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REPORT

Flurbiprofen and Its Derivatives of Many Therapeutic Uses—A Recent Report

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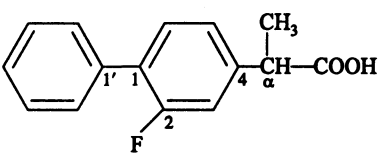
Flurbiprofen has shown an excellent therapeutic action against many diseases and has been reported to possess antiinflammatory, analgesic, antipyretic, antimicrobial, antipuritic, antithrombotic, antinociceptive, antitumour and radioprotective activities. The derivatives of flurbiprofen have been reported to contribute significantly in controlling various diseases. In this context, the present report deals with the summary of therapeutic uses of flurbiprofen and its various combinations that play an important role in controlling painful and deadly diseases along with reducing serious side effects caused by the usual medical treatment.

Key Words: Flurbiprofen, Nitroflurbiprofen, Antiinflammatory, Analgesic, Antipyretic, Antiperiodontitis, Antigingivitis, Antirheumatoid arthritis, Antitumour, Anti-Alzheimer's disease, Radioprotective properties.

Flurbiprofen (2-fluoro-α-methyl-1,1′-biphenyl-4-acetic acid), a nosteroidal antiinflammatory drug (NSAID) has also been found effective in the treatment of rheumatoid arthritis and degenerative joint diseases. R-flurbiprofen has been utilized in the treatment of neoplastic diseases such as breast cancer, lung cancer and prostate cancer as well as cystic fibrosis and Alzheimer's disease.



Flurbiprofen

In some cases, its derivatives have been found better than flurbiprofen itself, for example: (i) several flurbiprofen amides and hydrazones exhibited superior analgesic, antipyretic and antiinflammatory activities compared to flurbiprofen, (ii) nitroflurbiprofen (Flurbi-NO) caused significantly less gastric lesions than flurbiprofen, and many more. Some of the important therapeutic properties of flurbiprofen and its combinations are cateagorized in the following discussion.

Antiinflammatory, analgesic and antipyretic activitives: Flurbiprofen is an analgesic, antipyretic and antiinflammatory compound which is practically insoluble in water. The aqueous solution of flurbiprofen using various hydrotropes

has been attempted. The solubility increased ≤ 63x in the case of Na-benzoate. Using selected hydrotopes, aqueous injections of flurbiprofen were evaluated for antiinflammatory and analgesic activities with promising results[1]. The anti-inflammatory effect of flurbiprofen tape (FBP-T) by topical application has been investigated to adjuvant arthritic rats. The gastric damage induced by topical application of FBP-T was found significantly less than that seen in case of oral administration of flurbiprofen[2].

Several flurbiprofen amides and hydrazones have been found to exhibit superior analgesic, antipyretic and antiinflammatory activties compared to flurbiprofen[3]. Flurbinitroxybutylester, a novel antiinflammatory drug, has enhanced antithrombotic activity. It has been shown that the introduction of a nitroxybutylester moiety into flurbiprofen to form Flurbi-NO resulted in a compound with markedly reduced undesired effects in the gastrointestinal tract. This effect has been described to be linked to nitric oxide release from the Flurbi-NO[4]. Flurbiprofen with Eudragit, hydroxypropylmethyl cellulose and ethyl cellulose combination has been used in designing oral controlled release preparations with better antiinflammatory activity[5].

In order to reduce systemic side effects following oral administration, flurbiprofen has been formulated as transdermal gels consisting of the drug, Poloxamer 407 and EtOH in buffer solutions[6]. The adhesive preparations containing nonsteroidal antiinflammatory and analgesic agents like flurbiprofen has also been reported to show good adhesion to human skin and stretchability[7]. Anti-inflammatory activity of 1% flurbiprofen transdermal gel was evaluated using the carrageenan-induced rat paw edema method[8].

