Paracetamol: the forgotten drug

Paracetamol is one of the commonly used drugs worldwide and the commonest drug used in children, but its actual mechanism of action remains to be elucidated. This article highlights the current controversies surrounding paracetamol and discusses its mechanisms, in light of emerging evidence of potential drug interactions.

History

Paracetamol was first synthesized in 1878 by Morse and used clinically by von Mering in 1887. It was then overtaken by phenacetin until 1948, when Brodie and Axelrod discovered that N-phenylacetamide caused methaemoglobinaemia and, ultimately, hepatic and renal failure (Brodie and Axelrod, 1948). The analgesic effect of N-phenylacetamide was attributed to its active metabolite paracetamol. Paracetamol was thus 'rediscovered' and marketed in the 1950s. It has been used as an effective analgesic in both oral and rectal preparations. With the recent availability of an intravenous formulation and hence the advantage of 100% bioavailability, there have been significant advances in its use in the perioperative setting.

Suggested mechanisms of action

Thought to have a central antinociceptive effect, paracetamol has been found in significant concentrations in the CSF after infusions in children (Kumpulainen et al, 2007). There are currently three main hypotheses with respect to its mechanisms of action:

The first hypothesis relates to prostaglandin H2 synthase inhibition. It is well known that cyclooxygenase (COX) enzymes act on arachidonic acid to produce prostaglandin. This is mediated by prostaglandin H2 synthase, a site-specific and selective enzyme. These sites include COX, the target for non-steroidal anti-inflammatory agents, and peroxidase, the cosubstrate of which paracetamol reduces. There are two steps within the same enzyme at the two distinct sites. These are COX catalysed oxygenation, and reduction of hydroperoxides in the peroxidase site regenerating the resting enzyme. Paracetamol acts as a reducing cosubstrate for prostaglandin H2 synthase-peroxidase and reduces the oxidative state of the enzyme to the ferric or resting state (Kis et al, 2005). Essentially, paracetamol reduces the oxidized form of COX peroxidase in order to prevent it from acting on arachidonic acid to produce prostaglandin.

This COX model does not accommodate some of the characteristics of paracetamol. Although its antipyretic and analgesic effects may be explained by inhibition of COX-2, why is paracetamol not anti-inflammatory? A third COX splice variant of COX-1 was described in 2002 (Chandrasekharan et al, 2002), named COX-3. It was thought to be selectively inhibited by drugs such as paracetamol, and could represent a central mechanism by which paracetamol worked. This has generated considerable debate (Kis et al, 2005). Studies of the prostanoid-producing enzyme underlying pyrexia associate it neither to COX-1 nor COX-2.

In animal models, deletion of the COX-2 but not of the COX-1 gene (which also encodes COX-3) decreases pyrexia (Shuxin et al, 2008). It is thus suggested that multiple COX isoenzymes could be derived from the COX-1 and 2 genes, providing a continuum of enzymes and products with overlapping functions. Paracetamol may also act at a different site to the other non-steroidal anti-inflammatory agents. Unlike non-steroidal anti-inflammatory agents, paracetamol does not inhibit peripheral prostaglandin H2 synthase hence it only has a central antinociceptive effect. Prostaglandin H2 synthase inhibition is dependent on intracellular hydroperoxide level or 'peroxide tone'. Paracetamol is a poor platelet inhibitor, as platelets only express prostaglandin H2 synthase-1 and are high in 'peroxide tone'. It is a poor inhibitor of activates leucocytes, which rely on prostaglandin H2 synthase-2 and are high in 'tone', but it does cause prostaglandin suppression in vascular endothelial cells and neurons, which are low in 'tone'.

The second proposed mechanism of action relates to modulation of the serotoninergic system by stimulating the descending serotonin pathway (the inhibitory nociceptive signalling in the spinal cord). Tropisteron, a 5HT3 antagonist, blocks the antinociceptive effect of paracetamol (Allouia et al, 2002). In animal models, destruction of serotonin bulbospinal pathways reduces the antinociceptive effects of paracetamol (Tjolsen et al, 1991). In healthy volunteers, 5HT3 antagonists, including granisetron 3 mg and tropisetron 5 mg, may block the analgesic effects of paracetamol (Pickering et al, 2006).

The third proposed mechanism is the indirect activation of cannabinoid type 1 (CB1) receptors. Following deacetylation to p-aminophenol, paracetamol is conjugated with arachidonic acid to form N-arachidonoylphenolamine (AM404). However, AM404 is in fact an endogenous cannabinoid which activates vanilloid subtype 1 receptors and inhibits cellular anandamide uptake, allowing cannabinoids like anandamide to remain in the synaptic clefts. AM404 is also a transient receptor potential vanilloid type 1 (TRPV1) agonist, which is activated by capsaicin.

Similarly to cannabinoids, paracetamol probably produces descending spinal inhibition. They both lower body temperature clinically and have subjective effects of euphoria and relaxation shared by aniline analgesics. In animal models CB1 antagonists completely prevent the analgesic action of paracetamol, supporting this proposed mechanism of action (Ottani et al, 2006). COX, cannabinoids and TRPV1 in combination could also be involved in thermoregulation (Hogestatt et al, 2005).

Toxicity and drug interactions

Although there is a very low incidence of toxicity, paracetamol is a known hepatotoxic drug, causing 42% of cases of acute liver failure. Paracetamol is inactivated in the liver, being conjugated to glucuronic acid (60%), sulphuric acid (35%) and cystines (3%). Paracetamol is partly metabolized by cytochrome p450-dependent N-hydroxylation. This leads to the formation of N-acetylbenzochinonimin, a very reactive intermediate metabolite which usually reacts with sulphydryl

groups of glutathione. After high doses of paracetamol, glutathione stores in the liver are depleted and N-acetylbenzochinonimin reacts with sulphydryl groups of liver proteins, causing liver failure. Conversely, in liver failure not caused by paracetamol toxicity, the metabolism of paracetamol may be reduced, prolonging its action.

Elimination is through the kidneys. Although less than 5% of paracetamol is excreted unchanged, and its metabolites excreted through the kidney are inactive, renal failure patients may take longer to eliminate paracetamol and caution needs to be exerted in its use.

Enzyme-inducing drugs and alcohol can increase the metabolism of paracetamol. Oral anticoagulants such as warfarin with paracetamol can cause dose dependent anti-aggregatory effects on platelets. Paracetamol doses of 4 g a day with warfarin have been reported to induce profound hypocoagulation (Mahe et al, 2005).

Paracetamol interacts with 5HT3 antagonists too. As previously discussed, one of the proposed mechanisms of action of paracetamol is modulation of the serotoninergic system (Pickering et al, 2006).

Conclusions

Paracetamol is a safe and underestimated drug for use in the hospital and community setting. It has a central antinociceptive action although the exact mechanism still remains to be determined. The possibility of serotonergic action may have relevant clinical implications in the use of paracetamol and concurrent antiemetics during the perioperative period. BJHM

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KEY POINTS

- Paracetamol is a commonly used drug with a good safety profile.
- It has a central anti-nociceptive action although the exact mechanism still remains to be determined.
- However, there is the possibility of drug interactions, particularly with serotonin antagonists and warfarin.
- Availability in intravenous preparation with increased bioavailability has significant advantages in perioperative analgesia.