PARACETAMOL POISONING: CAN IT BE PREVENTED?

E. Norman, Medical Student, R. Dhairiwan, Medical Student, United Medical and Dental School of Guy's and St Thomas', London; P.I. Dargan, Registrar in Medical Toxicology, C. Wallace, Registrar in Medical Toxicology and A.L. Jones, Consultant Physician and Clinical Toxicologist, National Poisons Information Service, Guy's and St Thomas' NHS Trust, London

INTRODUCTION

Paracetamol first became available in the United Kingdom as an over-the-counter medicine in 1963 and is currently used by approximately 30 million people annually in the UK.[1] It is available for use in a range of forms as powders, capsules and tablets.

PARACETAMOL IS SAFE IN THERAPEUTIC USE

Whilst paracetamol can be given in therapeutic dose to just about every patient, aspirin and ibuprofen are unsuitable for people predisposed to gastric ulcers and asthma.[2-4] There is considerable controversy about whether a recent study predicts an increase in asthma after use of paracetamol: this study has a number of limitations including small odds ratios, a biologically implausible hypothesis and failure to exclude confounding factors such as non-steroidal drug use.[5, 6]

HOW LARGE IS THE PROBLEM OF PARACETAMOL OVERDOSE IN THE UK?

Each year, approximately 30,000–40,000 cases of paracetamol overdose present to Accident and Emergency departments across England and Wales, and it accounts for up to 48% of hospital admissions for self-poisoning.[7] The majority of these people suffer no long-term ill-effects, and only approximately 10% require treatment with its antidote.[8]

In the early 1990s, 200–300 deaths occurred every year from paracetamol poisoning in the UK.[9] This is less than 1% of the total number of reported overdoses in the UK each year, a fraction of the reported deaths for other commonly used prescribed drugs such as tricyclic antidepressants.[10]

HOW HAS PARACETAMOL GAINED A REPUTATION FOR BEING SO DANGEROUS?

There have, in the past, been calls to make paracetamol less widely available because it is 'so dangerous'. The media often emphasise factors that may be important in assessing the risk from an overdose, for example alcohol consumption, and extrapolate these to the general population; this information which may be true for people with complications, may be applied to the everyday situation. In addition, cases of bad outcome, for example the requirement for liver transplantation, may be overemphasised or not put into context of paracetamol poisoning in general.

It is also unfortunate that formerly, when overdoses proved fatal, paracetamol found in whatever quantity had been wrongly recorded as being the cause of death.[9] It is also all too easy for those working in Accident and Emergency departments to form unfavourable opinions of paracetamol because they tend to see more overdoses of this than of any other drug.

HOW DANGEROUS ARE OVERDOSES OF OTHER ANALGESICS?

A serious overdose of aspirin (well over 300 mg/kg body weight), resulting in a plasma concentration of over 700 mg/L, is fatal in 5% of cases.[11] Overdose with non-steroidal drugs usually causes little more than gastro-intestinal upset. However, large ingestions can cause seizures, hypotension, coma, metabolic acidosis and renal failure; seizures occur in 30% of cases of mefenamic acid overdoses.[12]

HOW MUCH DO PARACETAMOL OVERDOSES COST THE NHS EACH YEAR?

A blood test to establish the level of paracetamol in the blood costs approximately £1 per sample in a standard clinical chemistry laboratory. If an antidote is necessary, N-acetylcysteine costs approximately £20 per patient (more if infusions of more than 20 hours are used). An overnight stay in hospital costs approximately £250. Therefore, treatment of 30,000 overdoses of whom 10% need antidotal treatment,[8] and perhaps half of whom also require admission annually, comes to a substantial cost. In addition, about £100,000 is spent on liver transplantation for paracetamol-induced liver failure each year, with ongoing costs of immunosuppression, medical review and possible re-transplantation.[32]

POTENTIAL METHODS OF PREVENTING PARACETAMOL OVERDOSE

The adage that 'prevention is better than cure' would seem particularly cogent in paracetamol overdosage, especially when taking into account the costs, both economic (to the NHS) and emotional (to the patient and their family) of the treatment.

Addition of methionine to every paracetamol tablet

Methionine is an essential amino acid present in dietary meat (approximately 2 g per day) and it has been co-formulated with some paracetamol tablets in the UK (formerly Pameton, with 300 mg methionine in each tablet, SmithKline Beecham and currently Paradote, with 100 mg methionine in each tablet, Penn Pharmaceuticals). The advantage of such a combination tablet is that methionine is a substrate for glutathione synthesis. Therefore, in the event of a paracetamol overdose, it acts as an antidote and the levels of glutathione would be expected to be high enough to prevent significant tissue damage from occurring.[13] However, potential safety issues concerning methionine supplementation have been identified (Table 1).[14] A recent study shows that moderate methionine loading at the amount present in combination paracetamol/methionine tablets may not in fact raise homocysteine levels significantly, for cardiovascular problems to occur.[24] At high doses, methionine causes nausea, headache, vomiting, drowsiness, and irritability.[14]

TABLE 1
Potential risks of methionine.