Antiperiodontitis and antigingivitis activities: An ointment base for nonsteroidal antiinflammatory agent flurbiprofen has been found successfully effective in the treatment of periodontitis without irritation. When the ointment was applied to the wet oral tissue such as mucosa, it stayed locally with sustained drug release. Such type of an ointment[9] contained carboxyvinyl polymers 2.0, ethanol 30.0, water 15.0, vinyl acetate resion 5.0, flurbiprofen 0.2, 1N-NaOH q.s. and glycerol to 100.0%. Similarly, an application of a paste containing flurbiprofen 0.5, hydroxypropyl methyl cellulose-2910 10.0, carboxyvinyl polymer 2.0, glycerine 10.0, EtOH 10.0 wt. % NaOH and water to gingiva hamsters fed with soft food, suppressed alveoloclasia and gingivitis[10].

A semisolid formulation containing flurbiprofen for the treatment of gingivitis comprised hydroxyethyl cellulose (HEC : 3, 5, 10%), PVP (3, 5%), polycarbophil (PC : 1, 3, 5%) and flurbiprofen (5%)[11]. Administration of nonsteroidal anti-inflammatory flurbiprofen on tissue healing after periodontal surgery has been reported to be very effective[12].

Antirheumatoid arthritis activity: Flurbiprofen, a potent nonsteroidal anti-inflammatory, analgesic and antipyretic drug, has been reported to be effective in the treatment of rheumatoid arthritis and degenerative joint diseases. Emulsification-solvent evaporation technique was used for the preparation of flurbiprofen microcapsules to control the release of flurbiprofen[13].

It has been described that pyridinoline excretion increased markedly in untreated adjuvant arthritic (AA) rats, but was substantially normalized by either CMT3 alone or by CMT8 with flurbiprofen. CMT3 or CMT8 are chemically

modified non-antimicrobial tetracycline derivatives[14]. Recently, flurbiprofen has been reported to decrease the resorption of alveolar bone in naturally occurring chronic destructive periodontal disease in dogs. It primarily decreases disease symptoms rather than to halt the progression of a disease like arthrorheumatism[15].

In the treatment of Alzheimer's disease and antitumour properties: R-flurbiprofen has been found useful in the treatment of neoplastic diseases such as breast cancer, lung cancer and prostate cancer as well as cystic fibrosis and Alzheimer's disease. Interestingly, R-flurbiprofen was shown to be much less ulcerogenic than its S-enantiomer, yet suppreses cell proliferation in the distal colon[16].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been recognised for inhibiting growth of colon tumours in animal models and for reducing the risk of colon cancer in humans. R-flurbiprofen and S-flurbiprofen significantly reduced colonocyte labeling index by 34 and 23% respectively. R-flurbiprofen caused minimal ulcer formation (4.48 mm^2) compared with S-flurbiprofen (94.4 mm^2). These findings suggested that R-flurbiprofen mediated control of colonocyte proliferation is independent of prostaglandin biosynthesis[17]. In another report, chemopreventive effects of R-flurbiprofen (R-FBP), the noncyclooxygenase-inhibiting enantiomer, could be extended to humans for prophylaxis and in the treatment of colon cancer[18].

Radioprotective effects: Radioprotective effects of two nonsteroidal anti-inflammatory drugs (NSAIDs), flurbiprofen (FBP) and its novel nitro derivative flurbiprofen-4-nitroxybutylester (Flurbi-NO), which exhibited decreased gastrointestinal toxicity, were compared in mice. Because of its lower potential for gastrointestinal damage, Flurbi-NO seemed to be a promising drug, which can find use in the protection of post-irradiation myelosuppression[19].

Repeated administration of flurbiprofen, an inhibitor of prostaglandin synthesis (IPS), has been found to enhance hemopoiesis in mice exposed to sublethal dose of fractionated γ-irradiation (5×3 Gy, intervals between fractions 24 h). The findings suggested a possibility to extend the radiation dose range, also to higher lethal radiation doses, by administering flurbiprofen instead of previously studied IPS indomethacin or diclofenac[20].

