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Future Perspectives with Paracetamol

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Abstract

Paracetamol (acetaminophen) is well established as a leading non-prescription antipyretic analgesic drug. Future developments are likely to include new formulations to achieve rapid absorption for a fast onset of action, and prolonged absorption to extend the duration of action for regular long-term administration. Better dosage forms are also required for rectal administration. The availability of intravenous paracetamol has greatly extended the use of this drug as an adjunct to postoperative analgesia and for control of fever in the intensive care setting. Intravenous paracetamol is available in only a few countries at present, but it seems inevitable that it will be marketed much more widely in the future. The misuse of paracetamol as a fashionable agent for self-poisoning seems likely to continue, and liver failure may still occur in the small proportion of overdose patients who present too late for effective antidotal treatment with *N*-acetylcysteine. Much effort is being devoted to the study of the molecular mechanisms of paracetamol hepatotoxicity, and it is hoped that further advances may make it possible to prevent liver failure in all patients, irrespective of delays in presentation. At the same time, there is great interest in the mechanisms of the therapeutic actions of paracetamol and its effects on the different isoforms of cyclo-oxygenase. There will probably be important new findings in this area and these may lead to wider clinical use. Meantime, possible novel therapeutic applications for paracetamol include its use as an antioxidant to prevent atherosclerosis and cardiovascular disease by inhibiting the oxidation of low-density lipoproteins, and to prevent the formation of cataracts.

1. Introduction

Paracetamol (acetaminophen) has a well-established position as an effective non-prescription analgesic antipyretic agent and, when it is used correctly, it has an exemplary record of safety. Under most conditions, paracetamol has only minor and variable effects on prostaglandin synthesis and it does not cause the serious prostaglandin-dependent toxicity that characterises the adverse reaction profile of aspirin and the conventional NSAIDs. It can be used by all groups of patients, including the young and the elderly, and during pregnancy. With the exception of hepatic failure and a history of allergic reactions to the drug, there are no absolute contraindications to its use in any disease state and with correct use it does not cause serious interactions with other therapeutic agents, with the possible exception of oral anticoagulants. Because it is a major metabolite of phenacetin, paracetamol has come under suspicion as a cause of analgesic nephropathy. However, there is no clinical evidence that, as a single analgesic, it is an important cause of this condition.

Unfortunately, paracetamol has become fashionable as the preferred agent for self-poisoning in some countries, and in major overdose it can cause acute hepatic necrosis. Liver damage can be prevented by the early administration of *N*-acetylcysteine, but a small proportion of patients present too late for effective treatment. In such circumstances, liver damage may progress to acute

liver failure, and liver transplantation may offer the only hope of survival. It is unfortunate that the record of this effective and otherwise very safe drug should be compromised by the tiny proportion of the population who misuse it by deliberately taking it in overdosage. Liver damage has also been reported in patients who have allegedly taken paracetamol for therapeutic purposes, but these reports are anecdotal and in most cases the dose has clearly been excessive.

Despite these problems, paracetamol is likely to continue as a leading non-prescription analgesic antipyretic for many years to come. With regard to the future, the clinical utility of paracetamol is likely to be enhanced by the introduction of new dosage forms and much greater availability and use of injectable formulations. There will undoubtedly be continued interest in the mechanisms of action of paracetamol and a better understanding of its effects on the different isoforms of cyclo-oxygenase could lead to more specific therapeutic use. Paracetamol has antioxidant actions under certain conditions and this opens up the possibility of novel therapeutic indications for protection against cardiovascular disease and cataract.

2. New Dosage Forms

There are conflicting requirements for the formulation of a non-prescription antipyretic analgesic drug. Rapid absorption is required for the quick relief of acute pain and for the rapid reduction of fever; conversely, slow and prolonged absorption is desirable to extend the duration of action with regular administration in the management of chronic pain. The formulation of paracetamol has therefore been modified to produce both rapid- and slow-release dosage forms. Under certain conditions, with the use of effervescent tablets and formulation with sodium bicarbonate, the absorption of oral paracetamol can be accelerated to the extent that the C_{max} occurs within 10–15 min,[1,2] which allows a faster onset of analgesic activity (median time 20 min with effervescent formulations, rather than 45 min with the non-effervescent forms[3]). Conversely, extended-release dosage forms of paracetamol have been introduced in attempts to increase the dosage interval for use in chronic painful conditions such as osteoarthritis in the elderly.[4] It is likely that the clinical utility of paracetamol will be extended further by the introduction of more versatile formulations for specific indications.

3. Routes of Administration

In addition to the usual oral route, paracetamol is also given rectally and intravenously. Rectal administration is particularly useful for perioperative analgesia and in young children but, unfortunately, efficacy is often compromised by slow and unreliable absorption. In some countries, paracetamol has been available for intravenous administration as propacetamol, its soluble *N*,*N*′-diethylglycyl ester prodrug. After administration by this route, propacetamol is rapidly and quantitatively hydrolysed to paracetamol by plasma esterases.[5] Because of the ease and reliability of parenteral administration, propacetamol has been extensively used for pain relief and reduction of fever in a variety of circumstances, including paediatric practice, postoperative analgesia and intensive care.[6,7] However, the need for dose reconstitution and the issue of skin sensitisation in nurses have led to the development of a solution of paracetamol for intravenous use, which has already replaced propacetamol in some countries (see paper by Bannwarth et al. in this supplement). This new intravenous formulation of paracetamol is ready for use, comparable to propacetamol with respect to efficacy, and better tolerated at the site of administration. The single most important development in the future of paracetamol is likely to be its much wider availability for intravenous adjunctive analgesia in combination with narcotic analgesics and conventional NSAIDs.

