Restricting paracetamol in the United Kingdom to reduce poisoning: a systematic review

Oliver Morgan and Azeem Majeed

Abstract

Background Paracetamol poisoning is implicated in about 150–200 poisoning deaths per year in England and Wales. We review previous studies assessing the effectiveness of regulations introduced in 1998 to restrict sales of paracetamol and reduce paracetamol poisoning.

Methods We searched the following electronic databases: MEDLINE, EMBASE, CINHAL, HIMIC, COCH, APC, CENTRAL and DARE. English language publications between 1998 and 2003 were included. Studies were included if they took place in the United Kingdom and assessed changes in any aspect of paracetamol poisoning following the introduction of the 1998 regulations.

Results Twelve studies were identified, which examined several different outcomes. Three studies examined admissions to liver transplant units; all reported reductions. Eight studies evaluated severity of paracetamol poisoning; three reported reductions but five did not. Five out of six studies reported reductions in hospital admissions. One study reported reduced mortality in England and Wales after 1 year while another found no difference in Scotland 2 years after the regulations were introduced. Two studies observed a significant reduction in over-the-counter sales. Studies suffered from several limitations including short follow-up periods, no case definition for paracetamol poisoning and lack of comparison groups.

Conclusions The limitations of these studies makes it difficult to draw firm conclusions. They do, however, suggest that the 1998 regulations may have been associated with reduced admissions to liver units and liver transplants, reduced hospital attendance due to paracetamol poisoning and reduced sales of paracetamol. Further research is needed to fully evaluate the impact of the 1998 regulations. In the future, formal evaluation of the impact of similar interventions should be an integral part of policy formation.

Keywords: paracetamol, poisoning, drug regulations

Introduction

Paracetamol poisoning has been increasing since the 1970s. Between 1993 and 2000 paracetamol was detected in approximately 150–200 deaths per year in England and Wales. Paracetamol poisoning has been closely linked to its availability. A study of 80 patients admitted to the John Radcliffe Hospital in Oxford following an overdose reported availability as the main reason for taking paracetamol, with patients using loose preparations (i.e. from a bottle) more likely to take a larger number of tablets. In another study, Gunnell et al. reported that fatality rates from paracetamol poisoning were four times higher in the United Kingdom compared to France (0.4 versus 0.1 per cent), where legislation limits packets of paracetamol to 8 g.

To reduce harm and death from paracetamol poisoning, the Medicines Control Agency (MCA) introduced legislation in 1998 to limit the availability of paracetamol. The regulations limited sales at general outlets to a maximum of 16 tablets of 500 mg (8 g total). Packets containing 32 tablets (16 g) can be sold at pharmacies and up to 100 tablets can be sold at the discretion of a pharmacist. Larger quantities can be issued on prescription only. Specific warnings of the dangers of paracetamol are printed on the packets and on leaflets in the packets. At the same time, most paracetamol tablets were made available for sale only in blister packs.

Although there has been no formal evaluation of this intervention, several independent studies examining its impact have been published. Here, we review these studies and make recommendations for future research.

Methods

Search strategy

Criteria for selection

English language publications between 1998 and 2003 were included. Studies were included if they took place in the United Kingdom and assessed changes in any aspect of paracetamol poisoning due to the 1998 regulations.

Results

One hundred and sixty five publications were identified. One hundred and five studies did not consider use of paracetamol in overdose, 27 studied aspects of paracetamol poisoning not related to the 1998 regulations, 24 were letters or comments on other papers and two considered regulations in countries outside the United Kingdom (Australia and Ireland). Nine studies met the inclusion criteria,9–16 of which one was a conference abstract17 (Table 1). Three additional studies were recommended for inclusion by the referee.18–20

All studies were observational, reporting outcomes before and after the 1998 regulations. For all but one study, the follow-up period after the regulations was short, typically 1–2 years. Seven studies were conducted (wholly or partly) at a local level9,11,14–17,20 and only three compared results for paracetamol with other drugs.10,12,13 Several different outcomes were studied; three considered admissions to liver transplant units;9,11,15 eight evaluated severity of paracetamol poisoning;11,14–17,20 six studied hospital admissions;9–11,14,16,20 three reported trends in mortality;10–12 and two studies compared over-the-counter (OTC) sales of paracetamol.11–13

