Clinical Pharmacokinetics of Flurbiprofen and its Enantiomers

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Summary

Flurbiprofen is a chiral nonsteroidal anti-inflammatory drug (NSAID) of the 2-arylpropionic acid class. Although it possesses a chiral centre, with the $S$-$(+)$-enantiomer possessing most of the beneficial anti-inflammatory activity, both enantiomers may possess analgesic activity and all flurbiprofen preparations to date are marketed as the racemate. Flurbiprofen exhibits stereoselectivity in its pharmacokinetics. Stereoselectivity is exhibited at the level of protein binding and metabolite formation. Hence, the data generated using nonstereoselective assays may not be used to explain the pharmacokinetics of individual enantiomers.

The absorption of flurbiprofen is rapid and almost complete when given orally. The area under the plasma concentration-time curve of flurbiprofen is proportional to the dose administered to patients. Sustained release dosage forms are available, which may be beneficial due to the short terminal phase elimination half-life of conventional immediate release flurbiprofen (3 to 6 hours). They may also decrease local gastrointestinal adverse effects. Although with these preparations the peak plasma drug concentration is reduced and time taken to achieve peak concentrations is prolonged, the bioavailability is the same as that with regular release counterparts. Flurbiprofen binds extensively to plasma albumin, apparently in a stereoselective manner. Substantial concentrations of the drug are
Flurbiprofen, racemic 2-(2-fluoro-4-biphenyl) propionic acid (fig. 1), is a nonsteroidal anti-inflammatory drug (NSAID), which is a potent inhibitor of prostaglandin synthesis.\(^{[1]}\) Flurbiprofen was introduced into the North American market in 1986 and has been available internationally since 1977.\(^{[2]}\) In the treatment of osteoarthritis, rheumatoid arthritis, acute gouty arthritis and ankylosing spondylitis, therapeutic doses of flurbiprofen have proven to be as effective as the other commonly used NSAIDs.\(^{[3,4]}\) Although gastrointestinal complications are most common, renal dysfunction, fluid retention, jaundice, cutaneous reactions and dyspnoea also occur, albeit at a lower frequency.\(^{[5]}\)

Flurbiprofen has potent analgesic effects and therefore it is used in short term alleviation of postoperative pain in dental patients,\(^{[6]}\) and for gingival inflammation and alveolar bone resorption in periodontal disease.\(^{[7-9]}\) It has also been studied for use as an anti-inflammatory agent in the treatment of ocular disorders.\(^{[10,11]}\)

The majority of chiral NSAIDs are currently marketed as racemates (i.e. equivalent proportions of both enantiomers). Excellent articles describing stereoselectivity in the pharmacodynamic and pharmacokinetic behaviour of NSAID enantiomers are available.\(^{[12,13]}\) Similar to a large number of other clinically important drugs, flurbiprofen exhibits stereoselectivity in action and disposition.\(^{[14]}\) As with all currently marketed chiral NSAIDs, anti-inflammatory activity is attributed almost entirely to the $S$-enantiomer.\(^{[15]}\) However, it has been suggested that analgesic activity may be exerted by both flurbiprofen enantiomers.\(^{[16]}\) Several studies have addressed the stereoselectivity of flurbiprofen enantiomers.\(^{[17,18]}\) Data generated using nonstereospecific approaches may not be extrapolated to explain the pharmacokinetics of individual enantiomers because nonstereospecific assay methods cannot interpret the time-course of the individual enantiomers. Indeed, use of this information in such a way may be misleading in relating either toxicity or efficacy to the racemic drug concentration.

A general review article is available, which deals with the pharmacological and therapeutic uses of flurbiprofen.\(^{[2]}\) In the present article the clinical pharmacokinetics of flurbiprofen and its enantiomers are reviewed.

### 1. Analytical Methods

A number of analytical methods are available for quantitative analysis of flurbiprofen in biological specimens. Earlier methods employed thin layer and gas chromatography.\(^{[19,20]}\) Due to the ease of sample preparation and greater precision,