non-fatal poisoning in the UK and France: are restrictions on availability justified? *J Epidemiol Community Health* 1997; **51**: 175-9.
3. Larson AM, Polson J, Fontana RJ, *et al*. Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. *Hepatology* 2005; **42**: 1364-72.
4. Greene SL, Dargan PI, Jones AL. Acute poisoning: understanding 90% of cases in a nutshell. *Postgrad Med J* 2005; **81**: 204-16.
5. de Silva V, Ratnayake A. Increased use of medicinal drugs in self-harm in urban areas in Sri Lanka. *Arch Suicide Res* 2008; **12**: 366-9.
6. de Silva VA, Senanayake SM, Dias P, *et al*. From pesticides to medicinal drugs: time series analyses of methods of self-harm in Sri Lanka. *Bull World Health Organ* 2012; **90**: 40-6.
7. Galappatthy P, Kahaduwa KTD, Kannangara LS, *et al*. Clinical Audit on Paracetamol poisoning. Proceedings of the 5th International Congress of Asia Pacific Association of Medical Toxicology 2006.
8. Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. *Crit Care Clin* 2012; **28**: 499-516.
9. Bateman DN. Paracetamol poisoning: beyond the nomogram (in press). *Br J Clin Pharmacol* 2015.
10. Ferner RE, Dear JW, Bateman DN. Management of paracetamol poisoning. *BMJ* 2011; **342**: d2218.
11. Ayonrinde OT, Phelps GJ, Hurley JC, *et al*. Paracetamol overdose and hepatotoxicity at a regional Australian hospital: a 4-year experience. *Intern Med J* 2005; **35**: 655-60.
12. Craig DGN, Bates CM, Davidson JS, *et al*. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. *Br J Clin Pharmacol* 2012; **73**: 285-94.
13. Gow PJ, Angus PW. Paracetamol overdose in a liver transplantation centre: An 8-year experience. *J Gastroenterol Hepato* 1999; **14**: 817-21.
14. Reiter C. RE: Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. *Br J Clin Pharmacol* 2013; **75**: 271-2.
15. Rumack BH. Acetaminophen Hepatotoxicity: The First 35 Years 1. *Clin Toxicol* 2002; **40**: 3-20.
16. Rumack BH, Bateman DN. Acetaminophen and acetylcysteine dose and duration: past, present and future. *Clin Toxicol* 2012; **50**: 91-8.
17. Brok J, Buckley N, Gluud C. Interventions for paracetamol (acetaminophen) overdose. *Cochrane Libr* 2006.
18. Buckley N, Eddleston M. Paracetamol (acetaminophen) poisoning. *BMJ Clin Evid* 2007; **2007**: 2101.
19. Clemmesen JO, Ott P, Dalhoff KP, *et al*. [Recommendations for treatment of paracetamol poisoning. Danish Medical Society, Study of the Liver]. *Ugeskr Laeger* 1996; **158**: 6892-5.
20. Wallace C, Dargan P, Jones A. Paracetamol overdose: an evidence based flowchart to guide management. *Emerg Med J* 2002; **19**: 202.
21. MHRA. Benefit risk profile of acetylcysteine in the management of paracetamol overdose. 2012.
22. Bateman DN, Dear JW, Carroll R, *et al*. Impact of reducing the threshold for acetylcysteine treatment in acute paracetamol poisoning: The recent United Kingdom experience. *Clin Toxicol* 2014; **52**: 868-72.
23. Shihana F, Dissanayake D, Dargan P, *et al*. A modified low-cost colorimetric method for paracetamol (acetaminophen) measurement in plasma. *Clin Toxicol* 2010; **48**: 42-6.
24. Galappathy P, Dawson A, Fernando R. Management of paracetamol overdose. *The Sri Lanka Prescriber* 2006; **14**: 1-4.
25. Senarathna S, Ranganathan SS, Dawson AH, *et al*. Management of acute paracetamol poisoning in a tertiary care hospital. *Cey Med J* 2008; **53**: 89.
26. Management of poisoning 2012; Guidelines on paracetamol overdose. National Poisons Information Service, Ministry of Health, Colombo, Sri Lanka
27. Senarathna SG, Ranganathan SS, Buckley N, *et al*. A cost effectiveness analysis of the preferred antidotes for acute paracetamol poisoning patients in Sri Lanka. *BMC Pharmacol Toxicol* 2012; **12**: 6.
28. Eddleston M, Haggalla S, Reginald K, *et al*. The hazards of gastric lavage for intentional self-poisoning in a resource poor location. *Clin Toxicol* 2007; **45**: 136-43.
29. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clin Toxicol* 2009; **47**: 81-8.