4. Future Perspectives

4.1 Antioxidant Effects and Cardiovascular Protection

Increased concentrations of low-density

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lipoproteins (LDLs) are associated with atherosclerosis, myocardial infarction and stroke. The oxidation of LDL and its subsequent uptake by macrophages is believed to have a primary role in atherogenesis, and there has been much interest in the use of dietary and chemical antioxidants to protect LDL from oxidation and reduce the risk of cardiovascular disease.

In this context, paracetamol has antioxidant properties by virtue of its phenolic group. It can act as a free radical scavenger and it reduces the oxidative damage caused by peroxynitrite.[8] Paracetamol inhibited the oxidation of LDL induced by copper and azo compounds, in addition to the oxidation produced by activated human peripheral blood mononuclear cells.[9] In another study, paracetamol and some NSAIDs increased the binding of LDL to cultured hepatoma HepG2 cells and also increased the cell association and degradation of LDL by enhancing the expression of the mRNA of LDL receptor protein in HepG2 cells. These actions would lead to a decrease in circulating LDL-cholesterol concentrations, with a corresponding reduction in the risk of cardiovascular complications.[10] In healthy volunteers, the administration of paracetamol 1g every 6 hours for 2 days reduced the oxidation of LDL caused by copper ions and by activated human macrophages, and paracetamol added to LDL inhibited its oxidation in a dose-dependent manner.[11] In other studies, aortic atheromatous streak formation and oxysterol concentrations in hypercholesterolaemic rabbits were reduced by the administration of an average dose of paracetamol 28 mg/kg daily for 12 weeks.[12-14] In contrast to these findings, paracetamol has been reported to stimulate the oxidation of LDL by myeloperoxidase through the formation of a phenoxy radical.[8]

It is not known whether the inhibitory effects of paracetamol on the undesirable oxidation of LDL will prove to have any clinically useful effects on the progression of atherosclerosis in man. In this context, there has been anecdotal reference to a lack of increase, or a decrease, in arterial wall intimal thickness in seven hypertensive patients with a long history of paracetamol use.[15] Any such benefit with paracetamol would be a particular advantage, because all NSAIDs have important adverse effects in patients with cardiac failure and hypertension.[16,17]

4.2 Prevention of Cataract

Another potential use of paracetamol that follows from its antioxidant properties is protection against cataract. In case-control studies carried out in Oxfordshire, the use of paracetamol for at least 4 months was associated with a striking reduction in relative risk of cataract. In a comparison of 300 cases and 609 controls, the relative risk was reduced to 0.45 in those taking paracetamol and similar protection was observed with aspirin and ibuprofen.[18] These findings were confirmed in a subsequent larger study and protection was observed with as little as a total lifetime intake of 200g of paracetamol.[19] The mechanisms of protection against cataract by paracetamol and other analgesics are not known, but binding to the soluble lens proteins and inhibitory effects on lens zeta-crystallin have been proposed.[20,21] It remains to be seen whether this valuable effect of paracetamol will result in its therapeutic use for the prevention of cataract in individuals such as those with diabetes, who are at particular risk.

5. Conclusions

As the major metabolite of acetanilide and phenacetin, paracetamol has a long pedigree and it is the most commonly used of all non-prescription antipyretic analgesic drugs worldwide. It is available for oral, rectal and intravenous administration and is well absorbed and extensively metabolised, with an elimination half-life of 1–2.5 hours. These properties make it suitable for the treatment of acute pain and fever of diverse origin. Different dosage forms of paracetamol have been developed for specific indications, such as prolonged release formulations for the relief of chronic pain. Unlike NSAIDs, paracetamol appears to have only weak and inconstant effects on cyclo-oxygenase.

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Used correctly, paracetamol has an exemplary safety record and it can be used in virtually all patient groups and age groups, and during pregnancy. In contrast to the NSAIDs, it does not cause serious gastrointestinal, renal or cardiovascular toxicity. Cross-reaction with aspirin and other NSAIDs in patients who are intolerant of these agents is not common and is rarely life-threatening. With the possible exception of warfarin, paracetamol does not cause serious adverse interactions with other drugs. If taken in large doses, as for example with deliberate self-poisoning, it can cause hepatic necrosis through the formation of a minor but toxic metabolite. Fortunately, liver damage can be prevented by the early administration of *N*-acetylcysteine.

In most clinical models of pain, fever and osteoarthritis, the efficacy of paracetamol is comparable to that of conventional NSAIDs and the cyclo-oxygenase inhibitors, and because of its better safety record it is the non-prescription analgesic of choice for many indications. This is particularly the case for vulnerable elderly patients with chronic painful conditions such as osteoarthritis. Paracetamol has useful opioid-sparing effects and it is often used in combination with these and other drugs for postoperative 'balanced' or 'multimodal' analgesia. Depending on the circumstances, paracetamol can act as an antioxidant. Possible future novel therapeutic applications include cardiovascular protection through inhibition of the oxidation of LDL and the prevention of cataracts. Acute and chronic pain seriously limit the quality of life for many people and constitute an enormous economic burden on society. In this context, paracetamol is a valuable drug that is very cost-effective in terms of efficacy and safety.

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