International Journal of Current Pharmaceutical Research
Vol 2, Issue 3, 2010
ISSN-0975-7066

Mini Review

S+ IBUPROFEN (DEXIBUPROFEN): THE SUPERIOR NON STEROIDAL ANTI-INFLAMMATORY AGENTS FOR DEVELOPMENT OF PHARMACEUTICALS

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Received 07 Jan 2010, Revised and Accepted 29 Jan 2010

Abstract
Ibuprofen is an important drug in the group of non-steroidal anti-inflammatory agent (NSAIDS) consisting of the 2-arylpropionic acids (Profens). The racemic mixture of S-(+) Ibuprofen and R-(-) Ibuprofen being used, but the biological activity is mainly due to S-(+) Ibuprofen. The development of dosage forms with ibuprofen involves major problem to achieve bioavailability and stability. This review article is intended to explain about the various S-ibuprofen and ibuprofen derivatives, also describes on the potential advantages like solubility and pharmacological properties of ibuprofen derivatives.

INTRODUCTION

Ibuprofen is non-steroidal anti-inflammatory agent with anti-pyretic properties used in the therapy of rheumatism and arthritis, and also used to treat mild to moderate pain, fever, primary dysmenorrhea, and other conditions. Ibuprofen is available in prescription and nonprescription strengths. The racemate of various formulations is still extensively used worldwide, and there are no indications that the racemate will be replaced by the single enantiomer[1]. Ibuprofen is a racemic mixture S(+)-ibuprofen (Dexibuprofen) and R(-)-Ibuprofen. Ibuprofen was the most extensively researched drug in terms of chiral characteristics and mechanisms.

Enantiomers have same physical and chemical properties, but differ in three-dimensional spatial arrangement. This leads to difference in pharmacodynamics and pharmacokinetics. The differences often depend on whether the center of asymmetry of the drug is in close proximity to the points of attachment to the protein. For example: S+ Ibuprofen is over 100-fold more potent an inhibitor of cyclo-oxygenase-I than R-Ibuprofen[2]. It was logical then, that there was the potential for improving the selectivity and potency of ibuprofen formulations by marketing ibuprofen as a single-enatiomer products. This article is intended to explain the lessen side effects and improved therapeutic effect of the steroselective S+Ibuprofen (Dexibuprofen) obtained with half the dose racemic ibuprofen formulation.

S+Ibuprofen other ibuprofen derivatives:

S-Ibuprofen (dexibuprofen) is active form in both invitro and invivo. The R-isomer is ineffective, but the body has a mechanism whereby the R-isomer is converted to the S-isomer very slowly by enzyme catalyzed reactions in the body[3]. In cystic fibrosis high dose of Ibuprofen is required for children due to chiral inversion of racemate[4]. Up to 30-60% of inactive R-ibuprofen undergoes bioconversion to active S-ibuprofen in the body[5]. This does take time, so the pharmacological activity is slower in the racemic form of the drug than if the S-isomer was used exclusively. Therefore S+ Ibuprofen is faster acting than racemic mixture and has advantageous thereputic effect over racemic ibuprofen. Dexibuprofen, which is the most active species pharmaceutically, and racemic ibuprofen are inherently different solid-state materials[6]. Indications include pain and inflammation associated with osteoarthritis and other musculoskeletal disorders; mild to moderate pain and inflammation including dysmenorrhoea and dental pain. 900 mg daily for dysmenorrhoea, max. single dose 400 - 300 mg for dysmenorrhoea, and not recommended for childs[17].

Table 1: Per day dose requirement for rheumatoid arthritis18-21

S.No	Ibuprofen (mg)	Ibuprofen sodium (mg)	Ibuprofen Lysinate (mg)	Dexibuprofen (mg)	Dexibuprofen Lysinate (mg)
1	1200-2400	-	2052-4104	-	-
2	1200 -2400	1536 -3702	-	-	-
3	-	-	-	1000-1500	1795-2692.5

Dexibuprofen shows an equipotency with half of the racemic ibuprofen dose, and the introduction of dexibuprofen (Seractil) permits the prescription of lower doses[31]. In rheumatoid arthritis dexibuprofen is more effective than racemic ibuprofen because at high anti-rheumatic dosage dexibuprofen exerts sufficient anti-inflammatory and analgesic activity[6]. Compared with racemic ibuprofen, half the daily dose of dexibuprofen showed at least equivalent efficacy in patients with osteoarthritis of the hip[7]. The half dose of dexibuprofen, which exerts same effect as that of racemic ibuprofen in treating the rheumatoid arthritis. The comparative per day dose requirement for arthritis was given in Table I.

Ibuprofen and S+Ibuprofen can form salts with bases such as basic aminoacids, examples are lysine and arginine. The lysine part enhances, solubility of the ibuprofen in water and gastric solution ensuring expeditious systemic effect and consequent rate of absorption, which increases the rate of therapeutic response[2]. Ibuprofen lysinate is 100 times more soluble than ibuprofen. Ibuprofen Lysine preventing retinopathy of prematurity in neonates[9]

Dexibuprofen has equal efficacy and comparable safety and tolerability[28] with celecoxib in the treatment of the osteoarthritis[27]. Dexibuprofen shows excellent tolerability, safety than other NSAID like diclofenac sodium, dexibuprofen has stronger pain reducing effect than racemic ibuprofen. Maximum Daily Dose of 3200mg[27] (adult) of Ibuprofen racemate is required, but dose required for dexibuprofen lysinate is 2692.5 mg of S+Ibuprofen lysinate equivalent to 1500mg of dexibuprofen 200-300mg every 4-6 hrs for the relief of pain. S+ Ibuprofen is superior in anti-inflammatory action but equal to reacemic ibuprofen in analgesic action.

