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Paracetamol poisoning: beyond the nomogram

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Paracetamol poisoning is the commonest overdose seen in the UK. The management of patients with paracetamol poisoning has been little changed for the past 40 years, with a weight related dose of antidote (acetylcysteine) and treatment based on nomograms relating paracetamol concentration to time from ingestion. In 2012 the UK Commission on Human Medicines recommended a revision of the nomogram, following the death of a young woman, lowering the treatment threshold for all patients. As a result many more patients were treated. This has resulted in a large increase in admissions and in the proportion suffering adverse reactions to the antidote acetylcysteine since, interestingly, higher paracetamol concentrations inhibit anaphylactoid reactions to the antidote. New approaches to assessing the toxicity of paracetamol are now emerging using new biomarkers in blood. This article discusses new approaches to risk assessment and treatment for paracetamol overdose based on recent research in this area.

Introduction

Paracetamol poisoning and its management is one of the success stories of British clinical pharmacology. The first cases of poisoning with paracetamol were described in the British Medical Journal in 1966 [1, 2]. It was the recognition by Mitchell and colleagues shortly after this that the primary toxic effects of paracetamol were due to its conversion to a reactive metabolite, normally neutralized by glutathione in the liver, that led to the development of antidotes [3, 4].

Treatment of paracetamol overdose

Following the seminal work of Mitchell and Brodie in the 1970s demonstrating the mechanism of paracetamol toxicity [3–5] and the crucial role of glutathione as a natural antidote, a series of human studies were done in Edinburgh to establish the optimum human antidote, which was determined to be intravenous acetylcysteine (NAC) [6–9].

An intravenous antidote preparation was not licensed in the USA and so an oral regimen was developed there. This had the major problem that it was a 3 day course [10]. Adverse effects were different with oral and intravenous preparations, but the frequency of nausea and vomiting with oral NAC was a major issue. Intravenous antidote is now the most widely used treatment worldwide [11]. A *post hoc* comparative study of the original oral study with later Canadian patients suggests little difference in outcomes with oral or i.v. NAC [12]. The shorter regimen also guarantees that the full antidote dose is actually administered.

Development of treatment nomograms

For antidotes to be tested properly it was necessary to be able to select patients who were likely to develop toxicity from the ingested dose of paracetamol. This was achieved by studying a cohort of patients before the advent of antidotes in the early 1970s in Edinburgh. Initially Prescott *et al.* showed that patients with higher concentrations of paracetamol were more likely to develop hepatotoxicity, but also had slower elimination of paracetamol from body [13]. These observations led to the development of a series of parallel lines drawn on a graph relating paracetamol concentration 4 h or more after ingestion (on the y axis) and time from ingestion (on the x axis) [8, 14]. These lines all had nominal half-lives of 4 h, but commenced at different paracetamol concentrations, 300 mg l^{-1}, 200 mg l^{-1} and 100 mg l^{-1} at 4 h after the overdose, the 300 mg l^{-1}, 200 mg l^{-1} and 100 mg l^{-1} nomogram lines. In those with the

highest concentration of paracetamol, above the 300 mg line, liver damage, measured using the rise in ALT above 1000 IU l^{-1}, was almost universal, and it was only in this group that deaths occurred in this series [14].

At lower concentration nomogram lines risk of liver injury also fell and in this relatively small cohort no deaths occurred. In the UK the 200 mg l^{-1} nomogram line was therefore used for treatment decisions from the 1970s. A similar approach had been also recommended by Rumack & Matthew in the USA [15] but the US FDA required a larger safety margin, and hence US physicians adopted a line with a concentration of paracetamol at 150 mg l^{-1} at 4 h [10, 11].

