Prescribing within clinical toxicology

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ABSTRACT

In 2020, the first clinical toxicology advanced nurse practitioner and independent prescriber post was introduced in the United Kingdom. This article discusses the remit of clinical toxicology and the integration of nurse prescribing into this service by following a patient journey from admission to discharge. The case study describes an acute paracetamol poisoning presentation following intentional self-harm. Paracetamol is widely available and safe in therapeutic dosages however it is the drug most commonly taken in intentional overdose and the toxic effect can result in hepatic failure and fatality. The nurse prescriber conducted a holistic consultation, assessed pharmacological management and instigated timely treatment. Current research on benefits and disadvantages of paracetamol antidote regimes are discussed. Long-term physical and mental well-being following intentional overdose requires interprofessional liaison with access to psychological support arranged prior to patient discharge.

Key words: paracetamol; acetylcysteine; clinical toxicology; activated charcoal; SNAP regimen.

Key points

Paracetamol is an effective analgesic and antipyretic and safe to use in therapeutic dosages.

Paracetamol is the most commonly used drug in acute overdose with intent to self-harm.

Early presentation and timely management of paracetamol poisoning can reduce severity of hepatocyte damage.

Intravenous acetylcysteine has been the first line management for paracetamol poisoning since the 1970's.

Novel acetylcysteine regimens offer potential of shorter duration, equivalent efficacy and less adverse effects than historic regimens.

Reflective sentences

Do you highlight the limits of the therapeutic dosage when prescribing paracetamol?

Did you know how to access the National Poisons Information Service?

Do you routinely assess physical and mental well-being during consultation?

Introduction

There has been an exponential and welcome growth in the number of healthcare professionals with an independent prescribing qualification in the United Kingdom (UK) since legislation was passed in 2006 (Stewart et al, 2017). The benefits of prescribing rights beyond the traditional medical practitioners for service provision, patient centred care and professional development are well documented (Graham-Clarke et al. 2019). However, within clinical toxicology services the independent nurse prescribing role is a recent introduction, with the first UK clinical toxicology advanced nurse practitioner (ANP) and prescriber training post realised in Edinburgh in 2020 (EdinClinTox, 2020). This article will outline the remit of the clinical toxicology nurse prescriber and the UK National Poisons Information Service (NPIS) before presenting this novel prescribing role in a case study of paracetamol (acetaminophen) poisoning.

UK National Poisons Information Service

Regional NHS poisoning treatment centres were first established in the 1960's following the Atkins and Hill reports which highlighted significant concerns regarding poisoning management nationally (Good 2014). This informal network of poisoning centres subsequently amalgamated to become the UK National Poisons Information Service. The NPIS service is currently based in four NHS teaching hospitals: Birmingham, Cardiff, Newcastle and Edinburgh with links in London and York. Together they provide information on suspected exposures or poisonings involving a vast range of substances including pharmaceuticals, alternative medicines, drugs of

abuse, organic compounds, household and industrial chemicals. Their remit includes NHS staff education on poisoning therapies; public health surveillance and clinical toxicology specialist research. The primary role of NPIS is to provide a 24 hour clinical toxicology information service to healthcare professionals offering guidance on the management of poisoned patients. Most enquiries to the NPIS relate to paracetamol poisoning (NPIS 2020).

The UK NPIS centre in Scotland is based in Edinburgh and this has responsibility for the provision of TOXBASE, an online clinical toxicology database. This database provides global access to healthcare professionals to a reference resource for information on poisons and advice on the management of the poisoned patient. All NHS facilities can register for free web access and 24 hour enquiry service for individual advice on complex presentations is available (Box 1).

Website details: www.toxbase.org 24-hour information for healthcare professionals: 0344 892 0111 Members of the public should contact NHS advice centres, e.g. NHS 24, NHS 111 or NHS Direct. In Ireland contact NPIC. TOXBASE admin: mail@toxbase.org NPIS: www.npis.org

Box 1. National Poisoning Information Service

The Edinburgh NPIS centre initially employed specialist nurses but this role has evolved to clinical toxicology ANP and independent prescriber, creating a unique

opportunity to enhance the service. This is a first for UK clinical toxicology and the NPIS. As a speciality, clinical toxicology complements and supports the pillars of advanced practice and the underpinning drivers of nurse prescribing.

