INTRODUCTION

Chirality is defined as the geometric property of a rigid object (like a molecule or drug) of not being superimposable with its mirror image. Chirality is a property of matter found throughout biological systems, from the basic building blocks of life such as amino acids, carbohydrates, and lipids to the layout of the human body. The two mirror images of a chiral molecule are termed R and S enantiomers. Both enantiomers have the same chemical composition and structure, but in chiral environments such as the receptors and enzymes in the body, they can behave differently. A racemate or a racemic mixture is a mixture containing equal amounts of both enantiomers. In case of a drug, the two enantiomers may have different pharmacokinetic and pharmacodynamic properties. It is worth remembering the following important comments in the European Journal Of Clinical Pharmacology, 1984, 26, 663-8: “Too often, and even without it being noticed, data in the scientific literature on mixture of stereoisomers, racemates, are presented as if only one compound were involved. The neglect of stereochemical aspects of drug action ….. degrades many pharmacokinetic studies to expensive “highly sophisticated pseudoscientific nonsense…..” The development of ‘hybrid’ drugs, presented as a step forward in medicinal chemistry, tends to be step backward in therapy.” Clearly, 50% impurity in pharmaceuticals is not acceptable.

CHIRALITY AND NSAIDS

The NSAIDs have been intensively studied from the perspective of stereoselectivity. For NSAIDs, it is the enantiomer possessing the S configuration that almost exclusively possess the anti-inflammatory/analgesic activity while R enantiomers lacks such activity1 and may have some different activity2-4. For example, R-Flurbiprofen and R-Etodolac are undergoing development for the potential treatment of Alzheimer’s disease5 and cancer6, respectively. However, most of the NSAIDs are traditionally administered as racemates except Naproxen which is available as the single S enantiomer. In the following sections, new unichiral NSAIDs- Dexketoprofen, Dexibuprofen and S-Etodolac- are discussed.

DEXKETOPROFEN S(+)KETOPROFEN]
TROMETAMOL

Racemic Ketoprofen is a 50:50 mixture of S(+) and R(-) enantiomers7. Most or all COX inhibitory activity of Ketoprofen is attributed to the S(+)-enantiomer (Dexketoprofen)8. The R-enantiomer is 30 to 5000 times less potent as an inhibitor of COX-1 and about 100 times less potent as an inhibitor of COX-29. In addition, S-Ketoprofen less GI ulcerogenic potential as compared to the racemic Ketoprofen. In fact, R-enantiomer may contribute to the pathogenesis of intestinal ulcers10.

The absorption of S-enantiomer from racemic Ketoprofen and Dexketoprofen trometamol has been found to be equivalent and rapid11. The fast absorption could account for the suitability of Dexketoprofen in the management of acute pain. Dexketoprofen is effective at half the dose of racemate12. Several clinical trials conducted with orally administered Dexketoprofen trometamol in acute painful inflammatory conditions- dental pain, dysmenorrhea, acute musculoskeletal injuries, renal colic, orthopedic surgeries and chronic painful inflammatory conditions like osteoarthritis, have confirmed its high analgesic potency and good tolerability profile13,16. When compared to enantiomerically equivalent doses of Ketoprofen, Dexketoprofen trometamol has shown a comparable analgesic efficacy and tolerability13,16 but a faster onset of action13,14. In addition, Dexketoprofen improves the activity of opioid analgesics like Fentanyl15 and reduces the opioid requirement16.

SALIENT FEATURES OF DEXKETOPROFEN

- Most or all COX inhibitory activity of Ketoprofen is attributed to the S(+)-enantiomer (Dexketoprofen)
- R-enantiomer is 30 to 5000 times less potent as an inhibitor of COX-1 and about 100 times less potent as an inhibitor of COX-2
- Dexketoprofen is less ulcerogenic than the racemic Ketoprofen and R-Ketoprofen
• Dexketoprofen has faster absorption than racemate
• Dexketoprofen has established efficacy and tolerability in the treatment of acute and chronic painful conditions
• Dexketoprofen has comparable analgesic efficacy and tolerability but a faster onset of action than Ketoprofen

