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Commentary

Pack size and paracetamol overdose: 16 years later

D. Nicholas Bateman

University of Edinburgh, Edinburgh, UK

In 1998 the United Kingdom limited the availability of paracetamol sold over-the-counter in an effort to reduce serious paracetamol overdose. Since that time debate has continued on the effectiveness of this policy in reducing what is acknowledged as a major public health problem. This commentary reviews recent publications on this topic which suggest that the effects were small. Reasons for this are discussed using data from recent work.

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In 1998 the UK Medicines and Healthcare products Regulatory Agency (MHRA) directed that pack sizes of paracetamol for sale in the UK without prescription be limited to 16 g (32 tablets) in pharmacies and 8 g (16 tablets) in other outlets, all tablets to be individually packaged in foil containers. This attempt to control severity of overdose by paracetamol has since been watched with interest around the world.

In response to an ongoing review by the US FDA in 2009, this journal published a commentary on the effect of this change, as perceived at that time, and reviewed the then-available evidence on the impact of pack sizes and overdose. The conclusion then drawn from the available evidence was that there was no conclusive data to support pack size change as a means of effective suicide prevention, and that while there was some evidence to suggest that slightly smaller overdoses were taken, this difference was likely to be toxicological insignificant.

Subsequent to the publication of the article the FDA published its advice, and interestingly no expert on the FDA group voted in favour of pack size restriction. Nevertheless those concerned about the toxicity of paracetamol overdose continue to advocate limitation of paracetamol pack size, or even removal of paracetamol from over-the-counter sale, as potential policy options. In this current article, evidence on this topic published over the past 5 years will be placed in context.

The key question of the best estimate of the efficacy of limitations to pack sizes is still to be determined. At its simplest level one would expect a measure that reduces the overall risk of toxicity from paracetamol to reduce the mortality from the drug. Although it would be ideal to do a complete analysis involving other aspects, including a complete analysis of drug sales, presentations with poisoning and severity of poisoning, the data for such analyses are not readily available. Because reduction in mortality is the driver for reduction in pack size, it seems a reasonable measure to examine, and while potentially confounded by better treatment of liver failure is still the easiest and likely optimum measure to take. This approach has been a key part of the argument put forward, in particular by Hawton and colleagues in the UK, that pack size limitation has a role. Essentially they examined mortality rates in the 5 years prior to the pack size change and suggest in the figure presented that rates of mortality were increasing prior to the introduction of pack size limitation, but fell afterwards. An analysis in which a stable pre-change baseline is assumed was presented, and suggested a downward trend in mortality after the change.

In their most recent article, published in the British Medical Journal in 2013 the same group suggest that this effect has continued to impact on mortality over the 15 years since pack size limits were introduced. This paper has been enthusiastically received by some, thus a commentary in Nature Reviews Gastroenterology & Hepatology highlighted a recommendation in the paper, namely: 'One recommendation we have made, which was indeed the recommendation we made prior to the legislation, was that the number of tablets in packs of paracetamol should be set at an even lower level (in keeping with the pattern in France and Ireland). Others, commenting on a larger body of literature have been far more cautious, suggesting that the impact on death in the UK was very modest.

If mortality changes are really due to pack size limitations, smaller packs should reduce both overdose deaths, and the magnitude of dose ingested. Do these arguments stand up to close scrutiny?

Some recent publications illustrate why the situation may not be as Hawton and colleagues imply. The first is a report examining mortality from paracetamol poisoning, and in

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Address correspondence to D. N. Bateman, University of Edinburgh, Centre for Cardiovascular Science, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ, UK. E-mail: dmnickbateman@gmail.com
cases where paracetamol was identified at postmortem as part of a wider review of pharmaceutical-related poisoning in England over a far longer time frame. A problem is that there is no agreed definition for coroners in the UK to use to decide on paracetamol as a cause of death. Clinicians would include liver failure and an adequate time for this to occur from ingestion. This approach is not always adhered to, hence shown here. Close examination of the figure provided in this paper (Fig. 1) shows a stable but variable mortality rate from paracetamol in England and Wales for several years prior to the pack size change. This also applies when these data are corrected for population change in England and Wales (Fig. 2). The model applied by Hawton and colleagues focused on only 5 years prior to the change, and does not reflect this longer pattern. This is acknowledged in the publication as a potential problem, and as the authors admit.