The role of the clinical toxicology ANP encompasses cases within acute medicine, critical and emergency care and also outreach services. The progression from specialist nurse to advanced practitioner with prescribing rights enables complete care provision, thus more therapeutic and empathetic relationship formations with service users. Additionally, toxicology patients can deteriorate rapidly depending on the substances ingested, or may be actively suicidal or experiencing acute psychoses. This can be a particularly emotionally challenging environment for health care professionals and developing an already familiar, experienced and supportive service to a more advanced level has been met with positivity.

The following case discussion will focus on the prescribing role of the clinical toxicology ANP in a paracetamol poisoning presentation. Pseudonyms are used to protect patient confidentiality.

Case presentation

Alice presented to the emergency department three hours following a significant overdose of a single ingestion of 50 paracetamol tablets. She was a 21 year old female who was low in mood secondary to multiple social stressors. Clinically she was asymptomatic. On admission, she was regretful of the overdose and had actively sought help. She had no significant past medical history or previous contact with mental health services. The initial stage of the consultation focused on clarification of timings and content of the overdose. She was able to give the exact

time she had taken the tablets as it followed a phone conversation with her mother, which was logged on her mobile. She denied taking any other substances and had not drank alcohol.

Paracetamol pharmacology

Paracetamol is a low cost, widely available and effective analgesic and antipyretic which is licenced for use in mild to moderate pain, pyrexia and acute migraine (British National Formulary (BNF) 2020). In certain preparations it is only available on prescription but can be purchased as an 'over the counter' medication in a range of dosages and in combination with other compounds. Safe paracetamol dosage for an adult is 0.5 – 1 gram every 4-6 hours with a maximum dose of 4 grams per day (BNF 2020).

The pharmacodynamic action of paracetamol is not fully understood but proposed mechanisms suggested include inhibiting COX enzymes, inhibiting prostaglandin synthesis, binding to receptors and ion channels and blocking the generation of pain impulses in the central nervous system (Bennett 2016).

In therapeutic dosing, paracetamol is metabolised to produce the toxic metabolite N-acetyl-para-benzoquinone imine (NAPQI) through oxidation via Cytochrome P450 enzymes in the liver. Glutathione stored in the liver quickly combines with NAPQI in order to form non-toxic cysteine. Cysteine conjugates which can then be eliminated in the urine (Nelson et al. 2010). With a paracetamol overdose, it is believed that glutathione stores are depleted by the overwhelming volume of NAPQI. The accumulation of NAPQI will bind to key cell components, commencing a sequence of events which may result in hepatocellular death (Thomas 2014). The ease of

availability of paracetamol makes it one of the most commonly used drugs associated with intentional overdose with approximately 50,000 acute hospital admission recorded in the UK annually (Pettie et al. 2019).

Consultation

Consultation is described as a two-way social exchange between practitioner and patient focused on interactive decision making (Perry 2011). For clinical toxicology practitioners it is essential that consultations are holistic and empathetic. The opportunity to facilitate open and genuine interaction to discuss issues such as suicidal ideation and drug and alcohol misuse is paramount (Vandewalle 2019). This patient group may be in a distressed or agitated state and strongly benefit from clear, honest and cohesive information regarding treatment plans. Additionally, patients who self-harm report feeling marginalised by health care professionals in the acute care setting and previous experience of judgemental attitudes and behaviours may impede the formation of therapeutic relationships (Hamilton 2016).