In the UK occasional deaths were reported in patients presenting with blood concentrations apparently below the Prescott 200 mg l^{-1} cut-off. Because of concern caused by these events the UK National Poison Information Service advised that a risk assessment approach should be adopted for patients with nomogram concentrations between the 200 and 100 mg l^{-1} lines from 1995 [16]. This was based on history of starvation or malnutrition, consumption of enzyme inducing drugs, a history of chronic alcohol use and chronic debilitating disease, and appeared to work reasonably well. Thus a cost benefit analysis based on presentations to the liver units in Edinburgh and Newcastle upon Tyne suggested this approach was cost effective in terms of risk of liver unit admissions (not deaths). For patients with concentrations between the 150 and 200 lines, the 100 and 150 lines and below the 100 line, respectively, these risks would be approximately 1 : 1250, 1 : 1850 and 1 : 4400 patients. The authors indicated these estimates should be interpreted with caution. However they do illustrate the relationship of paracetamol dose to outcome in a population generally treated with NAC above the 100 mg l^{-1} nomogram if they had markers of high risk [17].

Cessation of NAC therapy

The duration of therapy with i.v. NAC was originally set empirically. The half-life of paracetamol is short (2 h) at therapeutic dose, but is longer in patients with overdose [13]. A 20.25 h infusion was used and bloods taken to determine if further antidote was needed [18].

The blood tests used have varied internationally, but ALT, INR, creatinine and paracetamol concentration are all used in various international protocols. The key measures are of liver injury (ALT) with INR to determine prognosis if ALT is raised [19]. A complication is that NAC alters INR by affecting clotting factors [20]. The degree of perturbation in ALT deemed an indication for extended NAC therapy is also varied, and in the UK guidance is currently to continue if the ALT has more than doubled since the admission measurement, or the ALT is two times the upper limit of normal or more, or the INR is greater than 1.3 (in the absence of another cause, e.g. warfarin). Infusions are continued at the rate in the third infusion bag of the Prescott regimen (150 mg kg^{-1} in 1 l over 16 h) until the INR is 1.3 or less, or the INR is falling towards normal on two consecutive blood tests, and is less than 3.0 [18]. It is important to stress the lack of good evidence to determine an exact cut off for treatment continuation, but the above approach has the benefit of extensive use.

Impact of changes in management in the UK in 2012

The use of paracetamol nomograms changed fundamentally in the UK in 2012, following a directive from the Medicines and Healthcare Products Regulatory Authority (MHRA) based on advice from the Commission on Human Medicines (CHM) in September 2012 [21]. A young woman had been reported to the Agency by a coroner, following her death from complications of management after an overdose of paracetamol. The coroner had expressed concern about the reliability of the UK risk assessment strategy in paracetamol overdose, since in this particular case it had not apparently being carried out in a way that detected her increased risk. The eventual CHM advice was to use a single line in the UK, but to place this at the 100 mg l^{-1} nomogram line. It is important to remember that the MHRA and CHM have no duty to consider cost–benefit in their deliberations. To the concern of clinicians who regularly treat patients internationally, this placed the UK at a different risk threshold than anywhere else in the world other than Ireland, where the MHRA advice was also adopted [22].

We therefore undertook a study based on three large acute hospitals in the UK to determine what effect the new advice would have on presentations, admissions and use of antidotes [23]. The results indicated an 8.9% (95% CI 1.9, 16.2, $P = 0.011$) increase in presentations, a 7.1% (95% CI 4.0, 10.2, $P < 0.001$) increase in admissions and a 13.2% (95% CI 10.0, 16.4, $P < 0.001$) increase in patients treated with antidote. The findings of this study, carried out in 1 year periods before and after the change, are in keeping with those found in a shorter study in York, and are supported by the national statistical data available in Scotland on admissions for paracetamol overdose. The estimated full effect in the UK was that another 31 000 patients would be treated in order to prevent the one death approximately every 2 years that the MHRA was seeking to prevent. The estimated excess NHS care costs, based on these data, suggest an estimated excess of £17.3 million [£13.4-£21.5 million] to prevent this one death [23].

This cost is clearly far more than normally considered reasonable for health care interventions. However it is also important to remember that the antidote, NAC, is not without its own problems. Adverse effects, notably nausea and vomiting and anaphylactoid reactions, are well recognized, although the true incidence has been

long debated [24]. It is generally accepted based on prospective studies that anaphylactoid reactions occur in about 20% of patients receiving NAC. Although deaths are extremely rare the reactions result in frequent treatment interruptions, patients refusing subsequent therapy and, occasionally, in doctors not treating patients in the mistaken opinion that these reactions are based on an immunological, rather than a pharmacological mechanism [19].

