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PARACETAMOL OVERDOSE CASES IN A POISON INFORMATION CENTRE: PATTERNS AND OUTCOMES

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Abstract

Paracetamol is the analgesic most often involved in poisoning calls to poison information centres, and it remains a leading cause of acute liver failure in several countries. This review summarises published poison-centre and hospital series on paracetamol overdose, with attention to who is exposed, how and why, how risk is assessed, and what outcomes follow treatment. Intentional ingestion by young adults and women predominates, staggered and late presentations carry more risk, and early acetylcysteine prevents most serious liver injury. Legislation limiting pack sizes appears to have reduced severe outcomes in the United Kingdom. Data quality, under-reporting and inconsistent definitions limit comparison between centres. The article is a review and reports no new case data.

1. INTRODUCTION

Few medicines are as familiar as paracetamol, and few cause as many emergency calls. It is sold without prescription in most countries, appears in dozens of combination products for colds, pain and sleep, and sits in nearly every household medicine cabinet. At the recommended dose it is remarkably safe. The margin between a therapeutic and a toxic dose is, however, narrower than most users imagine, and poison information centres in Europe, North America and Australasia consistently record it among the substances most often involved in calls about intentional and accidental ingestion [1, 2]. In some

countries it is also the commonest identified cause of acute liver failure [3, 4].

The hepatotoxicity of paracetamol was recognised in the 1960s after reports of liver necrosis in people who had taken large doses, and the following decades produced a detailed picture of the underlying biochemistry and an effective antidote [5, 6, 7]. Treatment protocols are now well established, and the role of the poison information centre has shifted from reporting that the drug is dangerous to advising clinicians on risk assessment in individual patients. Because these centres collect structured information on large numbers of calls, their data and the published series built from them offer a view of how overdose actually occurs outside clinical trials.

This article is a narrative review of that published evidence. It does not analyse the records of any particular centre and presents no new data, even though the title refers to cases handled in a poison information centre. The sections that follow cover how poison centre data are collected and what they can and cannot show, the patterns of exposure reported, the mechanism and risk assessment of toxicity, and the treatment outcomes recorded in large series. The final section sets out the limitations of the literature and some directions for research and for practice [8, 9, 10].

2. POISON INFORMATION CENTRES AND DATA SOURCES

Poison information centres provide telephone advice to the public and to health professionals about exposure to drugs, chemicals, plants and venoms. Operated usually by trained pharmacists, nurses or physicians with toxicologist back-up, they record the substance, the amount, the time since ingestion, the patient's age and sex, the circumstances and, where follow-up is obtained, the outcome. The World Health Organization has published guidance on how such centres should be organised and what information they should collect, which has helped harmonise practice in many countries [10]. Large national datasets, such as the American Association of Poison Control Centers' annual report, have grown out of this work [1].

Poison centre data have real strengths. They capture exposures that never reach hospital, including a very large number of unintentional ingestions by children and of accidental excess by adults, and they offer near real-time surveillance of emerging problems. Counts of paracetamol exposures reported to US poison centres have run into the hundreds of thousands each year, which dwarfs anything that single hospitals can provide [1, 2]. They are also valuable for describing product mix, because the formulations involved, from single-ingredient tablets to opioid combinations, can be recorded and compared across years.

The weaknesses are equally clear. Calls are voluntary, so the sample is not systematic. Information is often provided by a worried parent or a junior doctor and may be inaccurate, especially concerning the amount and timing of ingestion. Follow-up is incomplete, which means that outcomes are recorded for only a fraction of cases and that the more severe cases are over-represented among those followed [1, 2]. Definitions of what counts as a case, of what constitutes hepatotoxicity and of intentional versus unintentional exposure differ between centres. Comparison between published series should therefore be cautious and focus on broad patterns, not on the exact figures.

Hospital-based cohorts, liver failure registries and national mortality statistics complement poison centre data. The US Acute Liver Failure Study Group, for example, collected detailed clinical data on patients with severe liver injury and found paracetamol to be the leading identifiable cause, with a large share of cases attributable to unintentional or staggered ingestion rather than single suicidal overdose [3]. Such registries describe the tip of the iceberg, while poison centre records describe the base. Reading both together gives a more balanced view than either alone, and the more informative reviews do exactly that [4, 11].

3. PATTERNS OF EXPOSURE

In published series, the typical paracetamol overdose seen by poison centres is intentional and involves a young person, most often a

woman or girl in the teens or twenties, who ingests tablets impulsively after an interpersonal conflict. Hospital studies from the United Kingdom describe this pattern, with many patients having taken the drug in the setting of acute distress and often with alcohol [12, 13]. The ingestions are commonly of moderate amounts, but a few are very large. In many such patients, the tablets are taken without prolonged planning, a feature that has underpinned arguments for restricting easy access to large quantities [14, 15].

