

Preface

Ibuprofen is probably one of the most successful drugs used worldwide for the treatment of mild to moderate pain and various inflammatory conditions. Since its initial discovery half a century ago in December 1961 by Dr. (now Professor) Stewart Adams, the late Dr. John Nicholson and Mr. Colin Burrows of the Boots Co. Nottingham (UK) (see photo), ibuprofen has been developed in a wide variety of oral and parenteral formulations for use in an amazing variety of indications. My chapter on the “History and Development of Ibuprofen” written in the first monograph (which I also edited) on this drug details the twists and turns that took place in the discovery and development of ibuprofen from initial humble beginnings. It is a great tribute to Stewart Adams and his colleagues that their insight and persistence enabled the pharmacological activities of ibuprofen to be discovered and clinical potential to be realized at a time when little was known about inflammatory processes, let alone the techniques for quantifying clinical responses in arthritic and other painful inflammatory conditions. Indeed, it was only through screening several thousand compounds for anti-inflammatory, analgesic, and antipyretic activity in what were then relatively newly established animal models in guinea pigs and rats that the pharmacological activity of ibuprofen was identified, and found to be uniquely active compared with other compounds including that of aspirin, a reference standard employed at the time. These discoveries were essentially made on an empirical basis. It was a decade or so later before the discovery of prostaglandins and their actions in regulating inflammation. Also, it took longer before assays for detecting anti-inflammatory activity based on prostaglandin synthesis inhibition were developed, conditions understood and then refined as well as validated for screening potential therapeutic agents.

In the process of the early clinical trials with ibuprofen, initially in patients with rheumatoid arthritis, using the approach of cautious introduction using relatively low doses of the drug, that its efficacy and safety were appreciated. Later on, higher doses were found necessary for optimal effects, and proved relatively safe after long-term usage. This, and evidence from toxicological studies and extensive clinical investigations, showed that ibuprofen was safer as or more effective than

the established non-steroidal anti-inflammatory drugs (NSAIDs) (aspirin, indomethacin, and phenylbutazone).

As detailed in this book, ibuprofen has since been proven to be one of the safer NSAIDs. This is such that it has been used extensively as a standard for comparison in the large number of clinical trials of newly developed agents. These trials are reviewed here, and although some newer drugs (e.g., coxibs) have been found to have fewer gastrointestinal (GI) adverse effects, their margin of improved GI safety is relatively small, and this improvement has not come without other safety issues (e.g., cardiovascular reactions) or added costs to healthcare budgets or the individual.

One of the great successes with ibuprofen was its introduction in a low dose ($\leq 1,200$ mg/day) form for over-the-counter (OTC), non-prescription sale in the UK (in 1983), USA (in 1984) and now in 82 countries worldwide. Large-scale clinical and epidemiological studies have shown that this OTC form of the drug is relatively safe in the GI tract compared with aspirin and other NSAIDs, and is comparable in GI safety with paracetamol (acetaminophen), yet without the risks of liver toxicity seen with the latter. This is not to say that OTC ibuprofen is without adverse effects. As reviewed in this book, development of these untoward actions is now well-understood, and most reactions, though discomforting to some degree, are minor and preventable, or at least are reversible upon withdrawing the drug (indicating reversibility of toxic mechanisms).

This book also reviews the disposition and unique modes of action of ibuprofen. Studies on the pharmacological properties of ibuprofen have advanced in parallel with understanding of the cell and molecular biology of inflammatory processes, especially those underlying neuro-pathological reactions in pain and neurodegenerative diseases and cancer-related inflammatory reactions. Consequently, much interest has been shown in the past two decades or so in the potential for ibuprofen to prevent conditions such as Alzheimer's and atherosclerotic dementias, Parkinson's disease and neural injuries, as well as colo-rectal, mammary, and some other cancers. While these developments are undoubtedly exciting, there are, however, extensive investigations which will have to be performed to understand when ibuprofen should be employed in the various stages of these chronic and complex conditions, and at what dose(s). Indeed, special formulations of ibuprofen may need to be developed to ensure optimal biodisposition of the drug (e.g., localized delivery in the colon in colo-rectal cancer) or prolonged pharmacokinetics for specific applications in different chronic diseases (e.g., in cystic fibrosis) or special patient groups (young and the elderly) in which long-term safe use is required.

Recently, there has been much commercial and clinical interest in developing and use of combinations of ibuprofen with other drugs (e.g., paracetamol, codeine, caffeine) and some natural products. The objective of many drug combinations has been to raise the "analgesic ceiling" to achieve greater or more sustained acute pain relief. While in many cases the "jury may still be out" on most of these claims, there are already some indications of potential therapeutic benefits of the drug combinations in certain painful conditions, while still retaining the relative safety benefits of ibuprofen (at least at OTC dosages). Further investigations will be

required with some of these ibuprofen–drug mixtures to establish optimal conditions for their application and use in specific indications.

This book is intended for a broad readership for anyone interested in the properties, actions, and uses of ibuprofen. It is intended that this book be written in a more general style to reflect interest in it by a broad readership. There are several concepts that are presented diagrammatically but with sufficient detail such that key points are emphasized. For more in-depth information, the reader is referred to the specialist book “Ibuprofen: A Critical Bibliographic Review” (1999; 2nd edition in preparation), edited by myself.

This book would not have been possible without the privileged collaboration and valuable advice of my long standing research colleagues, among them Dr. Brian Callingham (University of Cambridge, UK), Professor Michael Whitehouse (University of Queensland & Griffiths University, Queensland, Australia), Professors Walter Kean and Richard Hunt and the late Watson Buchanan (McMaster University, Hamilton, Ontario, Canada).

I would also like to record my appreciation of advice of research colleagues in pharmaceutical companies that produce and market ibuprofen who have often given me valuable information on this drug, and access to their drug safety databases without prejudice. Among these, I have been privileged to have advice and receive important historical information from the discoverer of ibuprofen, Professor Stuart Adams, OBE, to whom this book is dedicated.

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