

# Paracetamol and pain: the kiloton problem

R Andrew Moore,<sup>1</sup> Nicholas Moore<sup>2</sup>

As a unit, the kiloton is most often linked to the explosive yield of nuclear weapons in tons of TNT (trinitrotoluene, an explosive). For drugs, we are more comfortable with milligrams, a unit one million million times smaller. With paracetamol, at a population level, the kiloton unit may be more appropriate: in Europe, paracetamol sales range from under 200 tons in Greece and Portugal to 6300 tons in the UK and 10 000 tons in France.<sup>1</sup> On a per capita basis the range is 4–5 tons per million to 30–50 tons per million. These figures relate to the total population exposure, including over-the-counter (OTC) sales, though prescribing of paracetamol is not negligible. In the UK in 2014, 42 million paracetamol-containing medicines were prescribed at a cost of £191 million,<sup>2</sup> and 200 million packs sold OTC.<sup>3</sup>

Paracetamol was discovered in the 1950s,<sup>4</sup> and the general view that it is effective and safe has led to such widespread use. Yet there has been considerable uncertainty over how it works. Only recently has it been generally accepted that it inhibits COX-1 and COX-2 isoenzymes, and is in fact a weak nonsteroidal anti-inflammatory drug (NSAID).<sup>5</sup>

The last few years have seen paracetamol and other commonly used drugs subjected to greater scrutiny, particularly the sharp focus of evidence-based medicine; 2015 and 2016 have seen pivotal new evidence appear. The picture is not quite as rosy as the general view would have us think.

In terms of efficacy, an overview review that examined paracetamol efficacy across acute and chronic conditions<sup>6</sup> has been complemented with more recent data. What we now know about paracetamol and pain is that:

- ▶ Paracetamol at doses between 500 and 1000 mg is in the least effective quartile of drugs for treating acute post-operative pain.<sup>7</sup>

- ▶ Paracetamol 1000 mg has modest efficacy in migraine and tension-type headache.
- ▶ Paracetamol at doses up to 4000 mg daily is ineffective in back pain.<sup>8 9</sup>
- ▶ Paracetamol at doses up to 4000 mg daily is practically ineffective in arthritis. Though marginally better than placebo, paracetamol has little chance of achieving clinically meaningful benefit in osteoarthritis.<sup>8 10–12</sup>
- ▶ No review evidence that paracetamol works for dysmenorrhoea, neck pain, rheumatoid arthritis or cancer pain.

We have considerable evidence that as well as not being particularly effective, neither is it particularly safe.

- ▶ A systematic review of observational studies found that compared with people not taking paracetamol, paracetamol use, especially at higher doses, was associated with increased mortality, cardiovascular adverse events (fatal or non-fatal myocardial infarction, stroke or fatal coronary heart disease), gastrointestinal adverse events (gastrointestinal ulcers and complications such as upper gastrointestinal haemorrhage) and estimated glomerular filtration rate decrease of at least 30 mL/min/1.73 sq m.<sup>13</sup>
- ▶ Acute liver failure leading to registration for transplantation was twice as common in non-overdose paracetamol-exposed patients than with NSAIDs in a large case-population study.<sup>14</sup>
- ▶ In clinical trials in chronic pain, patients taking paracetamol were four times more likely to have abnormal results on liver function tests than those taking placebo.<sup>8</sup>
- ▶ Paracetamol had very similar adverse event rates to ibuprofen over 3 months in patients with arthritis,<sup>15</sup> and was not better tolerated than ibuprofen for short-term relief of common pain.<sup>16</sup>
- ▶ Reports of patients with any adverse event in acute pain studies were the same for paracetamol (up to 1000 mg) and placebo.<sup>17</sup>

Oral paracetamol is rapidly absorbed, with maximum plasma concentrations achieved by 30 min in the fasted, but not fed, state.<sup>18</sup> Rapid absorption of NSAIDs is now recognised to be important for promoting good analgesia, though the precise mechanism is uncertain. That may

be why paracetamol has some analgesic action in acute pain.<sup>7</sup> But only a minority of people with acute pain or headache will have good pain relief with paracetamol, especially compared with fast-acting formulations of NSAIDs. For chronic pain we have evidence of absence of any clinically useful effect of paracetamol, either alone or in combination, and at doses of up to 4000 mg daily. There may of course be circumstances where paracetamol might be useful, in paediatric pain, for treating patent ductus arteriosus, or for intravenous use during surgery.

Balanced against this at-best-modest analgesic efficacy we have considerable evidence of harm, including all the concerns that also affect NSAIDs, but with liver failure and (possibly) renal failure added. These are dose-related; more risk of harm at higher doses.

If paracetamol were an unimportant and little-used drug, none of this might amount to much. But it is not. It is a drug whose use is measured in thousands of tons, has little or no effect in many conditions and has significant adverse events. Maybe it is time to consider the evidence again and think about the possibility of change.