A second group comprises children, mostly under five years of age, who ingest liquid or chewable preparations. Poison centres field a large volume of calls for such exposures, but serious toxicity in young children is uncommon, partly because the amounts swallowed are usually small and partly because the metabolism of the drug in the young favours sulfation over the pathway that creates the toxic metabolite [1, 2]. Dosing errors by parents using measuring devices incorrectly, or giving two products containing paracetamol at once, are a different source of risk and are picked up by poison centre calls rather than by emergency visits.

A third group is often called therapeutic misadventure or repeated supratherapeutic ingestion. These are people, often with pain or fever, who take more than the advised daily dose over several days, or who take several products without realising that each contains paracetamol. Combination cold remedies and prescription opioid combinations are common culprits [2, 16]. The patients have no intent to self-harm, and when they present late with abnormal liver tests the diagnosis may be delayed. Series from liver units report that unintentional cases make up a surprisingly large share of paracetamol-related acute liver failure, and that they carry outcomes at least as poor as those after deliberate overdose [3, 11, 17].

Product mix has changed over the years, and poison centres have often been the first to notice. Prescription combinations of paracetamol with opioids such as codeine, dihydrocodeine or hydrocodone contribute to both intentional and unintentional cases, adding respiratory depression to hepatic risk and, in some patients, delaying gastric emptying so that absorption is prolonged [2, 16]. Modified-release paracetamol preparations pose a related difficulty, as the plasma concentration may peak later than the four-hour sample suggests. Calls about these products require the handler to ask exactly which tablet was taken, and not merely whether it contained paracetamol [8, 18].

Timing matters as much as the amount. Staggered overdose, in which tablets are taken over several hours or days instead of at a single time, makes standard nomogram interpretation unreliable, because the plasma concentration at four hours does not capture total exposure. A UK cohort of patients with paracetamol-induced hepatotoxicity found that staggered ingestion and a delay of more than a day to hospital presentation were each linked with worse outcomes, including more frequent need for renal replacement therapy and higher mortality [19]. Delayed presentation is also typical of unintentional cases, in which symptoms are vague and patients do not think of poisoning.

Selected features of exposure and outcome reported in the published series are set out in table 1, and the numbers of entries in each category are given in fig. 1. The balance of the evidence shows that the epidemiological entries are broad and consistent between countries, whereas treatment entries are anchored by a relatively small number of landmark studies, many of them from the 1970s and 1980s. Entries on pack size legislation come from a limited number of before-and-after analyses in the United Kingdom, which may not transfer to other regulatory systems.

Table 1: Selected published findings on paracetamol overdose relevant to poison centre practice

Topic	Reported finding	Ref.
Intentional overdose young adults	Impulsive ingestion in teenagers and young women is the commonest pattern in hospital series	[12, 13]
Unintentional excess combination products	Repeated supratherapeutic use accounts for a notable share of acute liver failure	[3, 11]

Topic	Reported finding	Ref.
Children accidental ingestion	Frequent calls but serious toxicity uncommon; dosing errors are a separate risk	[1, 2]
Staggered ingestion late presentation	Associated with worse outcomes and unreliable nomogram interpretation	[19]
Treatment nomogram four-hour line	Concentration above the line at four hours predicts severe injury if untreated	[20, 21]
UK treatment line revision 2012	Single 100 mg/L line increased numbers treated	[18, 22]
Acetylcysteine timing antidote	Treatment within eight to ten hours prevents most severe liver injury	[21, 23]
Infusion reactions anaphylactoid	Mostly in first bag; modified regimen reduced reactions in a trial	[24, 25]
Pack size limits UK legislation	Followed by reductions in severe outcomes and transplant activity	[14, 26]
Access restriction international comparison	Availability linked to use of paracetamol in self-poisoning	[13, 15]

4. TOXICITY AND RISK ASSESSMENT

At therapeutic doses most paracetamol is conjugated with glucuronic acid or sulfate and excreted in urine. A small fraction is oxidised by cytochrome P450 enzymes, chiefly CYP2E1, to N-acetyl-p-benzoquinone imine, a highly reactive electrophile that is rapidly neutralised by glutathione [6, 27]. In overdose the conjugation pathways saturate, more drug is channelled into oxidation and hepatic glutathione is depleted. The reactive metabolite then binds covalently to cellular proteins, particularly in mitochondria, triggering oxidative stress and necrosis of hepatocytes in the centrilobular region where enzyme activity is highest [6, 28]. This chain of events is the reason the antidote works at all, since it targets the very first step that goes wrong.

