Large paracetamol overdose – higher dose NAC is required - CON

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Abstract

Paracetamol overdose is common in developed countries but less than 10% involve large ingestions exceeding 30g or 500mg/kg. High dose acetylcysteine (NAC) has been proposed in patients taking large paracetamol overdoses based on reports of hepatotoxicity despite early initiation of NAC treatment with the commonly used 300 mg/kg intravenous acetylcysteine regimen. The evidence from cohorts of patients treated with the standard NAC regimen after large paracetamol overdoses shows that it is effective in most patients. Small studies in patients whose paracetamol concentration are above the 300mg/L nomogram line show that modification of the standard NAC regimen to provide a total of 400-500 mg/kg NAC over 21-22h may reduce the risk of hepatotoxicity (peak ALT>1000 IU/L) but the impact on development of hepatic failure, liver transplantation and mortality with this approach is presently unknown. Better risk stratification of patients taking paracetamol overdose may allow higher dose NAC and adjunctive treatments such as CYP2E1 inhibition and extracorporeal removal of paracetamol to be targeted to those patients at the highest risk of hepatotoxicity after a large paracetamol overdose.

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Abstract:

Paracetamol overdose is common in developed countries but less than 10% involve large ingestions exceeding 30g or 500mg/kg. High dose acetylcysteine (NAC) has been proposed in patients taking large paracetamol overdoses based on reports of hepatotoxicity despite early initiation of NAC treatment with the commonly

used 300 mg/kg intravenous acetylcysteine regimen. The evidence from cohorts of patients treated with the standard NAC regimen after large paracetamol overdoses shows that it is effective in most patients. Small studies in patients whose paracetamol concentration are above the 300mg/L nomogram line show that modification of the standard NAC regimen to provide a total of 400-500 mg/kg NAC over 21-22h may reduce the risk of hepatotoxicity (peak ALT>1000 IU/L) but the impact on development of hepatic failure, liver transplantation and mortality with this approach is presently unknown. Better risk stratification of patients taking paracetamol overdose may allow higher dose NAC and adjunctive treatments such as CYP2E1 inhibition and extracorporeal removal of paracetamol to be targeted to those patients at the highest risk of hepatotoxicity after a large paracetamol overdose.

Paracetamol is one of the commonest drugs taken in overdose and a significant cause of acute liver injury in developed countries. The hepatic toxicity of paracetamol results from its metabolic oxidation to a reactive metabolite, N-acetyl-para-benzoquinoneimine metabolite (NAPQI) by cytochrome P450 enzymes when the normal sulphation and glucuronidation detoxification pathways become saturated in overdose. In human liver microsomes, CYP2E1, CYP1A2 and CYP2A6 isoforms have been shown to convert paracetamol to NAPQI, with a reported Km for the CYP2E1 isoform of 100-200 mg/L. Studies with healthy human volunteers pre-treated with the CYP2E1 inhibitor, disulfiram, confirmed the role of CYP2E1 in paracetamol oxidation. It is unclear whether the generation of NAPQI by CYP2E1 follows linear kinetics or is saturable at high paracetamol concentrations.

NAPQI is detoxified by conjugation with glutathione but when endogenous glutathione stores are depleted, NAPQI binds to cysteine groups on cellular proteins to form protein adducts. Intravenous acetylcysteine(NAC) was developed as an antidote to restore glutathione stores. The original total dose (300 mg/kg bodyweight) of intravenous NAC, given as three separate infusions (150 mg/kg over 15 minutes, 50 mg/kg over 4 hours and 100 mg/kg over 16 hours) was empirical and designed to deliver a high proportion of antidote rapidly.[1] This fixed weight-based regimen regardless of the paracetamol dose ingested has given rise to much debate about whether it can adequately replenish glutathione following massive paracetamol ingestions.

