Severity of overdose after restriction of paracetamol availability: retrospective study

Denise Robinson, Alice M J Smith, G Dennis Johnston

Paracetamol overdose is the commonest cause of intentional self harm in the United Kingdom, accounting for approximately 70 000 cases per year. It is the commonest cause of acute liver failure, although this is rare in adults if doses of < 12 g are ingested. To reduce this major health problem the government introduced legislation in September 1998 to limit the number of tablets in a single packet to 32 for packets sold in pharmacies and 16 in non-pharmacy outlets.

This study assesses the impact of reduced availability of paracetamol on the number and severity of overdoses by comparing self poisoning cases in two periods of six months before and after the change to smaller packets.

Subjects, methods, and results

Patients presenting with acute self poisoning to five general hospitals in the Belfast area during the months January to June in 1998 and 1999 were included in the study. For each case we estimated the amount of paracetamol ingested, whether as a single agent or with other drugs. Where appropriate we recorded concentrations of serum paracetamol and liver enzymes, the international normalised ratio, and whether an antidote was given. We also recorded the numbers of patients admitted to hospital, patients transferred to a specialist unit, and deaths related to paracetamol overdose. We used a χ² test to compare the numbers of patients admitted to hospital and the numbers who received an antidote during the two periods. A Mann-Whitney U test was used to compare the difference in estimated quantity of paracetamol ingested, serum concentration of paracetamol at 4-6 hours after the time of poisoning, and transaminase concentrations and the international normalised ratio at 24-48 hours.

Serum paracetamol concentrations were measured in 59% of the 590 patients who presented in the first period and 63% of 594 in the second. The estimated quantity of paracetamol ingested, the number of patients receiving the antidote, and the serum paracetamol concentration at 4-6 hours were significantly lower in the second period (table).

Two patients were transferred to a tertiary referral centre in 1998 and three in 1999. In 1998 neither patient required liver transplantation and both made a full recovery. However, in 1999 only one patient recovered completely; one died and one received a liver transplant.

Comment

Overdose behaviour changed after the introduction of smaller blister packs of paracetamol. The estimated
quantity of paracetamol ingested was reduced; this measure is often unreliable, but in this study it was associated with a reduction in paracetamol concentration at 4-6 hours and decreased use of antidote. Early administration of the antidote was probably the reason why tests of liver function revealed no changes after the introduction of smaller packets. Unlike Prince et al., we found no reduction in the number of severe paracetamol overdoses; the only benefit we noted was a reduction in costs because fewer antidotes were given and there were fewer hospital admissions.

As in other studies on the impact of reducing the availability of paracetamol, a cause and effect relationship could not be identified. A number of factors—notably a change in medical practice and case mix—could have influenced the results. Although necessarily retrospective, this study has a number of strengths that make it more likely that the findings represent a change in overdose behaviour: there was a single observer, almost all cases of poisoning were identified, there was a time lag of three months between the date of law change and the second study period, and relatively objective measures were compared (number of admissions, paracetamol concentration, and use of antidote).

We conclude that measures to restrict the availability of paracetamol have reduced the amount taken in single overdoses but not the incidence of severe liver failure.

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Competing interests: None declared.


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### Drug points

**Anaphylactic-like reaction associated with oral budesonide**

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Corticosteroids have antiallergic properties, which should reduce the likelihood of anaphylactic-like reactions. We describe a patient with an anaphylactic-like reaction associated with oral budesonide and apparent cross-reactivity with mesalazine.

In 1995 a 29 year old woman with Crohn’s disease started taking oral mesalazine (1 g three times daily) after ileocaecal resection. Within 48 hours her tongue and throat became swollen but returned to normal after the mesalazine was withdrawn. We evaluated her reaction to oral mesalazine (Pentasa, Yamanouchi Pharma; Asacol, Byk Nederland; and generic mesalazine prepared in the hospital’s pharmacy) by giving her test doses (10 mg) in an outpatient setting. Within 30 minutes of exposure to each product, her tongue, buccal mucosa, and lips became swollen. Challenges with other drugs containing the same active substances gave negative results. She had no history of asthma or nasal polyps.

In 1997 she started taking prednisone 20 mg daily and azathioprine 150 mg daily because of weight increase. Dose tapering of the prednisone and azathioprine was planned after four weeks of budesonide treatment. Five minutes after she took the first capsule, her tongue and throat swollen, accompanied by transpiration, wheeziness, bowel complaints, and diarrhoea. She recovered within four days of treatment with clemastine. Intracutaneous tests with dilutions of budesonide suggested a non-IgE mediated reaction. Concentrations of urinary methylhistamine outside the acute episode were normal, ruling out systemic mastocytosis. In 1999, after another ileocaecal resection, the patient’s tongue and throat swelled after she received intravenous dexamethasone for prophylaxis against stress. She recovered after discontinuation of the drug and treatment with clemastine.

Published reports suggest that corticosteroid molecules are able to cause anaphylactic-like reactions.1, 2 Our report shows that anaphylactic-like reactions may also occur with oral budesonide and that cross-reactivity may occur with mesalazine. Interestingly, sensitivity to aspirin, which is structurally related to mesalazine, has been postulated as a risk factor for anaphylaxis to steroids.3

The Dutch Medicines Evaluation Board and the manufacturer of budesonide, AstraZeneca, were informed. The manufacturer stated that allergic reactions to corticosteroids are more common than generally assumed and might be easily overlooked by clinicians.

Competing interests: None declared.


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**Cases of paracetamol overdose before and after the change to smaller packets (September 1998). Figures are medians (interquartile ranges) unless stated otherwise**

<table>
<thead>
<tr>
<th></th>
<th>Jan-Jun 1998</th>
<th>Jan-Jun 1999</th>
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<tbody>
<tr>
<td></td>
<td>(n=590)</td>
<td>(n=594)</td>
</tr>
<tr>
<td>Estimated quantity of paracetamol ingested (g)</td>
<td>10 (5-18)</td>
<td>8 (5-14)</td>
</tr>
<tr>
<td>Serum paracetamol concentration (mg/l) at 4-6 hours</td>
<td>37 (14-80)</td>
<td>27 (6-64)</td>
</tr>
<tr>
<td>No (%) of patients admitted to hospital</td>
<td>398 (67.4)</td>
<td>374 (63.2)</td>
</tr>
<tr>
<td>No (%) of patients given antidote*</td>
<td>183 (31.1)</td>
<td>149 (25.1)</td>
</tr>
<tr>
<td>International normalised ratio at 24-48 hours</td>
<td>1.1 (1.0-1.2)</td>
<td>1.1 (1.0-1.2)</td>
</tr>
<tr>
<td>Concentration of liver enzyme† at 24-48 hours (UI)</td>
<td>23.0 (18-37)</td>
<td>23.5 (19-52)</td>
</tr>
</tbody>
</table>

* N-acetylcysteine or methionine.
† Serum aspartate aminotransferase.

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