It was important to remain mindful of Alice's emotional distress following an acute intentional overdose. A private, calm and safe environment was provided within which Alice was able to talk openly and honestly about the multiple stressors she felt where negatively contributing to her low mood. The trigger which led to Alice consuming the overdose of paracetamol was a phone conversation with her mother and she volunteered that their relationship was emotionally complex. Nuttall and Rutt-Howard (2011) introduced the theory of ego-states which can be applied to consultation, namely adult, parent and child. Performing consultations with an adult ego state creates effective and supportive communication whereas a parental ego

state often generates a barrier to the interaction leaving the patient feeling ultimately disempowered and frustrated, effectively taking on the child persona (Morris et al, 2018). During consultation with Alice, active listening and reassurance was offered to demonstrate that her input was valued and taken into account. By engaging an adult ego-state this enabled Alice to be heard without interruption thus validated her concerns with the hope that this positive experience would continue to influence engagement with longer term support measures. The systematic but individualised approach allowed a rapport to be built with Alice, she felt listened to while all pertinent information was gathered and a full examination performed whilst involving her in the decision- making process (McLeish and Snowden 2017).

While following a consultation model is useful to guide assessment, it is equally important to maintain flexibility. Although the Calgary-Cambridge model provides a structure to follow while building a relationship, it does not cover all aspects of consultation and fusion with other models may be beneficial (Deness 2013). The 'house-keeping' aspect incorporated within the Neighbour model encourages the practitioner to ask whether they are equipped for the next consultation, acknowledging that fatigue, anxiety and stress can negatively affect clinical judgement (Mehay 2012). This approach may be particularly useful within clinical toxicology as patients are frequently emotionally labile, actively suicidal or suffering from acute withdrawals or psychosis. Taking time to ensure we are prepared to move on to the next consultation and reflecting on upsetting situations with colleagues is inherently valuable in this field.

Clinical Assessment

In the instance of paracetamol overdose many presentations are initially clinically asymptomatic. However, some do experience nausea and vomiting and a gradual onset of abdominal discomfort which may indicate liver damage. Alice was asymptomatic but had she felt nauseous or actively vomiting then a prescription of antiemetics is warranted (Table 1). The most concerning toxic effect of paracetamol overdose is hepatic necrosis, features of which occur approximately two to three days post overdose (Thomas 2014). Without treatment renal tubular necrosis may develop and progressive damage to the liver may result in encephalopathy, coma and eventual death (BNF 2020). It is therefore vital that there is an accurate timeline, particularly time of ingestion, in order to gauge potential for harm and treatment options. Paracetamol absorption is not complete before four hours post ingestion, therefore plasma concentration peaks at four hours (Chiew et al, 2016). The time and plasma concentration are plotted on a paracetamol nomogram to determine whether or not treatment is required (BNF2020) Within the UK, the nomogram categorises patients as requiring intervention if the concentration is above a 'treatment line' which begins at 100mg/L at four hours (Bateman and Dear 2019).

On review Alice's blood results showed a plasma paracetamol concentration of 190mg/L at four hours post ingestion. From the significant plasma paracetamol concentration, it was evident that Alice required prompt treatment in order to minimise harm specifically the potential of liver failure. Park, Dear and Antoine (2014) reviewed the efficacy and safety of interventions available as treatment modalities for acute paracetamol poisoning, which included activated charcoal, methionine and acetylcysteine. Non-pharmacological management included haemodialysis, for which Alice did not meet the criteria (Silvotti et al, 2013; Gosselin et al, 2014). Neither did Alice present at a late stage with hepatic damage severe

enough to consider the need for liver transplant (Scottish Liver Transplant Unit, 2016).

Activated Charcoal

Activated charcoal interferes with hydrolysis in the small intestine and actively absorbs many poisons within the gastric contents which limits their toxic effects (Wishart et al. 2020). If administered within one hour of ingestion activated charcoal can reduce the absorption of paracetamol (Chiew et al. 2017). However, it is inconclusive whether it improves long term clinical outcomes, specifically if it results in a reduction of mortality, hepatotoxicity or liver failure (Park et al. 2015). Additionally, activated charcoal can be unpalpable and difficult to consume. Activated charcoal should be considered if the presentation is within one hour of ingesting of a paracetamol overdose of greater than 150mg/kg (BNF 2020).

