levels (from local to national and international) and of successful and unsuccessful disease and vector surveillance systems needs to be recorded to allow adoption of best practices in other places.

The third stream relates to primary prevention through dengue vaccines and to secondary prevention through drugs. This aim requires better understanding of viral and host factors. Immune responses in natural infections and vaccine trials need to be better characterised, correlates of protective immunity must be identified as endpoint measures in vaccine trials, new vaccine candidates and adjuvants have to be tested, and alternative vaccination strategies need to be assessed. Better descriptions of viral-encoded proteins will accelerate drug design and testing of existing licensed drugs and natural or other products.

Finally, the fourth stream of research is aimed at enhancing the public-health response at national and international levels through health-policy research. Research is ongoing into the burden caused by dengue disease to societies and families, and there are scattered analyses of country dengue programmes that can help identify factors leading to success and failure. Health-policy research should also be extended to less studied regions, such as Africa, where dengue is especially neglected. In summary, with good synergy between research, policy, and prevention and control, there are real prospects for reversal of the upward trend of the global dengue pandemic.

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Paracetamol: are therapeutic doses entirely safe?

Paracetamol (acetaminophen in the USA) is thought to be safe in recommended doses, up to 4 g a day in adults.[1] In most countries, paracetamol can be purchased in retail stores as an over-the-counter preparation, and it is currently the most widely used analgesic and antipyretic drug worldwide.

Paracetamol is hepatotoxic and nephrotoxic at doses of more than 4 g a day in adults.[2] Over the past 15 years, especially in Europe and in the USA, paracetamol has become the most important cause of acute liver failure—a devastating disorder in which more than 85% of patients with a poor prognosis who do not have transplantation die.[3] Of particular concern is that in recent years, unintentional overdoses, rather than those that are intentional, have been the main cause of paracetamol-induced acute liver failure in the USA; the actual dose taken can be as low as 7 g a day.[4] The safety of paracetamol has been under considerable debate,[1] but a review[5] by the US Food and Drug Administration Office of Drug Safety concluded that no change was needed in how the drug is sold. However, a recent study by Paul Watkins and colleagues[6] has reopened the issue of the actual safety of therapeutic doses of paracetamol.[2]

Watkins and colleagues[6] did a participant-blinded diet-controlled study in 145 selected healthy volunteers. The study was designed to determine why abnormal liver-function tests had been recorded during early clinical development of a new combination of an opioid (hydrocodone) and paracetamol. Participants were randomly assigned placebo, paracetamol (4 g a day), or a combination of this dose of paracetamol with one of three opioids, with an intended duration of treatment of 14 days. Although trough paracetamol concentrations in any group did not exceed therapeutic limits, 31–44% of participants

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in the paracetamol-treated groups had concentrations of alanine aminotransferase that were more than three times the upper limit of normal (suggesting liver injury), whereas none of 39 participants given placebo had an increase to this level (p<0·001). In 27% of participants given therapeutic doses of paracetamol, increased alanine aminotransferase concentrations (to more than eight times the upper limit of normal) were recorded.

Three other studies[7–9] lend support to the idea that therapeutic doses of paracetamol might be associated with liver injury in some patients. For patients with severe acute viral hepatitis, recent ingestion of therapeutic doses of paracetamol was associated with higher serum transaminases and greater prolongation of prothrombin time compared with patients that did not have additional paracetamol.[10,11] In a preliminary study from France,[12] 52% of patients with biochemical and clinical evidence of acute liver injury while on antitubercular drugs had a history of recent paracetamol ingestion. Thus, at clinical onset of acute liver disease, use of paracetamol might be associated with exaggerated liver injury in some individuals. For patients who present with acute liver injury, markedly elevated serum alanine aminotransferase, and who have a history of recent paracetamol ingestion, physicians should consider paracetamol hepatotoxicity as a cause and consider treatment with acetylcysteine.[13]

Although the provocative data from Watkins and colleagues[6] need to be strengthened by other studies—particularly of patients on long-term continuous treatment with paracetamol—they raise many questions about the safety of commonly recommended doses of paracetamol. Review of the recommendations about how paracetamol is sold in the future might be appropriate. However, Watkins and colleagues' findings should not be taken out of context because unnecessary anxiety may encourage patients to switch to potentially more toxic alternatives.

Doctors, health workers, pharmacists, and patients need to be made aware that administration of paracetamol in doses that are thought traditionally to be safe might lead to raised transaminases, suggesting some degree of liver injury. Such awareness is particularly important for people who are likely to be at high risk of unintentional paracetamol hepatotoxicity—eg, those who are dependent on alcohol, are severely malnourished, consume paracetamol chronically, smoke tobacco, have acute liver disease, or who receive treatment with inducers of liver enzymes.

