

## FOREWORD

Most drugs become obsolete as they age, giving way to new, more effective or safer products. Yet paracetamol (acetaminophen) has escaped this dire fate. Indeed, more than a century after its discovery and more than 50 years after being included in our pharmacopoeia, paracetamol is the most widely used analgesic/antipyretic in the world. But for all that, has paracetamol revealed all of its secrets? This special issue of 'Drugs' attempts to answer this question by summarising our knowledge to date and defining the role of paracetamol in the treatment of pain.

Firstly, A. Eschalié and co-workers review the mechanism of action of paracetamol, a topic under constant debate. Improved understanding of this mystery would open up promising horizons for the discovery of new analgesics. Although it is certain that paracetamol is neither a nonsteroidal anti-inflammatory drug (NSAID) nor an opioid, and that it has a predominantly central action, its biological target remains a mystery. The recently identified cyclo-oxygenase isoenzyme, COX-3, within the central nervous system could be a candidate as it would appear to be inhibited by paracetamol and would thus explain the analgesic/antipyretic activity of the drug. Further research is needed to confirm this theory.

F. Péhourcq and myself have shown that the wide range of dosage forms is an unquestionable asset for paracetamol; the clinician can select the appropriate formulation and route of administration for each situation. However, the most important feature of this agent is its particularly favourable risk/benefit ratio that has earned paracetamol a place as the symptomatic treatment of choice for fever, particularly in children, and for mild-to-moderate pain, especially in the elderly or in frail patients. Paracetamol has also proved its worth in moderate-to-severe pain, where its combination with NSAIDs or opioid analgesics enables lower doses of the latter to be used, thus minimising NSAID and opioid-related adverse events. Therefore, as pointed out by H. Kehlet and M.U. Werner, paracetamol is an essential component in the treatment of acute pain, and post-operative pain in particular. And as underlined by K.D. Brandt, it is also the first-line analgesic for the treatment of osteoarthritis, where if necessary, long-term treatment can be continued as long as it provides adequate relief. In their critical analysis of the literature, G.G. Graham and colleagues confirm the excellent tolerability of therapeutic doses of paracetamol and highlight the existence of biases in the few epidemiological studies that have questioned the safety of this drug. According to C.J. Phillips, paracetamol can therefore be considered as not only cost-effective and but also as a valuable drug in public health terms.

In his conclusion, L. Prescott speculates on future perspectives with paracetamol. Certain studies have apparently demonstrated novel therapeutic applications such as prevention against cataract or atherosclerosis and cardiovascular disease. These have of course still to be confirmed by further

methodologically irreproachable prospective studies. Whatever the case, paracetamol, this spirited centenarian, is still making news.

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