Rumack & Bateman reported that a suggested toxic human paracetamol dose of 15.9g in an average 70kg patient with a 1.5 kg liver and a paracetamol half-life of 4h can be adequately detoxified using the 300mg/kg intravenous NAC regimen with a 6.25mg/kg/h infusion in the third infusion. They proposed using these assumptions that a patient ingesting 35g (500mg/kg) of paracetamol warranted an increase in infusion rate in the third bag to 13.75 mg/kg/h.[1] The median reported dose of paracetamol ingested in large cohort studies of patients treated with NAC in the UK and Australia is around 16g (210-250mg/kg) but the rates of hepatotoxicity (defined as peak ALT>1000 IU/L) is only around 4-8%, depending on the nomogram used to determine treatment[2,3], suggesting that the vast majority of patients ingesting >16g paracetamol fare well with the current 300 mg/kg NAC dose. Hendrickson used similar stoichiometric calculations to propose infusion rates of 12.5, 18.75 and 25 mg/kg/h for patients above the 300 mg/L, 450 mg/L and 600 mg/L nomogram lines respectively.[4] These theoretical calculations for the "average" patient assuming linear paracetamol pharmacokinetics most likely overestimate the infusion rate required in most patients as they do not account for the large inter-individual variability in metabolic clearance of paracetamol in overdose resulting from differences in glucuronidation, sulphation and CYP2E1 capacity which influence the paracetamol half-life.

Several studies have consistently reported a concentration-dependent increase in risk of hepatotoxicity (peak ALT >1000 IU/L) in patients despite early treatment with acetylcysteine. Overall 3.6-4.3% of patients in large cohort studies in the UK[3,5,6] and 8% in Australia[2] develop hepatotoxicity but a graded increase at higher nomogram-related concentrations is observed, with reported rates of hepatotoxicity of 10.2-15% and 13.6-30.8% in those patients with a 4h extrapolated paracetamol concentration greater than 300 mg/L and 500 mg/L respectively.[5,6] A recent retrospective review of 104 massive paracetamol overdoses treated with the standard 21h NAC regimen from a US poison centre reported hepatotoxicity in 25 cases (24%), of which 9 cases (14%) were in the 300-449 mg/L nomogram group, 1 case (7%) in the 450-599 mg/L nomogram

group, and 15 cases (56%) in the >600 mg/L nomogram group. Only 4/44 (9%) who were treated within 8h developed hepatotoxicity.[7] These findings have fuelled the debate over whether higher doses of NAC are required for these perceived "NAC failures" even though all of these patients recovered and no deaths and liver transplants were reported in these large cohorts of patients.

Smilkstein reported in their landmark study using the oral NAC protocol consisting of a 140 mg/kg loading dose followed by 70 mg/kg every 4h for 17 doses that hepatotoxicity occurred in 2-5% of all cases that receive NAC within 8h of ingestion even with increasing paracetamol concentrations. The total oral dose administered in the first 21h is 490 mg/kg and is delivered directly to the liver versus the 300 mg/kg intravenous dose which is dependent on hepatic extraction of NAC from the systemic circulation for efficacy.[8]

The ATOM-2 study, an observational study of massive paracetamol overdose (defined as 40g or more ingested over 8h or less) in several Australian hospitals, reported that 28/200 (14%) developed hepatotoxicity (peak ALT>1000), including 6/200 (3%) of those treated within 8h. 79/200 patients were above the 300mg/L nomogram line and were treated within 16h of ingestion with either a standard 300 mg/kg NAC regimen or an increased NAC dose consisting of doubling the dose in the 16-hourly infusion to 200mg/kg (infusion rate 12.5mg/kg/h), giving a total dose of 400 mg/kg. There was a significant reduction in the rates of hepatotoxicity from 10/36 (27.7%) in the standard regimen group to 4/43 (9.3%) in the increased NAC regimen (OR 0.27; 95% CI: 0.08–0.94), with most of the beneficial effect observed in those patients above the triple nomogram line (4h extrapolated concentration of 450 mg/L).[9] It is noteworthy that even in this very small high-risk subgroup of patients ingesting 40g paracetamol or more and above the 300 mg/L nomogram line, almost 75% of patients did not develop hepatotoxicity with the standard 300 mg/kg regimen. It is uncertain whether this modified regimen would actually alter clinically important outcomes such as the development of fulminant hepatic failure, liver transplant and deaths. The modified increased dose regimen used in the ATOM-2 study is a pragmatic alteration of the existing 21h regimen and it is unclear whether the benefit seen results from an increased total dose of NAC or the increased infusion rate and whether a similar benefit would not have been achieved by a regimen delivering the same total dose with a higher infusion rate.