Liver units

Prince reported a reduction in the median monthly number of referrals to the Freeman liver unit from 2.5 (inter-quartile range IQR 1–4) to 1 (IQR 0–2).15 There was also a reduction in the median monthly number of referrals to the UK Transplant Special Support Authority from 3.5 (IQR 2.25–5.00) to 2 (IQR 1–4). The number of admissions to five other liver units in England, assessed by Hawton, decreased by 30 per cent from 310 to 250 per year (31 per cent).9,12,13 In Scotland, Bateman found that hospital discharge rates due to paracetamol poisoning increased annually from 1995, peaking in 1997 at 118.9 and 160.2 per 100 000 for men and women, respectively.10

Discharge rates decreased in 1998 (8 per cent in men and 14 per cent in women compared to 1997) and in 1999 (18 per cent in men and 22 per cent in women compared to 1997). This was in contrast to discharges of antidepressant and opioid misuse poisoning, which continued to increase. In Birmingham, Hughes also observed a decrease in annual hospital admissions from 360 to 250 per year (31 per cent).9 Thomas reported a decrease in admissions for paracetamol poisoning to a general hospital in Pembrokeshire.20 As a proportion of all poisoning admissions paracetamol admissions fell from 45 (52/116) to 36 per cent (40/112). Only Robinson reported no change in the number of paracetamol poisoning cases presenting to hospitals in Belfast.16

Severity of poisoning

Prince observed no change in severity of poisoning (assessed by overdose size, substance taken or criteria for transplant) amongst referrals to the Freeman liver unit.15 In patients presenting at five hospitals in Belfast, Robinson reported a small reduction in the median quantity of paracetamol ingested from 10 to 8 g and a reduction in serum paracetamol concentrations at 4–6 h (37–27 mg/l).16 However, there was little change in the number of severe paracetamol poisonings (severity not defined) after introduction of the regulations. At Ninewells Hospital in Dundee, Sheen found little difference in the annual number of positive paracetamol assays or assays reporting potentially hepatotoxic poisonings (>1.3 mmol/l).17 Results from seven hospitals in England by Hawton found no difference in the mean highest blood paracetamol concentrations recorded and only a slight decrease in the mean number of tablets taken.11

There was, however, a decrease of 17 per cent in the number of patients taking more than 32 tablets. Data from the National Poisons Information Unit in Ireland reported by Donohoe showed 1044 calls for paracetamol poisoning in 1997 compared to 976 in 1998 (p > 0.1).18 There was no statistically significant difference in the number of cases taking more than 48 tablets. Laing analysed data from the National Poisons Information Service in Scotland and found no decrease in patients taking >8 g of paracetamol.19 However, there was a slight increase in the number of cases taking more than 16 g. Turvill observed a reduction in severity (measured by use of N-acetylcystine), with 64 per cent fewer severe paracetamol poisonings in the year following introduction of the 1998 regulations.14 Thomas also reported a reduction in severity (based on a small number of cases), with the proportion taking more than 16 tablets falling from 68 (n = 30) to 51 per cent (n = 18).20

Hospital attendance

Turvill reported a 21 per cent decrease in the number of patients presenting at the Royal Free Hospital, London due to paracetamol overdose.14 However, using benzodiazepine overdose as a comparison group may not have been appropriate as they are used as a drug of abuse and are only available on prescription. The number of presentations observed by Hawton also decreased by 11 per cent, although as a proportion of all cases of self-poisoning, there was no change.11 In Scotland, Bateman found that hospital discharge rates due to paracetamol poisoning increased annually from 1995, peaking in 1997 at 118.9 and 160.2 per 100 000 for men and women, respectively.10

Discharge rates decreased in 1998 (8 per cent in men and 14 per cent in women compared to 1997) and in 1999 (18 per cent in men and 22 per cent in women compared to 1997). This was in contrast to discharges of antidepressant and opioid misuse poisoning, which continued to increase. In Birmingham, Hughes also observed a decrease in annual hospital admissions from 360 to 250 per year (31 per cent).9 Thomas reported a decrease in admissions for paracetamol poisoning to a general hospital in Pembrokeshire.20 As a proportion of all poisoning admissions paracetamol admissions fell from 45 (52/116) to 36 per cent (40/112). Only Robinson reported no change in the number of paracetamol poisoning cases presenting to hospitals in Belfast.16