Risk Group	Reason	Reference
Pregnant women	Methionine is metabolised to homocysteine and raised plasma homocysteine is associated with birth defects, pre-eclampsia, spontaneous abortion and placental abruption.	15, 16
Schizophrenic patients	Schizophrenic patients given 10–20 g methionine daily developed functional psychoses.	17
Patients with pre-existing cancer	Animal studies have shown that restriction of methionine intake blocks division and metastasis of tumour cells.	18, 19
Ischaemic heart disease (IHD), peripheral vascular disease (PVD), stroke	Methionine is metabolised to homocysteine – raised homocysteine levels are associated with IHD, PVD and stroke.	20–22
Patients with chronic liver disease	The liver has an impaired ability to metabolise methionine.	23

To be effective in prevention of paracetamol overdoses, the combination tablet would have to be the only preparation of paracetamol sold or prescribed. As its only benefit is in the overdose situation, the question arises of whether it is ethical to add a chemical, which would only be advantageous to a minority (who take paracetamol overdoses), to a substance that is used by millions of people. This becomes a much more difficult issue when the safety of regular methionine intake is unproven.[14] In addition methionine has a fishy taste, making the combination tablet unpalatable to many and the combination product would be eight times more expensive than just paracetamol alone.[25]

Taking the above factors into account, it would seem that, whilst in theory the combination tablet would be a good idea in preventing death and hepatotoxicity from overdose, in practice its current drawbacks may outweigh its benefits.

Warnings on packs of paracetamol

The Medicines Control Agency has asked that the following warning be put on paracetamol packaging to reduce the mortality rate from overdose: 'Immediate medical advice should be sought in the event of an overdose, even if you feel well.' This is sensible as it has been clearly shown that time between taking an overdose and receiving NAC affects outcome, and there are few symptoms in the early stages of overdose.[26] However, if the individual was intent on self-harm such a warning would clearly not assist much. It also sadly does not help those who cannot read or those with English language difficulties.

The message 'Do not take with any other paracetamol containing products' is already being used by some manufacturers on paracetamol packaging, but its rationale is to aid compliance with the recommended dosage and to prevent accidental overdose.

Such warnings are unlikely to have much of an impact in preventing overdose, as the vast majority of paracetamol overdose cases are intentional or impulsive, rather than accidental.[27] However, they are still worth including.

Reducing paracetamol pack size

At the moment the packet sizes of paracetamol that one should be able to obtain in the UK are:

- 16–24 from supermarkets, corner shops;
- 24–36 from a pharmacy;
- Up to 100 from a pharmacy for a chronic condition;
- >100 from a pharmacy by prescription.

Larger paracetamol overdoses have been related to larger package sizes,[27] so it would seem sensible to limit package sizes available. This approach is clearly aimed at people who take an overdose on impulse, and if only small packets of paracetamol were available at the time, the theory is that the overdose would not be so severe. However, when we posed as patients with knee pain, problems of compliance with such restrictions were demonstrated in shops in the London area (Table 2). It is also possible to buy large quantities from dispensers which do not limit the amount sold, and these are installed in such places as the Royal College of Physicians and certain conference centres, such as that in Edinburgh!

Even if there were compliance with the restricted sales of paracetamol, individuals seriously intending to commit suicide would not be deterred, as they would simply buy more packets from multiple sources. It is too early to firmly establish whether the reduction in packaging of paracetamol has had any impact on poisoning with this drug but early studies are not surprisingly conflicting.[28, 29]

TABLE 2
Paracetamol purchased in 1999.*

Sources in London	Number of paracetamol tablets sold together to one of the authors
Supermarket	48; 48; 64; 48
Pharmacy	48; 48; 48; 64; 48
Corner shop/Newsagents	48; 48; 64; 48

**Regulations on pack size and supply came into effect from September 1998*

Removal of paracetamol from the market

Is it ethical to ban a drug of therapeutic benefit to many in order to protect a much smaller number of people who overdose with it? In addition, banning paracetamol would be very hard to enforce, as it would make it even more desirable and might lead to hoarding of large amounts and the creation of yet another product for the illegal black market.

Removal would also be anticipated to lead to an increase in use of other analgesics, such as aspirin and nonsteroidal anti-inflammatory agents that have side-effects

in therapeutic doses and significant toxicity in overdose, as discussed above.