Such an approach underpins the SNAP regimen which was based on the premise that an optimal NAC regimen should provide an initial loading dose to restore hepatic glutathione stores and an infusion high enough for glutathione synthesis to exceed NAPQI generation for the vast majority of patients. We calculated using probabilistic modelling that a regimen delivering a total dose of 300mg/kg with an initial loading dose of 100mg/kg over 2h followed by 200 mg/kg over 10h (infusion rate 20mg/kg/h) would be sufficient in most patients.[10,11]In the small minority of patients with liver injury or persistently elevated paracetamol concentrations, an extension of the 10h infusion would provide a 500 mg/kg total dose over 22h. 16/105 (15.2%) patients with paracetamol overdose above the 300mg/L nomogram line treated within 24h of ingestion with the SNAP regimen developed hepatotoxicity, of which 3/40 (7.5%) and 9/82 (11%) were treated within 8h and 16h respectively. All 16 patients who developed hepatotoxicity had evidence of acute liver injury (ALT>150) at the end of the 12h infusion (unpublished data).

There is no agreed definition of a massive overdose, with Marks et al[5] and Chiew et al.[9] using arbitrary cut-offs of 30 and 40g or an extrapolated 4h paracetamol concentration above 250mg/L and 300mg/L respectively and Hendrickson et al[4] suggesting a dose of 32g or a paracetamol concentration above the 300 mg/L nomogram line. It is also difficult to define precisely which group of patients might benefit from an increased dose of NAC and the optimal way of delivering this higher dose. Bateman and Dear suggested that those who may require a high dose NAC regimen include doses above 500 mg/kg bodyweight paracetamol, a nomogram concentration above the 500mg/L line for those with ingestions over a shorter time (e.g less than 2 h), or a dose likely to result in mitochondrial paralysis (˜1 g/kg).[12]However, in the presence of mitochondrial dysfunction associated with paracetamol concentrations greater than 900mg/L, extracorporeal treatment to enhance clearance of paracetamol is recommended by the EXTRIP international panel.[13] The anecdotal use of fomepizole as a CYP2E1 inhibitor in conjunction with haemodialysis and NAC has also been reported following massive paracetamol overdose. Although the evidence for benefit of higher NAC dose is scanty,

pending newer evidence which is difficult to generate for this small subset of patients, the most recent guidelines in Australia and New Zealand pragmatically recommend doubling the concentration of the 16-hour infusion of NAC from 100 mg/kg to 200 mg/kg (giving a total of 400 mg/kg over 21h) in patients who ingest more than 30g or 500mg/kg and in those with a paracetamol concentration more than the 300mg/L nomogram line.[14] Clinicians treating these patients need to balance the potential benefit in up to 15% of these high-risk patients against the risk of administration errors with a change of regimen in some patients. An alternative approach which appears similarly effective is an extension of the 10h infusion in those patients with abnormal ALT or persistently elevated paracetamol concentrations at the end of the 12h SNAP regimen.

It is evident from several large patient cohorts that most patients with large paracetamol overdoses do well with the 300 mg/kg intravenous NAC regimen (whether given over 12h or 21h) and do not require high dose NAC. There will undoubtedly be a small proportion of patients with either abnormally low glucuronidation and sulphation capacity, high CYP2E1 activity or low gluthathione stores who may benefit from higher NAC dose or adjunctive treatments. Further research is required to assess the effectiveness of modified NAC regimens, CYP2E1 inhibition, extracorporeal elimination either alone or in combination in at-risk patients. Better risk stratification of patients with paracetamol overdose at presentation to identify those at high risk of developing hepatotoxicity would facilitate multi-centre prospective studies to evaluate the optimal strategy for managing this small subset of high-risk patients with a view to improving clinically important outcomes other than a historically determined clinical endpoint of peak ALT>1000. Novel biomarkers including mir-122 and paracetamol adduct concentration at presentation have been shown to predict subsequent development of hepatotoxicity.[15,16]The development of point-of-care tests that can quantify paracetamol concentration, ALT and novel biomarkers would be a major advance in facilitating such stratified trials in future.

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