Inflammopharmacol (2014) 22:63–65
DOI 10.1007/s10787-013-0189-1

Inflammopharmacology

POINTS OF VIEW

Paracetamol (acetaminophen): a blessing or a hidden curse?

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Received: 20 August 2013 / Accepted: 22 August 2013 / Published online: 27 September 2013

Abstract This Journal has recently published a splendid review of all you need to know about paracetamol (Graham et al. 2013), an analgesic widely used in the long-term management of arthritis. It clearly presents the science and hard facts. This commentary, by contrast, discusses some aspects of the metapharmacology of paracetamol; particularly by asking questions of how we might extract more benefit and suffer less adverse reactions when using this analgesic in the context of non-transient inflammation. As both a drug and a toxin, paracetamol exemplifies how beneficial and/or deleterious responses may be conditioned by circumstances (disease stress, nutritional status, fasting, etc.).

Keywords Analgesics · Conditional pharmacology/toxicology · Gastrotoxicity · Hepatotoxicity · Sulphur nutrition

Few readers would dispute the universal facts of pain with the need for every household to have access to a safe, reliable and reasonably priced analgesic. In Western societies, aspirin, ibuprofen and paracetamol are now increasingly available from non-pharmacy sources, notably supermarkets, neighbourhood stores and service station shops. Less market-driven societies must still rely on alternative, more traditional analgesics. These include a number of 'hard' drugs to be found in coco leaves, kava root, opium poppies, betel nuts, etc. whose analgesic and/or mood elevating properties are fairly well understood; probably because they are quite dangerous too. These do-it-yourself medications are considered too addictive for legal marketing (in the West, at least).

Another class of phytochemicals can be bundled together as tolerable mild-pain suppressants. The analgesic action is partly understood—not necessarily totally explained—by their content of (a) salicylates, e.g. meadowsweet, willow and birch bark and many Australian bush remedies (Lassak and McCarthy 1997), or (b) inhibitors of eicosanoid production or TNF-α synthesis (Butters and Whitehouse 2009). Other plant products consumed to alleviate pain may act primarily as anti-microbials and/or anti-inflammatories (Mowrey 1973; Blumenthal 2000; Mills and Bone 2000), e.g. withania root, buchu leaves, hydrastis rhizomes, angelica root (dong quai), lapacho phloem (pau d'arco), valerian root, eucalyptus leaf and celery seed oils. These mainly suppress causes of pain rather than the actual pain responses.

In these days of 'quick-fix' prescription drugs, they are undervalued but thankfully, still cherished by healers following other traditions of pharmacy, e.g. (Australian) Aboriginal, Ayurvedic, Chinese, Persian, Pacific Islanders; often dating back over many centuries.

The problem with these traditional analgesics and anodynes is their variable qualities and consequently their uncertain efficacy. For example, the pau d'arco, prized for treating cancer pain in South America, may be considerably adulterated with the outer woody bark of the lapacho tree. So having available a cheap analgesic such as paracetamol (*N*-acetyl *p*-aminophenol) with defined and reproducible qualities (purity, stability and efficacy) is truly

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a blessing of our modern times; provided we remember the acerbic definition of a drug as 'a sub-toxic dose of a poison'. Paracetamol is no exception.

Now for some social history: we seem to owe the (re-) discovery of paracetamol to successful attempts to escape the nephrotoxicity of compound analgesics containing phenacetin (*N*-4 ethoxyphenyl acetamide, aka acetophenetidine). Analgesic nephropathy was at one time referred to as the Australian epidemic/disease, being so prevalent in Eastern Australia. This was because of uncontrolled access to analgesic powders containing aspirin plus phenacetin plus caffeine (APC), ingestion of which combined with dehydration (hot climate, caffeine diuresis) often severely damaged the kidneys in the long term and caused aspirin-induced gastropathy in the shorter term (Rainsford 2004). Today with the wide availability of cola beverages as a caffeine 'fix', consumers are no longer poisoned by phenacetin (replacing it with sucrose as their co-toxin and the risk of metabolic syndrome or other calorie-overdose morbidities as a consequence).

Studies of phenacetin metabolism in volunteers indicated it was detoxified by O-deacetylation and oxidation of the N-ethoxy group to form paracetamol before excretion as various conjugates (Brodie and Axelrod 1949). Related analgesic aniline derivatives, e.g. acetanilide, are similarly detoxified by hydroxylation forming paracetamol (Lester et al. 1947). Clinical studies soon disclosed that paracetamol, the metabolite, was itself an analgesic but not nephrotoxic. Subsequent experience showed we had just attained a change of organ toxicities, acquiring a hepatotoxin and an incipient gastrotoxin to replace the phenacetin nephropathy instead.

