

1-1-1998

## Paracetamol (acetaminophen) poisoning: no need to change current guidelines to accident departments

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### Citation

Routledge, P; Vale, J Allister; Bateman, D Nicholas; Johnston, G. Denis; Jones, Alison L.; Judd, Alan; Thomas, Simon; Volans, Glyn; Prescott, L F.; and Proudfoot, A T., 1998, Paracetamol (acetaminophen) poisoning: no need to change current guidelines to accident departments, 1609-1610.  
<https://ro.uow.edu.au/medpapers/187>

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## Paracetamol (acetaminophen) poisoning: no need to change current guidelines to accident departments

### Abstract

Paracetamol is an effective, simple analgesic that is well tolerated by adults and children at therapeutic doses. In many countries it is available without prescription. Unfortunately, its ready availability is associated with episodes of poisoning that prompt 3.3% of inquiries to US regional poisons centres, 10% of inquiries to the UK National Poisons Information Service, and up to 43% of all admissions to hospital with self poisoning in the United Kingdom.<sup>3</sup> In the United States paracetamol alone accounted for 4.1% of deaths from poisoning reported to American poisons centres in 1997. Most deaths are associated with deliberate self poisoning, but therapeutic misadventures do occur rarely, in both adults and children.

### Keywords

guidelines, change, current, accident, no, departments, need, poisoning, acetaminophen, paracetamol

### Disciplines

Medicine and Health Sciences

### Publication Details

Routledge, P, Vale, J. A., Bateman, D., Johnston, G., Jones, A. L., Judd, A., Thomas, S., Volans, G., Prescott, L. F. & Proudfoot, A. T. (1998). Paracetamol (acetaminophen) poisoning: no need to change current guidelines to accident departments. *British Medical Journal*, 317 (7173), 1609-1610.

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the Robin Hood index, a well validated measure of income differentials. Income differentials vary over time and from place to place,<sup>7</sup> suggesting that they are not just a fact of life. It could be argued that wide income differentials are an economic manifestation of people taking advantage of each other, and that it is the latter that causes premature mortality—through the emotional distress it generates.

Solutions to apparently intractable public health problems like inequalities in health and unhealthy lifestyles may therefore lie in research into emotional wellbeing. A broad range of studies is needed to test the hypothesis that emotional distress creates susceptibility to physical illness and a further range is to research interventions which can prevent emotional distress and promote mental and social health.

Two of the most promising approaches depend on a further body of research which shows that unresolved emotional distress in childhood is an important cause of emotional distress in adulthood.<sup>13 14</sup> These approaches are parenting programmes and mental health promotion programmes in schools. The evidence showing that parenting programmes can both reverse emotional and behavioural problems<sup>15</sup> and prevent their emergence<sup>16</sup> is robust. Several school mental health promotion programmes have been subject to controlled trials which show a positive impact on emotional wellbeing.<sup>17</sup> Through developing empathy and respect, both types of programmes improve self esteem in children and parents and increase their ability to give and receive social and emotional support. Long term follow up studies are needed to test the hypothesis that these programmes affect adult physical and mental health, but the epidemiological evidence suggesting that they could is strong.

Successful implementation of the agenda defined in *Our Healthier Nation* will depend on research and

development of such programmes. For this to happen doctors, and others who determine the allocation of NHS funds, will need to believe that emotional and social wellbeing are at least as important for health as physical wellbeing and invest both development and research funds accordingly.

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## Paracetamol (acetaminophen) poisoning

### *No need to change current guidelines to accident departments*

Letters p 1654

Paracetamol is an effective, simple analgesic that is well tolerated by adults and children at therapeutic doses. In many countries it is available without prescription. Unfortunately, its ready availability is associated with episodes of poisoning that prompt 3.3% of inquiries to US regional poisons centres,<sup>1</sup> 10% of inquiries to the UK National Poisons Information Service,<sup>2</sup> and up to 43% of all admissions to hospital with self poisoning in the United Kingdom.<sup>3</sup> In the United States paracetamol alone accounted for 4.1% of deaths from poisoning reported to American poisons centres in 1997.<sup>1</sup> Most deaths are associated with deliberate self poisoning, but therapeutic misadventures do occur rarely, in both adults and children.

In a recent lesson of the week Bridger et al, on the basis of four cases, advocated instigating treatment for paracetamol poisoning at levels below the normal "treatment line" of paracetamol concentrations at four and 15 hours advised in the current guidelines on

paracetamol poisoning issued by the UK National Poisons Information Service.<sup>4</sup> This paper has generated considerable debate, which is reflected in this week's letters columns (p 1654).<sup>5</sup> Is it time to revise the guidelines?