As Alice was now more than four hours post ingestion prescribing activated charcoal would not have been therapeutic.

Methionine versus Acetylcysteine

The action of both methionine and acetylcysteine are similar. Both are precursors to cysteine, which acts as a precursor to glutathione thus replenishing stores to conjugate with NAPQI (Wishart et al. 2020). The metabolism of paracetamol generates free radicals and both methionine and acetylcysteine have antioxidant qualities (Bateman and Dear 2019). However, within clinical toxicology literature there is little evidence to support methionine as a treatment option. Park et al. (2015)

proposed that there is the possibility that methionine reduces the risk of liver damage and mortality after paracetamol poisoning compared with supportive care, but the evidence is limited and inconclusive.

Acetylcysteine has been the first line treatment globally for paracetamol poisoning since the 1970s when it was shown to dramatically reduce mortality and potential of hepatotoxicity (Prescott et al. 1979). Acetylcysteine is the only antidote advised for paracetamol poisoning by both the BNF and the NPIS (BNF, 2020; NPIS TOXBASE,2020).). The Medicines and Healthcare products Regulatory Agency advises intravenous acetylcysteine is practically 100% effective in preventing liver injury if given within eight hours of overdose (Freeman 2014). Therefore, as Alice presented before eight hours and was clinically stable but at risk of hepatocellular injury with a significant plasma paracetamol concentration, the initial prescribing decision was to commence treatment with intravenous acetylcysteine.

Acetylcysteine Dosing & Regimens

Acetylcysteine may be administered intravenously using the dose calculated by Prescott et al. (1979) with a single standard dosage based on weight following a three-step regimen (Table 2). Following this treatment regimen blood tests are analysed for alanine aminotransferase (ALT) elevation indicating hepatocyte injury and international normalised ratio (INR) rise which may indicate impaired liver function. If required additional infusions with acetylcysteine are commenced if blood results indicate ongoing hepatic compromise (NPIS TOXBASE, 2020).

Although this regimen has been overwhelmingly successful globally and considered ‘standard’ treatment, the three-bag infusion course is complex, there is potential for miscalculation and there is a high incidence of side effects due to activated

histamine release (Hayes et al. 2008). Dose related vomiting and anaphylactoid reaction occur in up to 60% of patients in the initial treatment phase of the acetylcysteine regimen, which correspondingly leads to treatment interruption and refusal from 20% of patients (Sandilands et al. 2016).

As the severity of anaphylactoid symptoms appear related to higher concentrations of acetylcysteine and the complexities of the regimen, Chiew et al. (2018) reviewed alternative delivery of acetylcysteine compared with the three-bag regimen. Of the identified studies the most pertinent to UK clinical toxicology was the SNAP trial (Scottish and Newcastle Antiemetic Pre-treatment for paracetamol poisoning) (Bateman et al. 2014). This trial hypothesised that a 12 hour, two bag course could be designed as an alternative to the standard 20 hour 15 minutes three bag regimen, while providing the required 300mg/kg plasma concentrations for liver protection. Patients were eligible if they presented with a single acute paracetamol overdose requiring treatment with acetylcysteine as per UK guidelines (BNF 2020). Adopting the SNAP modified acetylcysteine regimen, the incidence of symptomatic adverse effects was significantly reduced compared to the standard three bag regimen (Bateman et al. 2014). In 2015 the SNAP regimen was adopted into clinical practice for all patients requiring treatment for paracetamol overdose presenting in Edinburgh. The safety and efficacy of both standard and SNAP regimens were audited within NPIS centres by comparing blood results for liver injury at ten hours, which showed that the 12 hour acetylcysteine regimen was both safe and effective (Pettie et al. 2019). Additionally, the SNAP regimen produced fewer adverse reactions and had comparable efficacy for preventing liver injury when compared to the original regimen. The shortened duration of therapy improved rates of adherence

to treatment. The SNAP regimen has now been approved by NPIS (2020) for national advice and has been adopted by many clinical areas globally.