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LESSON OF THE WEEK

Acute liver failure after administration of paracetamol at the maximum recommended daily dose in adults

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A total of 4 g of paracetamol repeated daily may be hepatotoxic in malnourished adults with low body weight

Paracetamol is the most commonly used analgesic and antipyretic in the world; it can be bought without prescription in most countries despite being the commonest cause of acute liver failure in western Europe. Prescribing information suggests that it is safe to use in adults in divided doses that total 4 g daily. Malnutrition, starvation, chronic alcohol misuse, and concomitant use of drugs that induce cytochrome P450 enzymes increase the risk of hepatotoxicity induced by paracetamol. Nevertheless, doctors commonly regard paracetamol 4 g daily as being safe as well as an effective analgesic. We describe two cases (one fatal) of acute liver failure secondary to maximum dose oral paracetamol; these highlight the importance of considering dose reduction in those with low body weight and/or other risk factors for hepatotoxicity.

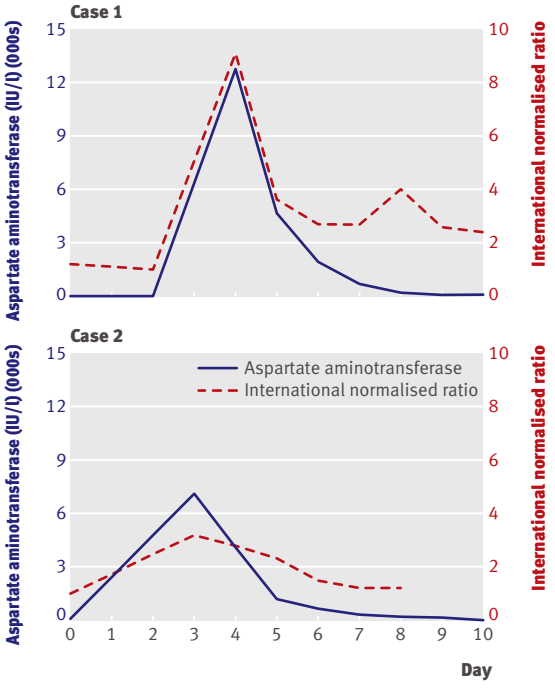
Case reports

Case 1

A 43 year old man was admitted with an exacerbation of Crohn's colitis. His nutritional status was poor, with an admission weight of 30 kg and a body mass index (weight (kg)/(height (m)^2)) of 12. He received intravenous hydrocortisone and metronidazole along with oral paracetamol at a total dose of 4 g daily. Four days later he became confused and tachypnoeic and was found to have developed acute liver failure with an aspartate aminotransferase of 12 769 IU/l, international normalised ratio of 9.1 (figure), and severe lactic acidosis. Liver function tests were normal at the time of his admission. His paracetamol concentration was raised (92 mg/l) despite him having received the standard maximum adult dose under direct supervision. No other cause of liver failure could be identified; he was never hypotensive, and serological studies for acute viral infection were negative. He was transferred to the regional liver failure service, but despite treatment with *N*-acetylcysteine and supportive care on the liver intensive care unit he died 12 days later of multiorgan failure.

Case 2

A 32 year old woman with a history of chronic alcoholism was admitted with acute alcohol withdrawal and abdominal pain secondary to alcoholic gastritis. She was prescribed vitamin supplements, chlordiazepoxide, and oral paracetamol (total 4 g daily). She weighed 44 kg on admission (body mass index 17). Blood tests and abdominal ultrasound on admission were unremarkable (aspartate aminotransferase 56 IU/l). Three days later she became increasingly agitated and complained of nausea. She was found to be in acute liver failure with a peak aspartate aminotransferase of 7116 IU/l and international normalised ratio of 3.2 (figure). Her paracetamol concentration was raised (105 mg/l). She was transferred to the liver intensive care unit and received full supportive care



Dynamic changes in aspartate aminotransferase (left axis) and international normalised ratio (right axis) for each patient. Both patients received oral paracetamol, each at a total dose of 4 g daily from the time of admission to hospital (day 0)

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- Proton pump inhibitors and acute interstitial nephritis (*BMJ* 2010;341:c4412)
- Opioid induced hypogonadism (*BMJ* 2010;341:c4462)
- Delayed diagnosis of primary hyperaldosteronism (*BMJ* 2010;340:c2461)
- Sexual precocity in a 4 year old boy (*BMJ* 2010;340:c2319)
- Treatment for lymph node tuberculosis (*BMJ* 2010;340:c63)

including *N*-acetylcysteine. Her liver function gradually recovered and she was discharged 15 days later.