Mortality

In England and Wales, Hawton reported a decrease in deaths from paracetamol alone from an average of 194 deaths in the 24 months before the regulations to 147 in the 12 months afterwards (12 per cent reduction, 95 per cent CI 5 to 34).11 In contrast,
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<th>Author</th>
<th>Study period</th>
<th>Study setting</th>
<th>Outcomes</th>
<th>Results</th>
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<tr>
<td>Prince et al.</td>
<td>October 1995 to December 1999</td>
<td>Freeman Liver Unit, Newcastle-upon-Tyne, England, UK Transplant Special Support Authority (UKTSSA)</td>
<td>Referrals to the Freeman liver unit and national transplantation requests.</td>
<td>After September 1998, median monthly referrals to the Freeman decreased from 2.5 to 1 (p &lt; 0.02) and from 3.5 to 2.0 (p &lt; 0.02) to the UKTSSA. Overdose severity at the Freeman did not change.</td>
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<td>Turvill et al.</td>
<td>September 1995 to August 1999</td>
<td>Royal Free Hospital, London, England</td>
<td>Number of paracetamol versus benzodiazepine overdoses and severity of paracetamol poisoning.</td>
<td>Paracetamol poisoning reduced from about 100 to 80 per year post regulations. Severe poisoning reduced 64%. In contrast, there was no change in the frequency of benzodiazepine overdose.</td>
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<td>Robinson et al.</td>
<td>January to June 1998 and January to June 1999</td>
<td>Five general hospitals in Belfast, Northern Ireland</td>
<td>Presentations due to paracetamol poisoning. Estimated amount of paracetamol ingested, serum concentrations, INR, liver enzymes and NAC use.</td>
<td>Approximately 600 presentations before and after regulations. A small reduction in paracetamol ingested (10 g versus 8 g, p = 0.004) and serum concentrations (37–27 mg/l, p = 0.003) was observed. There was no difference for INR, liver enzymes or NAC use.</td>
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<td>Hawton et al.</td>
<td>September 1996 to September 1999</td>
<td>England and Wales (mortality). England (liver units). Seven hospitals in Bristol, Oxford and Manchester (presentations). UK (sales).</td>
<td>For paracetamol alone and salicylates. Mortality, referrals to liver units, admissions to hospital, biochemistry results and sales of paracetamol.</td>
<td>Deaths reduces from 234 to 147 per year (21%, p &lt; 0.04). Admissions to liver units decreased by 30%. Small decrease in hospital admissions, 17% decrease in overdose of &gt;32 tablets. About 40 000 million paracetamol tablets sold were sold before and after the regulations.</td>
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<tr>
<td>Sheen and Dillon</td>
<td>September 1995 to September 2000</td>
<td>Ninewells hospital, Dundee, Scotland</td>
<td>Acetaminophen biochemistry and cost of treatment.</td>
<td>About 375 positive and 27 toxic biochemistry results per year, with no change due to regulations.</td>
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<th>Outcomes</th>
<th>Results</th>
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<tr>
<td>Bateman et al.</td>
<td>1900–1999</td>
<td>Scotland</td>
<td>Hospital discharge rates and mortality for paracetamol, antidepressants and opiates.</td>
<td>Discharge rates per 100, decreased from 160 to 120 (male) and 120 to 100 (female) between 1997 and 1999. There was no change in paracetamol mortality.</td>
</tr>
<tr>
<td>Hughes et al.</td>
<td>April 1995 to January 2002</td>
<td>University Hospitals and Queen Elizabeth Hospitals, Birmingham, England</td>
<td>Admission to hospital and a tertiary liver unit due to paracetamol poisoning.</td>
<td>Hospital admissions reduced from an average of 360/year to 250/year following the 1998 regulations. Referrals to liver unit reduced from 76/year to 38/year.</td>
</tr>
<tr>
<td>Donohoe and Tracey</td>
<td>1997–1998</td>
<td>National Poisons Information Unit, Ireland</td>
<td>All cases of reported acute paracetamol overdose and number of tablets ingested.</td>
<td>There were 1044 cases reported in 1997 and 976 in 1998. No statistically significant difference in the number of tablets taken or the number of cases involving more than 48 tablets.</td>
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<tr>
<td>Laing et al.</td>
<td>1996–2000</td>
<td>National Poisons Informations Service, Scotland</td>
<td>Reported cases of paracetamol poisoning and amount ingested.</td>
<td>The proportion of enquiries for paracetamol fell slightly. The proportion of calls taking &gt;16 g increased slightly. The number of patients taking &gt;8 g changed little.</td>
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<tr>
<td>Thomas and Jowett</td>
<td>February to August 1998, February to August 1999</td>
<td>Withybush General Hospital, Pembrokeshire, UK</td>
<td>Number of patients admitted for paracetamol poisoning.</td>
<td>In the first 6 month period there were 52 cases, 30 took &gt;16 tablets. In the second 6 month period there were 40 cases, 18 took &gt;16 tablets. Non-paracetamol overdose increased from 64 to 72 cases.</td>
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Sheen found that between 1994 and 2000 there was an average of 28 deaths per year due to paracetamol poisoning in Scotland.\textsuperscript{12} Although the number decreased to 20 deaths per year in 1998 and 1999, it rose again to 31 deaths in 2000.