In the treatment of dry eye disorders: Compounds containg a nitric oxide generator (NOG) and methods of use for treating dry eye have been now discarded. The compounds of the invention promote nitric oxide (NO) production when administered to the eye. It is believed that NO stimulates mucin production in human conjunctival epithelium and are therefore believed to be useful in treating dry eye. Examples of NOG include NO-ketroprofen, NO-diclofenac and many others including NO-flurbiprofen. However, the most preferred NOG of the invention is molsidomine[21].

Antinociceptive effects: The antinociceptive effects of the S(+)-enantiomer of flurbiprofen (potent inhibitor of cyclooxygenase) and the R(–)-enantiomer (500 times less potent) have been investigated in the spinal cord of 20 anesthetized rats. S(+)-flurbiprofen was more potent than R(–)-enantiomer. When injected directly into the knee joint, S(+)-flurbiprofen (50 and 80 μg), but not the

R(–)-enantiomer (100 and 180 μg) reduced the hyperexcitability in 12 of 12 neurons. The doses used in these experiments did not produe any sedative effects in rats subjected to behavioural testing[22].

In a review with 85 references, the S-enantiomer of flurbiprofen has been shown to have both antiinflammatory and antinociceptive effects, whereas R-flurbiprofen is antinociceptive but not antiinflammatory. Importantly, only S-flurbiprofen inhibited prostaglandin biosynthesis *in vitro* at therapeutic concentrations. R-flurbiprofen did not undergo significant chiral inversion to S-flurbiprofen in rats and humans. The findings may be of clinical relevance, as it was demostrated that both enantiomers also were antinociceptive in humans. Because R-flurbiprofen caused less toxicity in rats than the S-enantiomer or the recemic compound, the most important side effect in the gastrointestinal tract might be achieved with the use of R-flurbiprofen for pain therapy[23].

Protective effects on gastric lesions: Nitroflurbiprofen caused significantly less gastric lesions than flurbiprofen, probably because of its capacity to release nitric oxide (NO) in the stomach[24]. Flurbiprofen (FBP) has been esterified with a histamine H_2-antagonist, PPA (N-[3-{3-(1-piperidinylmethyl)phenoxy}-propyl]-2-(2-hydroxyethylthio) acetamide), to yield a chimera drug, FBP-PPA and its protective effect towards gastric lesions, other toxicities and the deposition kinetics were investigated, as compared to those of flurbiprofen. The results obtained here indicated clearly that the chimera drug FBP-PPA scarcely forms any disorder of the gastric mucosa, even after multiple oral administration and thus is a potential candidate for oral use[25].

Nitric oxide (NO) has been reported to have paradoxical effects in experimental endotoxic shock, contributing to the hemodynamic consequences of endotoxin administration, but apparently protecting the gastrointestinal mucosa. A novel class of NO-releasing nonsteroidal antiinflammatory drugs (NSAIDs) has recently been described which exert antiinflammatory activities but produce less gastrointestinal injury than the parent nonsteroidal antiinflammatory drugs from which they are derived. These results demonstrated that flurbiprofen-4-nitroxybutyl ester is capable of protecting the gastrointestinal mucosa from injury, possibly through preservation of mucosal blood flow[26].

Many more therapeutically important activities of nonsteroidal antiinflammatory drugs (NSAIDs) including flurbiprofen are available in the literature. Some of them are: (i) flurbiprofen supported aspirin like drugs (ALD) in protection of human T lymphocytes against benzoquinone (BQ) cytotoxicity[27], (ii) nonsteroidal antiinflammtory drugs efficiently reduced the transport and cytotoxicity of adefovir mediated by the human renal organic anion transporter 1. Adefovir is a nucleotide analog with anti-human immunodeficiency virus (HIV) activity that has been extensively studied in clinical trials[28], (iii) flurbiprofen has been found useful in controlling the neurovascular deficit in diabetic rats, from which a potential therapeutic advantage could be derived[29], (iv) the importance of flurbiprofen in bone supporting dental implants has also been described[30], etc.

Thus, from the above findings, it seemed that flurbiprofen and its various combinations/derivatives are potentially very important for the cause of pharmacological interest.

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