Discussion

Paracetamol is metabolised in the liver by processes of glucuronidation and sulfation. Most of the drug is metabolised into non-toxic metabolites, but 5-10% is converted by the cytochrome P450 system into the reactive toxic intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI).[1] In healthy individuals taking therapeutic doses of paracetamol this metabolite is usually rendered non-toxic by binding to glutathione.[2] Overdose of paracetamol, induction of cytochrome P450 enzymes, or glutathione deficiency may result in the metabolic pathway becoming overwhelmed, producing an excess of NAPQI, which binds to hepatocyte macromolecules causing enzymatic dysfunction, structural and metabolic disarray, and eventually necrotic cell death. Hepatocytes are increasingly susceptible to oxidative stress when glutathione is depleted.[3]

Glutathione is synthesised from glutamate, cysteine, and glycine by two cytosolic enzymes (γ-glutamylcysteine synthetase and glutathione synthetase).[4] Thus protein or amino acid deficiency secondary to malnutrition, malabsorption, or synthetic failure leads to glutathione deficiency. Alcoholics have low serum and intrahepatic glutathione concentrations, and chronic illness and fasting are risk factors for glutathione deficiency.[5]

Paracetamol has a narrow therapeutic index, and severe hepatocellular necrosis may follow the oral ingestion of a single dose of 150 mg/kg. Both of the patients we describe were underweight and had additional factors that made them at increased risk of hepatotoxicity. Patient 1 weighed 30 kg and his daily dose of 4 g was therefore 133 mg/kg. The daily dose received by patient 2 was 91 mg/kg. Doses of this magnitude repeated daily in individuals with inadequate metabolic capacity may lead to liver injury, which in severe cases may result in acute liver failure.

Several cases of acute liver failure secondary to oral paracetamol at the maximum recommended daily dose have been reported, and in all these cases the patients had identifiable risk factors for hepatotoxicity.[6-10] Although these cases are rare, it is likely that they are an underrepresentation of the true incidence as some practitioners may not identify the correct cause of liver injury owing to a low index of suspicion. Patients who develop milder hepatic impairment may not be identified at all if liver function tests are not measured. A prospective study of acute liver failure at 17 tertiary care centres in the United States identified 21 patients with acute liver failure secondary to paracetamol at doses of ≤4 g daily over a 41 month period.[11]

The widespread use of paracetamol in hospitals and in the community, coupled with the high prevalence of chronic alcoholism and malnutrition, particularly in hospital inpatients, means that more cases will probably occur. However, if awareness is raised, further cases of acute liver failure may be preventable through reduced doses in those who are most at risk.

Intravenous paracetamol is now increasingly used in secondary care; at our hospital the annual number of prescriptions for intravenous paracetamol rose by 30% between 2007 and 2009 (from 2438 to 3174). The bioavailability of intravenous paracetamol (1.0) is higher than that of oral paracetamol, which is dose dependent and ranges from 0.7 to 0.9.[12] Thus, there may be a greater potential for liver injury if a total of 4 g daily intravenous paracetamol is prescribed to malnourished patients with low body weight.

The *British National Formulary* (*BNF*) states that the daily dose of intravenous paracetamol should not exceed 60 mg/kg when prescribed for adults weighing <50 kg.[13] The latest edition also cautions for the first time that the maximum daily dose of infusions should be reduced to 3 g for patients with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition, or dehydration. However, it contains no recommendations to reduce the dose of oral paracetamol for adults weighing <50 kg or in the presence of other risk factors. This disparity between the maximum recommended dose of oral and intravenous paracetamol for adults with low body weight and/or other risk factors for hepatotoxicity is surprising, given that the systemic bioavailability of oral paracetamol may be as high as 90%.

We reviewed oral and intravenous paracetamol prescriptions issued at our hospital to adults weighing <50 kg over eight weeks. Eighty two per cent (47/57) of patients were prescribed oral paracetamol at the maximum recommended daily dose. Two of these patients had a transient rise in aspartate aminotransferase during treatment (from 29 IU/l to a peak of 526 IU/l over four days in a patient weighing 39 kg, and from 29 IU/l to 138 IU/l over three days in a patient weighing 40 kg). Moreover, in 17 of the 18 patients given intravenous paracetamol, the dose was not reduced as recommended by the *British National Formulary*. This shows that few practitioners in secondary care reduce the dose of either oral or intravenous paracetamol in adults with a low body weight and confirms that many patients are potentially at risk. The fact that we were able to identify two susceptible adults with evidence of liver injury secondary to maximum dose paracetamol at a single centre in a period as short as eight weeks suggests that these cases may be under-recognised.

We have raised awareness of this matter locally via email bulletins, pharmacists, and the introduction of an alert message on our electronic prescribing system recommending the reduction of the daily dose of paracetamol (oral and intravenous) to 2 g for adults weighing <50 kg.

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