With analgesic doses of up to 4 g/day (less in the USA) about 3 % is oxidised in vivo to the hepatotoxic quinone-imine, acetimidoquinone, (MW 149) which requires at least 250 mg of the glutathione (MW 307), a tripeptide thiol to detoxify it. This may not seem much, but for people on impoverished diets, do they have this much glutathione to lose every day? [It is an essential regulator of redox-linked cellular physiology]. Furthermore, they must also acquire/generate sufficient sulphate ions (ca.800 mg) to detoxify about 30 % (1.2 gm) of the daily optimal paracetamol dose to facilitate its excretion as the phenolic sulphate metabolite. An important part of the physiological economy of sulphur in mammals is the generation of hydrogen sulphide, a gastroprotectant (Fiorucci et al. 2005), naturally sourced from cystathionine, a thio-dipeptide and normal intermediate in the transfer of sulphur from methionine to cysteine. So sulphur nutrition may become a conditional factor for paracetamol detoxication and tolerance. [Is it too ridiculous to wonder if some of the benefits of using glucosamine sulphate, so often consumed with paracetamol, for osteoarthritis—might be simply mimicked by another source of sulphate ions?]

The gastrotolerance of paracetamol is often contrasted with the gastric damage caused by aspirin and many acidic NSAIDs used as analgesics. The accepted explanation is that paracetamol does not inhibit COX-1, the enzyme normally producing cytoprotective PGE_2 in the stomach wall. This is a convenient generalisation but it does not always seem to hold true. A few clinical reports (admittedly the minority) have indicated that elderly patients on long-term high dose paracetamol (Rahme et al. 2002, Gonzalez-Perez and Rodriguez 2006) and paediatric patients (Li Voti et al. 1997) may indeed suffer gastric injury. Studies in rats have indicated some factors predisposing the gastric mucosa to haemorrhage as a response to orally administered paracetamol. They include (1) fasting, (2) disease stress and (3) gastric (hyper)acidity. The disease 'stress' could be elicited by an acute inflammation or pre-established polyarthritis or injecting methacholine to mimic activation of the vagal nerve and increase acid secretion. The concentration of HCl as subtonic solutions ($\leq$0.15 mol/L) was an important trigger factor for eliciting rapid mucosal damage (Rainsford and Whitehouse 2006). Considerably more work should have been done, e.g. studying possible benefits of proton-pump inhibitors. [The reluctance of Animal Ethics committees to approve such studies in academia effectively terminated this line of enquiry]. Nevertheless there is a clear take-home message that some patients, through the misfortunes of their circumstances and severity of stress activation, might be at greater risk than the majority. It is another example of Conditional Toxicology; a little harder to comprehend perhaps because it is multifactorial—in this case the susceptible stomach lining may have suffered a 'triple whammy' even before the gastrotoxin is presented. This raises the first question: should we juggle two paracetamol formulations, one for day and another (slower release) for night-time use when gastric contents are minimal? Then there is the related question: for how long could one safely adjust gastric acidity, e.g. with bicarbonate to still support the essential role of gastric acid in processing/sterilising food but ensuring it never exceeded paracetamol-tolerable levels?

Paracetamol also offers an example of how circumstances can determine drug efficacy, a phenomenon described as Conditional Pharmacology. At low levels of oxidant stress/inflammatory 'tone', it is a potent inhibitor of COX-2 when only low levels of arachidonate are released from tissue stores (Boutaud et al. 2002). Escalation of the peroxide tone and increasing local arachidonate concentrations, occurring with severe inflammation or during platelet aggregation, effectively reduce paracetamol's efficacy (Graham et al. 2013). This helps explain why leukocyte-driven inflammation (as in gout, rheumatoid arthritis) and platelet activation are much less responsive to

paracetamol as an anti-inflammatory, thereby limiting its local analgesic action in the more stressful and painful forms of arthritis. Paradoxically, paracetamol may be rather useful in another context, potentially suppressing tissue injury rather than algesia. This is because defensive but pro-inflammatory peroxidases can oxidise paracetamol to a dimer while simultaneously reducing normal halide/pseudo-halide oxygenation to form hypochlorite, hypobromite, hypothiocyanite, etc. which are all natural sterilants against micro-organisms but quite damaging to collateral host tissues.

Looked at rather objectively, it sometimes seems that paracetamol can be a bit too hard to handle at times, at least until we know rather more about the cycling phenomena, i.e. rise and fall of the peroxidative tone and other pro-inflammatory factors within sites of inflammation—or indeed within the nervous system. As the Jewish teacher (Qoheleth) wrote so long ago, "Everything has a time—including a time to break down and time to build up" (Ecclesiastes 300BC).

Inhibiting COX enzymes may indeed diminish some forms of pain but there are counter-productive consequences in the longer term including: (1) delaying healing, and (2) disrupting acquisition of tolerance to immunogenic arthritigens. With respect to this latter property (Whitehouse 2005), paracetamol is no different to other NSAIDs in model studies in rats (Whitehouse et al. 2008) and should certainly be considered a cryptotoxin.

In conclusion, a pessimistic summary of paracetamol's pharmaco-activity must include (a) the largely irreversible hepatotoxicity and (b) the chronic suppression of (often helpful) low-level prostanoid synthesis: things we might prefer not to know about—but should. And we should be clearly aware of its incipient gastrotoxicity especially in treating nocturnal pain—particularly when ingested with minimal fluids (and so rarely with food).

Optimistically it is a blessing being cheap, widely available (almost), non-addictive and really helpful for minor or short-lived incidences of pain.

But is it safe? This is the question we must continually (re-)consider.

Conflict of interest The authors declare that they have no conflict of interest.

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