Alice was prescribed acetylcysteine as per SNAP protocol, prepared in sodium chloride rather than dextrose as she was not hypoglycaemic, a symptom associated with evolving liver impairment. She did not suffer anaphylactoid reactions during the initial phase of treatment, however if she had, the infusion could have been paused and antihistamine administered if required alongside a bronchodilator if any evidence of bronchospasm (Table 1). It is essential that the infusion is restarted once the reaction settles and it may be beneficial to slow the rate of infusion by running the first bag over four hours with the second bag running at the usual rate.

Alice did not require extended treatment and was hospitalised for 18 hours in total. She made a full recovery with no long-term liver impairment or ongoing clinical issues. The clinical toxicology team works cohesively with the liaison psychiatry team ensuring all patients who have taken an intentional overdose with self-harm intent are cared for under a dual approach emphasising effective communication and shared learning. Alice was referred to the liaison team for ongoing support.

Conclusion

For a presentation of post single acute paracetamol overdose it is essential to clarify the history and timing of the event and obtain plasma paracetamol levels at appropriate time intervals in order to assess potential risk of liver injury. Within one hour of ingestion administration of activated charcoal can reduce paracetamol absorption and after four hours intravenous acetylcysteine is recommended to minimise toxic impact. The three-bag acetylcysteine regimen has been standard

practice but novel protocols including the SNAP regimen are now being adopted globally (Chiew et al. 2016). Monitoring of biomarkers of hepatocyte injury should guide further pharmacological management. Long-term health and well-being following intentional overdose requires interprofessional liaison to optimise both physical and mental health outcomes. This case study highlights the potential of the clinical toxicology advanced practitioner to provide holistic and timely management of the complete patient journey in this unique independent prescriber role.

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Table 1. Medications indicated in paracetamol poisoning.

Medication	Indication	Dose	Duration	Comments
Antiemetic	Nausea and/or vomiting.	Cyclizine 50 mg up to 3 times a day. Ondansetron 4 mg 8 hourly.	As clinically indicated.	May be early feature of overdose itself or reaction to acetylcysteine.
Antihistamine	Flushing, urticaria, angioedema.	Chlorphenamine 4 mg 4-6 hourly max 24 mg/day.	As clinically indicated.	Anaphylactoid adverse drug reaction to acetylcysteine.
Bronchodilators	Bronchospasm.	Salbutamol nebuliser 2.5- 5 mg up to 4 times daily.	As clinically indicated.	Anaphylactoid adverse drug reaction to acetylcysteine.
Activated charcoal	Paracetamol overdose.	50 g dose.	Single dose.	Presenting within 1 hour of ingestion of paracetamol.
0.9% Sodium chloride	Acetylcysteine infusion.	As per acetylcysteine regimen.	As per acetylcysteine regimen.	Solution for preparation of acetylcysteine infusion.
Glucose 5%	Acetylcysteine infusion with presenting hypoglycaemia.	As per acetylcysteine regimen.	As per acetylcysteine regimen.	

(BNF,2020; NPIS TOXBASE, 2020)

Table 2. Intravenous acetylcysteine dosing regimens

Regimen	1st infusion	2nd infusion	3rd infusion	Total duration	Extended infusion (blood test dependent)
Prescott regimen (Prescott et al. 1979)	150mg/kg over 15 minutes.	50mg/kg over 4 hours.	100mg/kg over 16 hours.	20 hours 15 minutes.	100mg/kg over 16 hours.
BNF (2020)	150mg/kg over 1 hour.	50mg/kg over 4 hours.	100mg/kg over 16 hours	21 hours.	100mg/kg over 16 hours.
SNAP regimen (NPIS 2020)	100mg/kg in 200mls over 2 hours.	200mg/kg in 1000mls over 10 hours.		12 hours.	200mg/kg over 10 hours.