Clinical illness follows a recognisable course. In the first 24 hours patients have nausea, vomiting and malaise or may feel quite well, which is why the overdose may be dismissed. Liver enzymes begin to rise after 24 hours and peak at about three days, and in severe cases coagulopathy, encephalopathy, metabolic acidosis and renal failure develop [4, 16]. Patients who survive generally recover without chronic liver disease. The delay between ingestion and symptoms is the reason that risk assessment must be done on the basis of a blood concentration and time of ingestion, and not on how the patient looks when they first attend.

The Rumack-Matthew nomogram, introduced in the 1970s, plots the plasma paracetamol concentration against time after a single acute ingestion, and a concentration above a treatment line at four hours predicts a high chance of severe liver injury if untreated [20, 21]. Its derivation came from observation of untreated patients and it has been revised only slightly since. Different jurisdictions have used different treatment lines. In the United Kingdom, a single treatment line starting at 100 mg/L at four hours replaced a two-line system with a high-risk subgroup in 2012, which increased the number of patients treated and prompted debate about cost and adverse reactions [18, 22].

Further risk markers have been proposed, because the nomogram has well-known limits. It does not apply when the time of ingestion is unknown, in staggered overdose, or in patients who present more than 24 hours after ingestion. For these cases, clinicians combine the history with paracetamol concentration, alanine aminotransferase, prothrombin time or international normalised ratio, creatinine and lactate. Newer approaches to risk prediction include the paracetamol-to-aminotransferase multiplication product and biomarkers such as microRNA-122 and keratin-18, which were being assessed in research settings but are not yet routine [29, 30]. Guidelines advise a low threshold for treating anyone about whom there is doubt [8, 9].

Co-ingested drugs change both the kinetics and the clinical picture. Opioids, anticholinergic agents and tricyclic antidepressants slow gastric emptying, so absorption of paracetamol may continue well beyond the usual window and a single early concentration can underestimate eventual exposure. Guidelines therefore advise a repeat sample at four hours or later after co-ingestion with such agents, in order to detect a rising concentration [8, 18]. Mixed

overdoses are common in poison centre series, and the paracetamol component can be overlooked when the patient is drowsy or when attention is focused on a more dramatic co-ingestant, which is one reason that many centres test routinely for paracetamol and salicylate in any unexplained overdose [9, 31].

Several host factors are said to increase susceptibility. Chronic alcohol use induces CYP2E1 and may deplete glutathione, malnutrition and fasting reduce glutathione stores, and drugs that induce cytochrome P450 enzymes, such as carbamazepine, phenytoin and rifampicin, have been implicated. The evidence for each is mixed, and for alcohol in particular, large studies have not shown a clear rise in the risk of hepatotoxicity after acute overdose, though case reports and series of repeated supratherapeutic use describe injury at doses near the recommended maximum [16, 17]. Most guidelines nevertheless advise a lower treatment threshold in patients with such risk factors [8, 18].

5. TREATMENT AND OUTCOMES

Telephone triage is one of the main tasks of the poison centre, and paracetamol is a good test of how well it works. Out-of-hospital guidelines set amounts, below which patients can be reassured at home, and a set of circumstances in which referral to an emergency department is needed whatever the stated dose, including intentional ingestion, unreliable history, symptoms and ingestion of large amounts [8]. Using such rules, centres can safely keep a large proportion of callers out of hospital, mainly children with small accidental ingestions. The success of this approach depends on calibrated advice and on call-handlers asking about co-ingestants, timing and intent, in that order.

Acetylcysteine is the antidote of choice, and it is thought to work by replenishing glutathione, by conjugating the reactive metabolite directly and by improving mitochondrial function and microcirculation. Early evidence that intravenous acetylcysteine could protect against liver damage came from UK work in the late 1970s, and a large series from the United States showed that oral treatment begun within eight to ten hours of ingestion reduced severe hepatotoxicity to a small minority [21, 32]. The 72-hour oral regimen was later evaluated in a national US study, and review articles agree that benefit declines as treatment is delayed, though it persists in late presenters [23, 31].

Activated charcoal may be given if the patient presents within about an hour of a large ingestion and the airway is protected, but its value has not been confirmed in randomised trials and it is recommended for selected cases. Gastric lavage and induced emesis are no longer advised [8, 9]. Because most patients present after the period in which gut decontamination makes sense, the main decision at the first assessment is whether to start acetylcysteine at once or after a timed paracetamol level. Guidelines recommend treatment without waiting for the result if presentation is later than eight hours and the amount ingested was potentially toxic [8, 18].

Adverse reactions to intravenous acetylcysteine are common enough to matter. They are anaphylactoid rather than allergic, consist of flushing, rash, bronchospasm or hypotension, and appear mostly during the first infusion bag, where the drug is given at a high rate [25]. Reaction rates are higher in patients with low plasma paracetamol concentrations and in those with a history of atopy or asthma. A randomised trial in the UK showed that a shorter, modified regimen with a slower initial infusion and pre-treatment with an antiemetic reduced the number of vomiting and anaphylactoid events, an important point since the lower treatment threshold means more patients are exposed [24].