Reducing adverse reactions to NAC.

NAC is infused in three doses, 150 mg kg^{-1} body weight in 200 ml over 15 min (1 h since September 2012 [21]), 50 mg kg^{-1} in 0.5 l over 4 h and 150 mg kg^{-1} in 1 l over 16 h. Experiments conducted in the 1980s studying skin responses to intradermal injections of both NAC and other components of the intravenous infusion indicated that such reactions only seemed to occur at concentrations of NAC found in the initial infusion of the antidote [25]. The key suspicion has therefore been that the initial high dose of NAC is responsible for the anaphylactoid and, probably, the vomiting responses. It has also been suspected that paracetamol itself may be protective against the anaphylactoid reactions caused by NAC [26]. Although the mechanism of this interaction is unclear it was possible to study the impact of plasma concentration and reaction incidence in the cohort study we conducted following the MHRA change. Although paracetamol concentration did not interact with the incidence of vomiting, measured using the rates of prescription of anti-emetic therapy, there was an approximate five times greater incidence of anaphylactoid responses in patients with paracetamol concentrations at and below 100 mg l^{-1} compared with that in patients with paracetamol concentrations above 100 mg l^{-1} [23].

The MHRA advice has therefore had the effect of many more patients being treated, many of whom who now also at greater risk of anaphylactoid reactions.

While it is easy to see the problems with the MHRA changes the key challenge is to determine a better way of risk assessing patients for antidote therapy. In addition the development of an antidote regimen that causes less adverse effects while retaining efficacy would obviously also be advantageous. Recent work shows the potential for change in both these areas and is discussed below.

The original NAC intravenous regimens delivered large doses of antidote rapidly [9, 27]. The investigators were aware of adverse reactions occurring with the antidote, but at a time when there was no other effective therapy, these problems were deemed acceptable. At the time the regimen was developed patients were treated at the 200 mg line in the UK. Thus anaphylactoid responses were far less likely at that time than in today's patient cohort. Interestingly the first case report of an anaphylactoid reaction was in a patient with a very low paracetamol concentration [28].

We hypothesized that it would be possible to give NAC at a different rate, and duration of infusion, since the vast majority of patients do not get hepatic injury and they clear paracetamol with a half-life of approximately 2 h [29]. In such patients, therefore, a 12 h regimen of NAC would complete at least 16 h after the initial ingestion, assuming patients are risk stratified using a paracetamol concentration measured 4 h or more after overdose. By the end of a 12 h infusion it should be possible to determine whether or not hepatic injury will occur based on a profile that includes paracetamol concentration, liver function tests, INR and renal function, all measured at presentation and at the end of the infusion 12 h later. In the modified regimen the same total dose of NAC is given as in the standard protocol, but it is given as 100 mg kg^{-1} in 2 h followed by 200 mg kg^{-1} over 10 h. Monte Carlo modelling was used to determine this regimen which was tested in a factorial study in which the traditional and modified NAC measurements were compared with and without the anti-emetic, ondansetron [29]. The results of this show a very significant reduction in all adverse effects with the 12 h modified regimen of NAC. For vomiting the ORs (95% CIs) at 12 h were: modified *vs*. conventional NAC 0.37 (0.18, 0.79, $P = 0.003$) and ondansetron *vs*. placebo 0.35 (0.17, 0.74, $P = 0.002$). For anaphylactoid reactions ORs at 12 h for modified *vs*. conventional NAC were 0.23 (0.12, 0.43, $P < 0.0001$) and ondansetron *vs*. placebo 1.4 (0.78, 2.53, $P = 0.198$). Reassuringly in this small study, which was not powered on comparative efficacy, there was no signal of excess toxicity in the modified regimen cohort [30].