30. Pakravan N, Waring WS, Sharma S, *et al*. Risk factors and mechanisms of anaphylactoid reactions to acetylcysteine in acetaminophen overdose. *Clin Toxicol* 2008; **46**: 697-702.

31. Bateman DN, Dear JW, Thanacoody HKR, *et al*. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. *Lancet* 2014; **383**: 697-704.

32. Craig DGN, Bates CM, Davidson JS, *et al*. Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. *Br J Clin Pharmacol* 2011; **71**: 273-82.

33. Yarema MC, Johnson DW, Berlin RJ, *et al*. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. *Ann Emerg Med* 2009; **54**: 606-14.

34. Rajanayagam J, Bishop JR, Lewindon PJ, *et al*. Paracetamol-associated acute liver failure in Australian and New Zealand children: high rate of medication errors. *Arch Dis Child* 2015; **100**: 77-80.

35. Starkey Lewis PJ, Dear J, Platt V, *et al*. Circulating microRNAs as potential markers of human drug-induced liver injury. *Hepatology* 2011; **54**: 1767-76.

36. Antoine DJ, Dear JW, Lewis PS, *et al*. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. *Hepatology* 2013; **58**: 777-87.

37. Dear JW, Antoine DJ. Stratification of paracetamol overdose patients using new toxicity biomarkers: current candidates and future challenges. *Expert Rev Clin Pharmacol* 2014; **7**: 181-9.

38. Al-Hourani K, Mansi R, Pettie J, *et al*. The predictive value of hospital admission serum alanine transaminase activity in patients treated for paracetamol overdose. *QJM* 2013; **106**: 541-6.

39. McPhail MJW, Wendon JA, Bernal W. Meta-analysis of performance of Kings's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure. *J Hepatol* 2010; **53**: 492-9.

40. Craig DG, Zafar S, Reid T, *et al*. The sequential organ failure assessment (SOFA) score is an effective triage marker following staggered paracetamol (acetaminophen) overdose. *Aliment Pharmacol Ther* 2012; **35**: 1408-15.

41. Remien CH, Adler FR, Waddoups L, *et al*. Mathematical modeling of liver injury and dysfunction after acetaminophen overdose: early discrimination between survival and death. *Hepatology* 2012; **56**: 727-34.

42. Craig DGN, Reid T, Wright EC, *et al*. The sequential organ failure assessment (SOFA) score is prognostically superior to the model for end-stage liver disease (MELD) and MELD variants following paracetamol (acetaminophen) overdose. *Aliment Pharmacol Ther* 2012; **35**: 705-13.

43. Wlodzimirow KA, Eslami S, Chamuleau RAFM, *et al*. Prediction of poor outcome in patients with acute liver failure-systematic review of prediction models. *PloS one* 2012; **7**: e50952.

44. Kalsi SS, Wood DM, Waring WS, *et al*. Does cytochrome P450 liver isoenzyme induction increase the risk of liver toxicity after paracetamol overdose. *Open Access Emerg Med* 2011; **3**: 69-76.

45. Statutory Instrument. No. 2045: The Medicines (Sales or Supply) (Miscellaneous Provisions) Amendment (No 2) Regulations 1997. 1997.

46. Hawton K, Bergen H, Simkin S, *et al*. Impact of different pack sizes of paracetamol in the United Kingdom and Ireland on intentional overdoses: a comparative study. *BMC Public Health* 2011; **11**: 460.

47. Hawton K, Bergen H, Simkin S, *et al*. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. *BMJ* 2013; **346**.

48. Bateman DN. Pack size and paracetamol overdose: 16 years later. *Clin Toxicol* 2014; **52**: 821-3.

49. Claridge LC, Eksteen B, Smith A, *et al*. Acute liver failure after administration of paracetamol at the maximum recommended daily dose in adults. *BMJ* 2010; **341**.

50. Chun LJ, Tong MJ, Busuttil RW, *et al*. Acetaminophen hepatotoxicity and acute liver failure. *J Clin Gastroenterol* 2009; **43**: 342-9.

51. Sabaté M, Ibáñez L, Pérez E, *et al*. Paracetamol in therapeutic dosages and acute liver injury: causality assessment in a prospective case series. *BMC Gastroenterol* 2011; **11**: 80.

P Galappatthy, *Department of Pharmacology, Faculty of Medicine, University of Colombo, Sri Lanka,* **A H Dawson,** *National Poisons Register and Clinical Toxicology, Royal Prince Alfred Hospital, Sydney and Sydney Medical School, University of Sydney, Australia.*

Correspondence: PG, *email: p.galappatthy@pharm.cmb.ac.lk*