Sales

Data covering 97 per cent of sales of OTC paracetamol to manufacturers and wholesalers in the United Kingdom is collected by Intercontinental Medical Statistics. Both Hawton and Sheen reported this data in different ways.\textsuperscript{11,13} Hawton reported sales of packets of <100 tablets in the 12 months before and after regulations were implemented.\textsuperscript{11} The mean number of tablets per packet decreased from 32.6 to 24.2 while the number of packets increased from 1280 to 1614 million. The total number of tablets sold remained similar at about 40 million. Sheen reported sales of paracetamol (including packets of 100 tablets) for 1998–2000 and found that compared to 1998 levels, the mass of paracetamol sold was 48 per cent lower in 1999 and 41 per cent lower in 2000.\textsuperscript{13} The total number of packets increased in 1999 but reduced to 1998 levels in 2000. A similar pattern was observed for aspirin, which was subject to similar restrictions. Sales of ibuprofen by mass increased 174 per cent in 2000 compared to 1998.

Discussion

Main findings

The three studies of liver units all suggest that admissions and transplants decreased following the introduction of the 1998 regulations limiting the sale of paracetamol. Only Prince considered use of N-acetyl-cysteine (an antidote for paracetamol poisoning) as a possible explanation for this reduction, but found no change in the numbers receiving N-acetyl-cysteine. Furthermore, as there has been no significant change in treatment guidelines during this period, it is unlikely that this explains the decrease. Hospital attendance due to paracetamol poisoning also appears to have decreased, with five out of six studies reporting decreases ranging from 11 to 31 per cent. However, Bateman found that decreases in hospital discharge started in 1997, a year before the regulations were implemented, suggesting that the decrease might not be due to the 1998 regulations alone. Both studies of paracetamol sales analysed the same data in different ways and concluded that the amount of paracetamol sold decreased significantly. However, the subsequent rise in ibuprofen sales may be a cause for concern because of its association with gastrointestinal haemorrhage.\textsuperscript{13}

The evidence for mortality is conflicting; Sheen reported that the regulations had not reduced mortality in Scotland while Hawton reported a significant decrease in England and Wales. If England and Wales experienced a similar to increase in deaths as Scotland during 2000, the follow-up period in Hawton’s study would have been too short to observe this. The decrease reported by Hawton may therefore be artefactual rather than due to different effects of the 1998 regulations in these countries. Severity of poisoning does not appear to have changed in four studies. Robinson reported no change in severe poisonings while the small decrease in the amount of paracetamol ingested has limited clinical significance. Thomas reported a decrease in the proportion of patients admitted to a general hospital taking more than 16 tablets, although the number of patients was small. Only Turvill observed a reduction in the number of patients receiving N-acetyl-cysteine. However, this may reflect clinical practice rather than a real change in the use of paracetamol.

Study limitations

Due to the diverse outcomes studied, a quantitative synthesis was not possible. Most studies had very short follow-up periods, and it is unlikely that the 1998 regulations would have led to such rapid changes in the first few months after their introduction. One of the intentions of the regulations was to reduce paracetamol stocks in the household. Therefore, sufficient time for existing stocks to be used up would be required. Also, the conflicting conclusions from Hawton and Sheen about mortality reflect the problems of short-term follow-up. The regulations may have caused a reduction in mortality initially, but such gains may be lost over time. Similarly, such trends are lost with the ‘before and after’ analysis used by several studies; results may differ depending on which before and after time periods are selected for comparison. Further differences may occur when analysing data from just one or two hospitals, which are more likely to be subject to local or random variations.

Only three studies distinguished between poisoning due to paracetamol alone and due to paracetamol compounds.\textsuperscript{11,12,15} However, about two thirds of all paracetamol-related deaths and about 10 per cent of hospital presentations involve paracetamol compounds, many of which are not sold over the counter. Including all paracetamol-related deaths would therefore inflate the number of poisonings and possibly reduce any observed effect due to the regulations.