**DEXIBU PROFEN [S(+)]IBU PROFEN**

Racemic Ibuprofen contains equal quantities of R(-)-Ibuprofen and S(+)-Ibuprofen. R-Ibuprofen and Dexibuprofen differ in their physicochemical, pharmacological and metabolic properties. S-Ibuprofen or Dexibuprofen is the pharmacologically active enantiomer of racemic Ibuprofen. Dexibuprofen is the S(+)-enantiotomer of Ibuprofen and accounts for virtually all pharmacodynamic (analgesic, anti-inflammatory, antipyretic) activities of the racemic compound. In vitro, Dexibuprofen is over 100 times as potent as the R-enantiomer as an inhibitor of prostaglandin biosynthesis. In therapy, potential advantages of Dexibuprofen over racemic Ibuprofen include lesser toxicity, greater clinical efficacy and/or less variability in therapeutic effects achieved, and easier dose optimization, all at half the dose of Ibuprofen. Several clinical trials and post marketing surveillance studies have been performed to elucidate the efficacy and safety of Dexibuprofen. The findings from these studies demonstrate that Dexibuprofen is effective and very well tolerated in patients with acute dental pain and chronic osteoarthritis pain. These effects are comparable to Diclofenac, Celecoxib and enantiomerically equivalent dose of racemic Ibuprofen.

**SALIENT FEATURES OF DEXIBU PROFEN**

- Dexibuprofen is the pharmacologically active enantiomer of racemic Ibuprofen
- Dexibuprofen is over 100 times as potent as the R-enantiomer
- Dexibuprofen has lesser toxicity, greater clinical efficacy, less variability in therapeutic effects achieved and easier dose optimization, all at half the dose of Ibuprofen
- Dexibuprofen is effective and very well tolerated in patients with osteoarthritis and dental pain
- Efficacy comparable to Diclofenac, Celecoxib and double dose of racemic Ibuprofen

**S(+)-ETODOLAC**

S-Etodolac is a chirally pure, pharmacologically active form of Etodolac containing only S(+)-enantiomer. The racemate Etodolac has analgesic, antipyretic, and anti-inflammatory properties with more selectivity for induced COX-2 (associated with inflammation) over COX-1 (cytoprotective). Numerous studies have established the efficacy and tolerability of racemic Etodolac compared to other NSAIDs in the treatment of osteoarthritis, rheumatoid arthritis and post-operative pain. S-Etodolac has shown better gastrointestinal tolerability when compared with non-selective NSAIDs. Etodolac possesses a more favorable therapeutic index between anti-inflammatory effects and gastric irritation as compared to other NSAIDs. However, it is the S-enantiomer of Etodolac that possesses almost all of the anti-inflammatory activity while R-Etodolac is almost inactive. S-Etodolac is 2.6 times more potent than the racemate and 100 times more potent than R-enantiomer. Furthermore, S-Etodolac achieves greater concentrations in synovial fluid than plasma compared to R-Etodolac. S-Etodolac rapidly attains the peak plasma concentration and is rapidly cleared from plasma compared to R-Etodolac. R- and S-Etodolac competitively interact with each other for binding to human serum albumin and are displaced by each other. In an open label, multicentric, comparative clinical trial in 108 Indian patients with osteoarthritis, it was found that S-Etodolac extended release 300 mg tablet was equally effective in improving pain, stiffness and physical function when compared to Etodolac extended release 600 mg tablet. Both the drugs were very well tolerated in this study. Thus, it is justified to use a single active, potent enantiomer with the anti-inflammatory activity i.e. S-Etodolac.

**SALIENT FEATURES OF S-Etodolac**

- S-enantiomer of Etodolac possesses almost all of the anti-inflammatory activity while R-Etodolac is almost inactive
- S-Etodolac is 2.6 times more potent than the racemate and 100 times more potent than R-enantiomer
- S-Etodolac achieves greater concentrations in synovial fluid than plasma
- S-Etodolac has a favorable pharmacokinetic profile compared to R-Etodolac
- Efficacy and tolerability of S-Etodolac is comparable to the racemate

**CONCLUSION**

The NSAIDs used in clinical practice contain both R and S enantiomers, which have different pharmacological properties. Since, it is the S-enantiomer that has the anti-inflammatory/analgesic activity while R-enantiomer lacks such activity, it is thus imperative to perform the chiral switch i.e. to develop only the therapeutically effective S-enantiomer. This avoids the use of 50% impurity in the form of R-enantiomer and thus provides a less complex pharmacokinetics, avoids the enantiomer interactions and reduces the metabolic load on the body. The development of Dexketoprofen, Dexibuprofen and S-Etodolac is certainly a step forward in this direction.

**REFERENCES**

Chirally Pure Non-Steroidal Anti-Inflammatory Drugs


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366.


57. Data on File 3- a multicentric, randomized, Comparative Clinical trial to Evaluate the Efficacy and Safety of S-Etodolac in the Treatment of Osteoarthritis.