Patients with pain regard only large reductions in that pain to be relevant, and large reductions in pain are accompanied by major improvements in associated symptoms, including quality of life, function and work, and lower costs to health services.<sup>19 20</sup> We know that only a minority of patients have adequate pain relief on any particular drug.<sup>21</sup> We know that the majority of people with chronic pain still have moderate or severe pain while on treatment, indicating that treatment to be inadequate.<sup>22</sup> We know that switching to another medicine in that situation results in major benefits for many.<sup>23</sup>

The future for treating pain lies in new thinking about how we deal with analgesic failure, rather than remorselessly continuing to use kilotons of a drug that we know will fail and may do harm.

**Competing interests** None declared.

**Provenance and peer review** Commissioned; internally peer reviewed.



CrossMark

**To cite** Moore RA, Moore N. *Eur J Hosp Pharm* 2016;**23**:187–188.

Published Online First 27 April 2016

*Eur J Hosp Pharm* 2016;**23**:187–188.  
doi:10.1136/ejpharm-2016-000952

<sup>1</sup>Pain Research, Nuffield Division of Anaesthetics, University of Oxford, Oxford, UK; <sup>2</sup>Department of Pharmacology, Université de Bordeaux, Bordeaux, France

**Correspondence to** Dr R Andrew Moore, Pain Research, Nuffield Division of Anaesthetics, University of Oxford, The Churchill, OX3 7LE Oxford, UK; Andrew.moore@ndcn.ox.ac.uk

## REFERENCES

- 1 Gulmez SE, Larrey D, Pageaux GP, *et al.* Transplantation for acute liver failure in patients exposed to NSAIDs or paracetamol (acetaminophen): the multinational case-population SALT study. *Drug Saf* 2013;36:135–44.
- 2 Prescribing & Medicines Team. *Prescription cost analysis England 2014*. Health and Social Care Information Centre, 2015.
- 3 Proprietary Association of Great Britain. <http://www.pagb.co.uk/media/pdfs/Hawtonparacetamolstudy8.2.13.pdf> (accessed 18 Mar 2015).
- 4 Axelrod, J. Journey of a late blooming biochemical neuroscientist. *J Biol Chem* 2003;278:1–13.
- 5 Hinz B, Brune K. Paracetamol and cyclooxygenase inhibition: is there a cause for concern? *Ann Rheum Dis* 2012;71:20–5.
- 6 Moore RA, Derry S, Wiffen PJ, *et al.* Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. *Eur J Pain* 2015;19:1213–23.
- 7 Moore RA, Derry S, Aldington D, *et al.* Single dose oral analgesics for acute postoperative pain in adults—an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2015;9:CD008659.
- 8 Machado GC, Maher CG, Ferreira PH, *et al.* Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ* 2015;350:h1225.
- 9 Williams CM, Maher CG, Latimer J, *et al.* Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial. *Lancet* 2014;384:1586–96.
- 10 Hazlewood G, van der Heijde DM, Bombardier C. Paracetamol for the management of pain in inflammatory arthritis: a systematic literature review. *J Rheumatol Suppl* 2012;90:11–16.
- 11 van Walsem A, Pandhi S, Nixon RM, *et al.* Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. *Arthritis Res Ther* 2015;17:66.
- 12 da Costa BR, Reichenbach S, Keller N, *et al.* Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet* 2016; (March 17, epub ahead of print)
- 13 Roberts E, Delgado Nunes V, Buckner S. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis* 2016;75:552–9.
- 14 Gulmez SE, Larrey D, Pageaux GP, *et al.* Liver transplant associated with paracetamol overdose: results from the seven-country SALT study. *Br J Clin Pharmacol* 2015;80:599–606.
- 15 Doherty M, Hawkey C, Goulder M, *et al.* A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. *Ann Rheum Dis* 2011;70:1534–41.
- 16 Moore N, Van Ganse E, Le Parc J, *et al.* The PAIN study: Paracetamol, Aspirin and Ibuprofen New tolerability study. A large scale, randomized clinical trial comparing the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. *Clin Drug Invest* 1999;18:89–98.
- 17 Moore RA, Derry S, Aldington D, *et al.* Adverse events associated with single dose oral analgesics for acute postoperative pain in adults—an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2015;10:CD011407.
- 18 Tanner T, Aspley S, Munn A, *et al.* The pharmacokinetic profile of a novel fixed-dose combination tablet of ibuprofen and paracetamol. *BMC Clin Pharmacol* 2010;10:10.
- 19 Moore R, Derry S, Taylor RS, *et al.* The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Pract* 2014;14:79–94.
- 20 Moore RA, Straube S, Aldington D. Pain measures and cut-offs—'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013;68:400–12.
- 21 Moore A, Derry S, Eccleston C, *et al.* Expect analgesic failure; pursue analgesic success. *BMJ* 2013;346:f2690.
- 22 Conaghan PG, Peloso PM, Everett SV, *et al.* Inadequate pain relief and large functional loss among patients with knee osteoarthritis: evidence from a prospective multinational longitudinal study of osteoarthritis real-world therapies. *Rheumatology (Oxford)* 2015;54:270–7.
- 23 Lin HY, Cheng TT, Wang JH. Etoricoxib improves pain, function and quality of life: results of a real-world effectiveness trial. *Int J Rheum Dis* 2010;13:144–50.