Making paracetamol a prescription-only medicine
Paracetamol could be made available only on prescription, therefore preventing people from obtaining large amounts of it when it is not needed. However, this would greatly increase the workload of general practitioners by at least 30 million scripts per year. Alternatively it could be made obtainable from pharmacists only, but it would be very difficult for the pharmacist to determine whether an individual wanted the paracetamol for a genuine complaint or intended self-harm, and from our data (Table 2) this would not necessarily limit the amount supplied.

Reducing publicity about the drug
In Australia, a country with approximately half the population of the UK, paracetamol is just as readily available, but the overdose rate and number of severe liver problems resulting from the drug are much lower.[30] Reasons for this might include less publicity about the drug in overdose, or earlier presentation of overdoses. Certainly, evidence to date points to the difference being culturally determined in some way.[33] Perhaps less publicity about fatal overdoses and any toxic side-effects may make paracetamol appear to be a drug less suitable for overdoses. There is certainly evidence that depicting overdoses on television leads to increased overdose incidence with that substance afterwards.[31]

Addition of an emetic or bittering agent
An emetic when added to paracetamol in small amounts would not have much effect, but if many tablets were taken the individual would vomit. The amount that would need to be put into tablets would have to be sufficient to make the patient vomit before sufficient paracetamol had been absorbed to cause damage. It might conceivably also help prevent accidental overdosage as it would give a warning signal to alert the patient of a potential problem at an early stage when antidotal therapy is still effective. Alternatively a bittering agent such as Bitrex® would cause the tablet to taste unpleasant, therefore deterring people from taking large amounts.

Neither of these measures would be expected to be widely welcomed by the pharmaceutical industry, which might reasonably fear falling sales of their product. Both techniques have their advantages, but once again the question of whether it is fair to penalise people who are not abusing the drug, to protect those who are, is raised.

CONCLUSIONS

Paracetamol is taken by approximately 30 million people each year in the UK and less than 1% of those taking the drug attend hospital with paracetamol overdose, the vast majority of those having no sequelae. Sadly, however, up to 300 patients die every year after paracetamol overdose with acute liver failure, usually those presenting late. The vast majority of people who take overdoses do so on purpose, either as a suicide attempt or a 'cry for help'.

If paracetamol availability were to be limited, other analgesics, which have potential for toxicity in therapeutic dose and overdose, would be used. Restriction of pack size is not being enforced from our data and evidence to date is contradictory about effectiveness of such a policy. The result is that paracetamol remains widely available in the UK, in large quantities. Whilst a number of options to reduce paracetamol overdose deaths have been considered, few are practical. Reduced publicity and addition of a substance to reduce toxicity are potential ways forward.

ACKNOWLEDGMENT

This work was undertaken as an undergraduate special study module, funded by the United Medical and Dental Schools of Guy's and St Thomas' and National Poisons Information Service (London). We are grateful for the contributions to discussions about this work made by Dr M. Tredger, King's College Hospital London, Dr B. Robinson, UMDS and Dr G. Brandon, Paracetamol Information Centre, London.

CONFLICT OF INTEREST

A.L. Jones has acted as adviser to Oxford Pharmaceuticals, SmithKline Beecham, Cumberland Pharmaceuticals and Astra-Zeneca Novartis. All other authors have no conflict of interest to declare. The NPIS receives support for educational activity from Oxford Pharmaceuticals Ltd.