'The intervention point was moved back nine months to the beginning of 1998 to take account of earlier introduction of packaging changes, there remained a significant reduction in mortality in suicide and open verdict deaths involving paracetamol during 1998-2009 but no step change. What is perhaps more interesting, though less well understood, is the apparent downturn in morality rate in 'paracetamol alone' that seems to be occurring after 2006, and is associated with the removal of coproxamol from the UK market (Figs. 1 and 2).

If one expects pack change to affect mortality in a big way, then a large step change in the years after the legislation compared with those before it seems a likely outcome. This absence of a large change is a problem in understanding any benefit of pack size limitation, although changes were introduced in retail outlets over some months prior to the implementation date. If self-harm behaviour was stable over this period in the UK, then a reduction in dose available would be expected to cause a fairly clear reduction in deaths around this time. Other work has indicated overall changes in self-harm behaviour in the population at large, and as a result been suggested that the actual result on mortality is very small.

One major problem with mortality data in this context is the lack of uniformity of diagnostic criteria used to determine paracetamol-induced death by coroners across the UK. In addition other factors that cannot be accurately measured play in. These include population trends in overdose and policy on management of paracetamol poisoning, and its access, and better care of hepatic failure over time. For example the UK NPIS provided poisons information on line by TOXBASE from 2000, and their annual reports show the increase in usage of the service over the decade that Hawton studied. A further aspect is the background population behaviour in terms of suicide and self-harm rates. This is again extremely challenging to assess, and has not been reported in detail over such a long time period. There is no doubt that the lethality of potential overdose agents has also changed. Thus tricyclic antidepressants are now replaced largely with safer SSRIs, and paracetamol and coproxamol have been banned. However many more prescription drugs are now used than in 1971, and more products are available over the counter. Use of drugs of abuse and prescriptions for substitution opiates have also greatly increased.

It is also interesting to contrast the change (Figs. 1 and 2) caused due to reduced availability of the prescription analgesic combination coproxamol and that caused by pack size change in a drug available OTC. While these are not
directly comparable, as coproxamol was a prescription only drug, the effect of the latter, introduced over a 2-year period, was clear and rapid, whereas the effects of pack size are far less obvious examining data presented over a longer period.

A second issue is the nature of severe paracetamol poisoning, and the epidemiology of severe overdose. In the UK it is increasingly apparent that 'staggered', that is, repeated ingestion overdoses, often the result of therapeutic misadventure due to confusion on the ingredients in branded over-the-counter analgesics, represent a major component of both overdose presentations but more importantly severe poisoning.9,10 Pack size limitation is unlikely to affect this, which seems in part to arise because of confusion in the general public caused by branded labels including different components. For example in the UK the Beechams brand contains no paracetamol or aspirin. Similar problems apply to other branded products sold over the counter. These labels may confuse even physicians!

A third aspect is that of the quantity of paracetamol included in the packs. The initial advice from the UK regulator had been for a 12-g maximum, in order to keep the dose per packet less than a potentially fatal dose, based on calculations of glutathione stores in human liver.11 This recommendation was not accepted by the UK Medicines Commission, and the eventual maximal dose available became 16 g. In contrast in Ireland a 12-g maximum was decreed. Comparison of Irish and English data and these data demonstrate the lack of impact of 12 g versus 16 g in the overdose pattern seen.12 The authors' conclusions were: ‘The difference in paracetamol and paracetamol size legislation between England and Ireland does not appear to have resulted in a major difference in sizes of overdoses. This is because more pack equivalents are taken in overdoses in Ireland.’

A telephone survey performed in England provides further evidence as to why pack size changes have been less effective than might have been anticipated.13 In this survey over one-third of households questioned had over 32 tablets of paracetamol in the household. Taken with the relative ease of obtaining supplies from single, or multiple sources in a single UK high street14 is clear that for most patients paracetamol availability remains easy, and often above the levels likely to be potentially seriously toxic.

In conclusion it seems that the initial optimism that restriction of pack size would reduce mortality from paracetamol poisoning was misplaced. Assessment of the effect is confounded by the many factors discussed above. As with much regulatory change, a failure to establish a proper research assessment of success in advance has caused uncertainty over benefit. While there is a suggestion of a small effect on total deaths from paracetamol, further restriction is unlikely to counterbalance the public health hazard of a switch to potentially more toxic analgesics, particularly non-steroidal anti-inflammatory drugs or weak opioids.

Declaration of interest
The author reports no declarations of interest. The author alone is responsible for the content and writing of the paper.

References

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