Clearly this regimen now requires testing in a larger patient group, and it is hoped that this can be facilitated over the next few months. Aspects that need clarification are whether this regimen is equally efficacious in later presentations and repeated ('staggered') overdose. As such patients have lower paracetamol concentrations and a higher risk of adverse effects from NAC, it is important to be sure that the advantages of fewer adverse effects are not at the cost of increased toxicity risk. This is a challenge, however, as proper non-inferiority studies are unlikely to be easily performed, as these cases are less common. There is in fact no evidence that rapid NAC administration makes a clear difference to outcome and this practice is not evidence based.

As adverse reactions to NAC are related to increases in plasma histamine [31] pre-treatment with an antihistamine might be expected to reduce anaphylactoid adverse effects. However there are no adequate clinical trials to address this possibility. Pre-treatment with ondansetron was associated with less vomiting from NAC [30] and it may also be that pre-treatment with an anti-emetic antihistamine would provide even better prophylaxis. Such an approach is often advised in patients with previous history of an adverse event, since there is evidence that such patients may be more

susceptible to the effects of NAC [25]. Again there are no controlled data to show efficacy in this situation.

Better identification of 'at risk' patients in paracetamol poisoning

Whichever approach to treatment is used we are still left with the problem of which patients to treat. The weaknesses of the present nomogram approach are obvious from the discussion above. Patients at low risk are treated to prevent liver injury or deaths in a small minority. From the regulatory perspective any death is undesirable. However a key difficulty facing clinicians is the fact that many patients who develop toxicity present late to hospital, or take multiple ingestions of paracetamol [32]. Deciding which of these patients are at particular risk of liver damage is a major problem, since the nomogram approach cannot be applied to the latter group of multiple ingestions, and late presenters are at increased risk of hepatic injury. Rises in ALT occur too late to be useful at first presentation in most patients [33], and a strategy using the product of ALT and paracetamol concentration [34], seems unlikely to be helpful in determining treatment in less severe overdose.

New developments should allow us to move from using paracetamol concentration or dose ingested alone as the decision tool. The use of proteomic and other biomarkers in patients with paracetamol poisoning offer real promise as diagnostic tools. In a study of patients with paracetamol overdose who did and did not develop liver injury, it was possible to separate patients into groups based on their admission concentrations of circulating biomarkers such as the liver specific microRNA miR-122 and the necrosis-reporting protein HMGB1 [35]. Receiver operator curves (ROC) indicated the specificity and sensitivity of this approach, and it was thus possible to identify patients who subsequently developed liver injury based on their presentation concentrations of miR-122 [36]. Recent studies suggest that it may be possible to refine this even further by combining measurements of miRs that rise, in particular miR-122, with those that fall, such as miR-483 (Vliegenthart et al. personal communication).

The potential for such improved techniques for detecting whether injury not only offers the potential to better focus treatment with NAC, but potentially to introduce therapies in man that have been shown to be effective in animals with paracetamol-induced liver injury [37]. This would offer a potential therapeutic opportunity for patients in the early stages of developing liver failure, at a time when they may be opportunity to prevent further life-threatening hepatic injury. A further, as yet less well tested, approach would be to use proteomic markers in the decision process prior to thetransplantation in acute liver injury caused by paracetamol poisoning [36].

Conclusion

In conclusion after 40 years new clinical pharmacological techniques using novel biomarkers now offer the opportunity to direct therapy better in patients with paracetamol overdose. Combining this with new approaches to giving the antidote NAC should allow a significant reduction in adverse reactions and requirement to treat far fewer patients, while retaining the necessary protective action of the antidote in patients with potentially hepatotoxic paracetamol overdoses.

Using patients with paracetamol poisoning as a test bed to develop new biomarkers of liver injury should also provide useful information for both drug developers and regulators to improve the way novel drugs and chemicals are screened for their potential hepatotoxic effects in man, particularly as recent evidence suggests that miR 122 rises 24 h before ALT in human subjects given regular doses of paracetamol, thus potentially offering an 'early warning' of potential injury [38].

Competing Interests

The author declares that other than support from the BPS for the Lilly Prize Lecture he has no conflicts.

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