REFERENCES

1 Paracetamol Usage Study, Paracetamol Information Centre, London: 1993.
2 Hirschowitz BI, Lanas A. Intractable upper gastrointestinal ulceration due to aspirin in patients who have undergone surgery for peptic ulcer. *Gastroenterology* 1998; **114(5):**883-92.
3 Sturtevant J. NSAID-induced bronchospasm – a common and serious problem. A report from MEDSAFE. *NZ Dent J* 1999; **95(421):**84.
4 Szczeklik A. Adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. *Ann Allergy* 1987; **59(5):**113-8.
5 Shaheen SO, Sterne JAC, Songhurst CE *et al*. Frequent paracetamol use and asthma in adults. *Thorax* 2000; **55:**266-70.
6 Shin G-Y, Dargan P, Jones AL. Paracetamol and asthma. *Thorax* 2000; **55:**882.
7 Hawton K, Fagg J. Trends in deliberate self poisoning and self-injury in Oxford, 1976–1980. *BMJ* 1992; **304(6839):**1409-11.
8 Thomas SHL, Horner JE, Chew K *et al*. Paracetamol poisoning in the North East of England: presentation, early management and outcome. *Hum Exp Toxicol* 1997;**16:**495-500.
9 Spooner JB, Harvey JG. Paracetamol overdosage – facts not misconceptions. *Pharmaceutical Journal* 1993; **250:**706-7.
10 Henry JA, Alexander CA. Relative toxicity from anti-depressants in overdose. *BMJ* 1995; **28(3):**221-4.
11 Chapman BJ, Proudfoot AT. Adult salicylate poisoning: deaths and outcome in patients with high plasma salicylate concentration. *QJM* 1988; **268:**699-707.
12 Smolinske SC, Hall AH, Vandenberg SA *et al*. Toxic effects on nonsteroidal anti-inflammatory agents in overdose. An overview of recent evidence on clinical effects and dose-response relationships. *Drug Saf* 1990; **5(4):**252-74.
13 Crome P, Vale JA, Volans GN *et al*. Oral methionine in the treatment of severe paracetamol (acetaminophen) overdose. *Lancet* 1976; **2:**829-30.
14 Jones AL, Hayes PC, Proudfoot AT *et al*. Should methionine be added to every paracetamol tablet? *BMJ* 1997; **315:**301-3.
15 Ray JG, Laskin CA. Folic acid and homocysteine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss. *Placenta* 1999; **20(7):**519-29.
16 Wong WY, Eskes TK; Kuijpers-Jagtman AM *et al*. Nonsyndromic orofacial clefts: association with maternal hyperhomocysteinaemia. *Teratology* 1999; **60(5):**253-7.
17 Cohen SM, Nichols A, Wyatt R *et al*. The administration of methionine to chronic schizophrenic patients: a review of ten studies. *Biol Psychiatry* 1974; **8:**209-25.

[18] Breillout F, Hadida F; Echinard-Garin P *et al*. Decreased rat rhabdomyosarcoma pulmonary metastases in response to low methionine diet. *Anticancer Res* 1986; **76:**629-39.
[19] Guo H, Lishko VK; Herrerd H *et al.* Therapeutic tumour specific cell cycle block induced by methionine starvation *in vivo*. *Cancer Res* 1993; **53:**5676-9.
[20] Arnesen E, Refsum H *et al*. The Tromsö study: a population based prospective study of serum total homocysteine and coronary heart disease. *Int J Epidemiol* 1995; **346:**1395-8.
[21] Perry IJ, Refsum H; Morris RW *et al*. Prospective study of serum total homocysteine concentrations and risk of stroke in middle-aged British men. *Lancet* 1995; **346:**1395-8.
[22] Stampfer MJ, Malinow R. Can lowering homocysteine levels reduce cardiovascular risk? *N Engl J Med* 1995; **332:**328-9.
[23] Morgan MY, Marshall AW, Milsom JP *et al*. Plasma amino-acid patterns in liver disease. *Gut* 1982; **23(5):**362-70.
[24] McAuley DF, Hanratty CG, McGurk C *et al*. Effect of methionine supplementation on endothelial function, plasma homocysteine and lipid peroxidation. *Clin Tox* 1999; **37(4):** 435-40.
[25] Krenzelok EP. Controversies in management: should methionine be added to every paracetamol tablet? Yes: but perhaps only in developing countries. *BMJ* 1997; **315:**303-4.
[26] Prescott LF, Illingworth RN, Critchley JAJH *et al*. Intravenous N-Acetylcysteine: the treatment of choice for paracetamol poisoning. *BMJ* 1979; **2:**1079-100.
[27] Hawton K, Ware C, Mistry H *et al*. Why patients chose paracetamol for self poisoning and their knowledge of its dangers. *BMJ* 1995; **310:**164-8.
[28] Robinson D, Johnston GD, Smith AMJ. The effect of limiting the availability of paracetamol on overdose severity. *Clin Tox* 2000; **38:** 250-1. [abstract]
[29] Donoghue E, Tracey JA. Restrictions on the sale of paracetamol in Ireland had no impact on the number of tablets ingested in acute deliberate overdose. *Clin Tox* 2000; **38:**251. [abstract]
[30] Gow PJ, Smallwood RA, Angus PW. Paracetamol overdosage in a liver transplant centre: an 8-year experience. *J Gastroenterol Hepatol* 1990;**14(8):**817-21.
[31] Veysey MJ, Kamanyire R, Volans GN. Effects of drug overdose in television drama on presentations from self poisoning. Antifreeze poisonings give more insight into copycat behaviour. *BMJ* 1999; **319:**1131.
[32] R Bates, Scottish Liver Transplant Unit, Personal Communication.
[33] Dr I Whyte, Newcastle, Australia, Personal Communication.