Table 2: Side effects

S.No	Ibuprofen	Ibuprofen Na	Dexibuprofen and its lysinate salt
1	Adverse effects may be mediated by the (R)-enantiomer or by its metabolites.	Tolerable and safe[10]	Rare and mostly disappear quickly after the medication is discontinued.
2	R(-)-ibuprofen should be avoided if they are not essential for the anticipated therapeutic activity[12].		Lower rate of gastroduodenal and intestinal mucosal injury[13].

Table 3: Advantages over Racemic ibuprofen-general

S. No	Ibuprofen Lysinate	Ibuprofen Sodium[22]	Dexibuprofen	Dexibuprofen Lysinate
1	Ibuprofen lysine has been shown to have more rapid onset of action compared to base ibuprofen[3].	Quick therapeutic response[2]	Half the dose of ibuprofen is enough to attain therapeutic response of ibuprofen[7,13].	Attains analgesically effective threshold twice as fast as ibuprofen and had a significantly greater intensity of effect[7, 23].
2	Stronger pain reducing effect than ibuprofen[23].	Better disintegeration, dissolution rate due to solublizing effect of sodium[9]	Better clinical effect and tolerability to osteoarthritis, rheumatoid arthritis and dysmenorrhoea[25]	Peak plasma concentration attained three times more quickly than ibuprofen[6-14]
3	When given in the empty stomach significantly higher concentration in plasma, occurs[2].	It could be also formulated as a parentral preparation.		Can be formulated as injection[16].
4	Can be formulated as injection[16]	Other formulations as suspension, syrup, oral drops appear to be more uniformly dispersed/stable as compared with normal grade of ibuprofen.		Upon comparing orally given ibuprofen lysinate against IV injections of ibuprofen. it is found that complete absorption of ibuprofen was achieved from lysine salt[5]

Table 4: Other advantages over racemic Ibuprofen- pharmacological and pharmacokinetic considerations

S.No	S+ Ibuprofen S (+) Ibuprofen Lysinate[24]
1	The recipient is exposed to less of xenobiotic and therefore a reduced metabolic and renal load
2	Adverse effects which may be mediated by the (R)-enantiometer or by its metabolites would be avoided.
3	The effects of factors such as altered physiology, disease and co-administration of other drugs on the pharmacokinetcs of the NSAID would be easier to assess and as a result more reliable dosage recommendation could be made
4	The risk of pharmacodynamic or pharmacokinetic interaction of the NSAID with other drugs might be reduced.
5	Enantiomer-enantiomer pharmacokinetic interactions, which may lead to non-linearity in the pharmacokinetics of the active enantiomer, would be avoided.
6	Pharmacokinetic properties[29] and metabolic fate of the drug would be easier to define.
7	The variability in fractional inversion within and between individual would be avoided.
8	Relationship between drug concentrations in plasma or synovial fluid and therapeutic response would be easier to assess; enantioselective methods would not be required to measure total and unbound drug concentration.

Table 5: International Brands Availability [17,18]

Derivatives	Brand	Company	Country
S(+)Ibuprofen	Seractil	Gebro	Austria
	Dolomin	Bago	Argentina
	Seractil	Genus	UK
	Artiscal	Laser	Spain
	Seractil	GiEnne Pharma	Italy
Ibuprofen Lysine	Dolormin	Woelm	Germany
	Ibu-Fonal	Merckle	Germany
	Imbun	Merckle	Germany
	Ibuprof von CT	Arezeimittel	Germany
	Aciril	Delalanade	Itally
	Arfen	Lisapharma	Itally
	Duvium	Zambon	Itally
	Lisa-Budol	Seber	Spain
	Ibuprofen-L	Amino	Switzerland
	Doctril	Abello Pharmacia	
	Neoprofen[16] (Injectable, Intravenous)	Farmacon IL	US
S + Ibuprofen Lysinate	Dyspactile	UPHA	Peru
	Lertus	Elvetium-Greco	Uruguay

CONCLUSION

The amino acid salt can be properly regarded as a 'potentiator', or 'augmentor' of the activity of the parent molecule via their enhanced solubility and consequent rate of absorption, which increase the rate of therapeutic response.

The biologically active Dexibuprofen is now available and is being commercialized internationally. In Germany, Austria and United Kingdom the dexibuprofen is marketed for treatment of the same

conditions as ibuprofen. It has significant pharmaceutical benefit over the racemate. The addition of salt into the base improves the invitro solubility and bioavailability of ibuprofen, with the clear clinical evidence of superiority of Dexibuprofen over Ibuprofen now established, the availability of the lysine salt of dexibuprofen provides an increased dimension of benefit over dexibuprofen itself. Dexibuprofen Lysine is therefore the preferred compound of the 'Ibuprofen family" of NSAID-analgesics.

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