The optimum study design to assess the effect of the regulations would have been a randomized controlled trial.\textsuperscript{22} However, as this is not possible post-implementation, observational studies are required. These need to include a control or comparison group to assess whether observed changes are due to the intervention or some other factor. Only three studies included a comparison group: all of them reported differences in outcomes for paracetamol compared to the control group.\textsuperscript{10,13,14}

Non-UK studies

Two studies from countries outside the United Kingdom have also reported the effect of paracetamol availability. Ott \textit{et al.} found that overdose and mortality associated with paracetamol in Denmark did not appear to be associated with availability.\textsuperscript{23} Between 1984 (when paracetamol was made available OTC) and 1987, sales of paracetamol in Denmark doubled. During
the same period, there was a decrease in the rate of hospital admissions due to paracetamol overdose from 7.1 per million defined daily doses (DDD) to 5.0 per million DDD. Similarly, mortality from paracetamol overdose decreased from 0.14 deaths per million DDD in 1984 to 0.07 deaths per DDD in 1987.

In Australia, deliberate contamination of paracetamol-containing products in 2000 led to a product recall by manufacturers. Balit et al. studied the effect of reduced paracetamol availability on calls made to the New South Wales Poisons Information Centre and cases of poisoning presenting at the Hunter Area Toxicology Service. Compared to the same period over the previous 3 years, there was no difference in calls to the poisons information centre for deliberate self-poisoning with paracetamol or aspirin, but there was an increase in calls for ibuprofen (RR 1.86, 95 per centCI 1.41 to 2.44). For presentations to the toxicology service there was no significant difference for paracetamol or ibuprofen, but there was a large increase in presentations due to aspirin overdose (RR 3.33, 95 per centCI 0.97 to 11.4). The authors conclude “restriction of paracetamol-containing products may inadvertently increase poisoning with potentially more toxic agents”.

**Future research**

Toxicity following paracetamol poisoning takes many hours to develop, during which time an effective antidote can be administered. When the regulations were introduced, there was therefore considerable concern that individuals would instead take other more toxic drugs for which an antidote is not available. If this is indeed the case, the regulations may have increased harm and death from poisoning from other drugs. Future studies should therefore consider poisoning due to other drugs. Increased use of ibuprofen is of particular concern because it is associated with gastrointestinal haemorrhage. Future analysis should also consider whether there have been differential effects on intentional or unintentional poisoning as well as accidental poisoning, especially amongst children.

Adherence to the regulations is another area that needs investigation. There is anecdotal information to suggest that some retailers do not restrict the quantity of paracetamol sold. In a study in London, large quantities of paracetamol could be bought in all non-pharmacy outlets visited. Adherence to the regulations could be studied by ‘mystery shopping’ and using purchase information collected by supermarket award cards. To prevent regulations being breached, electronic cash registers could be programmed to automatically notify the cashier if large quantities of paracetamol are being purchased.

In 2003, a report by the National Audit Office criticized the Medicines Control Agency (now the Medicines and Healthcare products Regulatory Agency) for lacking a transparent decision making process. The objectives of the 1998 regulations restricting paracetamol and the evidence upon which they were based are still not in the public domain. Furthermore, no formal evaluation to assess the impact of the regulations was planned at the time the regulations were formulated. With moves to provide drugs such as statins without prescription, evaluating the public health impact of changes in the regulations about the sale of drugs should be considered by the Agency at the time of policy formation.

**Conclusions**

Current studies of the 1998 regulations on paracetamol suffer from several limitations including short follow-up periods, no case definition for paracetamol poisoning and lack of comparison groups. It is therefore difficult to draw firm conclusions from these studies. They do, however, suggest that the regulations may be associated with reduced admissions to liver units and liver transplants, reduced hospital attendance due to paracetamol poisoning and reduced sales of paracetamol. There is conflicting evidence for an association with reduced mortality and little evidence to support a reduction in the severity of poisoning. Further research is needed to fully evaluate the impact of the 1998 regulations. In the future, formal evaluation of the impact of similar interventions should be an integral part of policy formation.

Despite the introduction of nationwide legislation to restrict sales, paracetamol is still implicated in a large number of drug poisoning deaths. This suggests that restricting access to paracetamol is insufficient in itself. Future efforts to reduce overdose from paracetamol and other drugs should therefore be considered within a broader public health strategy.

**Acknowledgements**

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**References**


Sheen C, Dillon J. The effect on toxicity and healthcare costs on reducing the size of available acetaminophen pack sizes in the Tayside region of Scotland. Gastroenterology 2001; 120(Suppl. 1): A-228.


Appendix

paracetamol.mp
restrictS.mp

limit 1 to (human and english language and yr = 1998–2004)
limit 2 to (human and english language and yr = 1998–2004)
3 and 4
Acetaminophen/po [Poisoning]
Overdose/pc [Prevention & Control]
6 and 7
Analgesic, Non-Narcotic/po [Poisoning]
9 and 7
Liver Diseases/ci [chemically induced]
11 and 4
5 or 6 or 10 or 12