A small number of patients develop acute liver failure despite treatment, usually because they presented late or took very large amounts. They are managed in specialist units, where acetylcysteine may be continued, and where criteria such as arterial pH, lactate, creatinine, prothrombin time and encephalopathy grade guide the decision to list for liver transplantation [3, 4]. Spontaneous survival after paracetamol-induced liver failure is better than after most other causes, which has to be

balanced against the risks of transplantation. Early outcome studies reported mortality in untreated severe cases of a few per cent to far higher, and modern series of treated patients show markedly lower figures [11, 21].

Overall outcomes recorded by poison centres are favourable. Most exposures are minor or lead to no toxicity, and among patients who receive treatment promptly, the great majority recover without liver injury [1, 30]. Deaths are rare relative to the number of calls, and they cluster in late presenters, in massive ingestions and in patients with co-ingestants such as opioids. Systematic review of interventions for paracetamol overdose, however, found that most trials of acetylcysteine were small and at risk of bias, meaning that the strongest evidence for its effectiveness is observational and historical [30, 31].

Psychiatric assessment is a part of management that is sometimes left out of discussions about toxicology. A substantial share of patients presenting with intentional paracetamol overdose have depressive illness, substance use or acute life stress, and repeated self-poisoning is common. Reports from the UK suggest that hospital staff may need to balance the medical need for rapid treatment against the patient's wish to leave, and that mental health assessment must wait until medical stability but should not be skipped [12, 13]. Poison centres can help by reminding callers that medical clearance is not the same as psychiatric clearance and by encouraging referral.

6. LIMITATIONS AND FUTURE DIRECTIONS

The published literature on paracetamol overdose has strengths, but it has gaps. Many series are from the United Kingdom, the United States and Australia, and data from low- and middle-income countries, where paracetamol use and regulation differ, are sparse. Studies differ in how they define intentional and unintentional exposure, and the proportion with complete follow-up is often low. Because poison centres respond to calls rather than recruit patients, the sample can neither be assumed to represent all overdoses nor used to estimate incidence in the community [1, 2, 10]. Standardised reporting would remove some of this noise.

Questions for research include the optimal treatment regimen, in particular the dose and duration of acetylcysteine and the best approach to patients with very high concentrations or large staggered ingestions; the usefulness of novel biomarkers to identify patients who will not need a full course; and methods to minimise adverse reactions to infusions [24, 29]. Large prospective studies using standard definitions would also help, as would linkage of poison centre records with hospital and mortality data to measure outcomes without relying on telephone follow-up. The cost-effectiveness of the more inclusive UK treatment line remains debated [18, 22].

For practice, the main messages are straightforward. Pharmacists and call-handlers can reinforce the importance of checking labels for paracetamol content, of using the measuring device supplied with liquids, and of keeping medicines out of reach of children. Because patients with staggered or late ingestion are at greater risk, a poison centre should ask carefully about timing, and refer when in doubt [8, 19]. Policy measures that limit access to large quantities have supporting evidence and deserve continued attention, together with broader efforts to improve access to mental health care for people at risk of self-harm [13, 15, 26].

7. CONCLUSION

Published poison-centre and hospital series paint a consistent picture of paracetamol overdose. Intentional ingestion by young people is the commonest scenario, young children generate many calls with few serious outcomes, and unintentional repeated excess produces a smaller but more dangerous group, often identified late [3, 12, 19]. Risk assessment relies on a timed plasma concentration and the nomogram, with extra caution when timing is uncertain, and acetylcysteine given early prevents most serious liver injury [20, 21, 23]. Limits on pack size have the best supporting evidence among preventive measures [14, 26].

The evidence is shaped by the way it is collected. Poison centre data are broad but

incomplete, and many of the treatment findings come from older studies whose methods would be hard to repeat today [1, 30]. Better definitions, linked follow-up, evidence on regimens that reduce infusion reactions and the use of new biomarkers are the main areas for progress [24, 29]. In the meantime, careful history taking, prompt treatment of doubtful cases and attention to the patient's mental health remain the practical priorities for pharmacists and clinicians [8, 9].

8. ABBREVIATIONS

ALT-Alanine aminotransferase, CYP-Cytochrome P450, INR-International normalised ratio, NAC-N-acetylcysteine (acetylcysteine), NAPQI-N-acetyl-p-benzoquinone imine, OTC-Over the counter, PIC-Poison information centre, WHO-World Health Organization, NPDS-National Poison Data System

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10. AUTHORS CONTRIBUTIONS

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11. CONFLICT OF INTERESTS

Declared none

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