The paper by Bridger et al was inappropriately entitled "Deaths from low dose paracetamol poisoning" because at least three of the four subjects ingested potentially hepatotoxic amounts ("150 mg/kg body weight or 12 g in total, whichever is the smaller"). Nevertheless, since there are effective antidotes in those who present relatively early after overdose, we are concerned about all possibly avoidable deaths due to paracetamol poisoning.

Paracetamol is predominantly metabolised to glucuronide and sulphate conjugates, which are excreted in the urine. Hepatotoxicity is related to the conversion of a small proportion of the ingested dose to N-acetyl-p-benzoquinoneimine. In therapeutic doses N-acetyl-p-benzoquinoneimine is detoxified by

BMJ 1998;317:1609-10

conjugation with glutathione in the liver, but once the protective intracellular glutathione stores are depleted hepatic and renal damage may ensue. N-acetylcysteine and methionine replenish glutathione stores in the liver and kidney.<sup>6</sup> Methionine is given orally whereas N-acetylcysteine is available in oral and intravenous formulations. However, as up to three quarters of severely poisoned patients develop vomiting after a paracetamol overdose,<sup>7</sup> intravenous N-acetylcysteine given over 20-25 hours is generally the agent of choice in the UK. In the US the intravenous formulation is not licensed but the drug is administered in a 48 hour regimen by this route as well as orally (72 hour regimen). There is also some evidence that N-acetylcysteine reduces mortality in paracetamol induced liver failure, although the drug is acting via a different mechanism from glutathione repletion.<sup>8</sup>

Apart from nausea and vomiting, there are often few symptoms in the first 12 hours after paracetamol overdose and this may deter patients from seeking medical attention. Of patients presenting to emergency departments in north east England with suspected paracetamol poisoning, most (over 90%) did not have plasma paracetamol concentrations above the appropriate treatment line and did not receive an antidote.<sup>9</sup> Although it is often stated that liver function tests are invariably normal in the first 24 hours after paracetamol overdose, increases in aspartate aminotransferase and alanine aminotransferase activities have been seen as early as eight hours after the stated time of ingestion.<sup>10</sup> Indeed, in the same study over half the patients had a raised aspartate aminotransferase activity in the first 24 hours, including six of the eight who went on to develop severe liver damage (aspartate aminotransferase activity > 1000 IU/l).<sup>10</sup>

Plasma paracetamol concentrations are also diagnostically and prognostically useful, and several treatment nomograms were introduced in the 1970s. The one that became most widely accepted internationally joined plasma paracetamol concentrations of 200 mg/l at 4 hours and 30 mg/l at 15 hours in a first order decline.<sup>11</sup> A similar nomogram based on the same dataset, but extending the line to 24 hours, was also published.<sup>12</sup> Finally, a nomogram joining values of 150 mg/l at 4 hours and 5 mg/l at 24 hours was used in a multicentre open study in the US, although the justification for this change was not given.<sup>13</sup> Case reports of patients taking long term enzyme inducing drugs or misusing alcohol chronically suggest that such patients may develop hepatotoxicity at paracetamol concentrations below the conventional treatment line. Because of such cases we recommended that a second "high risk patient" line at half the concentration of the conventional treatment line should be adopted,<sup>6</sup> and we incorporated this into national guidelines that were disseminated in wall chart form to emergency departments in the UK in 1995.<sup>14</sup>

Before the publication of national guidelines, only 10 of 24 UK emergency departments surveyed had a formal written policy on managing paracetamol poisoning.<sup>15</sup> After publication, 23 of these units had formal written treatment policies, with 20 using the national guidelines.<sup>15</sup> We are currently revising these recommendations to highlight the value of measuring aspartate aminotransferase and alanine aminotransferase activities as well as plasma paracetamol

concentrations and the international normalised ratio in certain situations. Although the present guidelines clearly state, "If there is doubt about the timing or the need for treatment, treat," this crucial advice will be further reinforced. Nevertheless, we do not believe that there is yet sufficient evidence to advocate reducing the "normal risk" treatment nomogram line for patients.

The appropriate use of intravenous N-acetylcysteine, advances in medical management of severe hepatotoxicity, and the increasing availability of transplantation offer the best hope of survival. Nevertheless, preventing severe paracetamol poisoning must be the way forward, and we hope that the new UK legislation (introduced in September 1998) that limits the quantity of paracetamol available as a single purchase might contribute to this.

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PR has been on the board of the Paracetamol Information Centre (funded by an industry association) and has received research funds from the centre; AJ has been reimbursed for attending meetings organised by the centre; and DNB has been paid for attending meetings funded by the centre.

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