

Joanna Siódmiak^{1*}, Tomasz Siódmiak², Agata Tarczykowska², Katarzyna Czirson², Jacek Dulęba², Michał Piotr Marszałł²

¹Department of Laboratory Medicine, Faculty of Pharmacy, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

²Department of Medicinal Chemistry, Faculty of Pharmacy, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

Metabolic chiral inversion of 2-arylpropionic acid derivatives (profens)

Corresponding author:

Joanna Siódmiak
Department of Laboratory Medicine,
Collegium Medicum,
Nicolaus Copernicus University
Collegium Medicum
No. 9 Skłodowskiej-Curie Street,
85-094 Bydgoszcz, Poland
Phone: +48 52 585 44 90
Fax: +48 52 585 36 03
E-mail: asiapollak@wp.pl

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ABSTRACT

2-arylpropionic acid derivatives (profens) are one of the most popular anti-inflammatory, analgesic, and antipyretic drugs. They belong to a group of nonsteroidal anti-inflammatory drugs (NSAID) and exhibit metabolic chiral inversion. Enantiomers of these chiral drugs are often characterised by different pharmacological activity. It is estimated that the values of metabolic chiral inversion of (*R*)-ibuprofen in humans are between 35 and 70%, depending on the condition of the liver and the intake of other medicines, while (*R*)-flurbiprofen undergoes chiral metabolic inversion to its opposed (*S*) form only in small range. The described phenomenon in the case of (*R*)-ketoprofen is limited to a maximum of around 10%. The metabolic chiral inversion is associated with potentially important pharmacotherapeutic and toxicological consequences, and so an attempt was made to analyse this phenomenon for the most commonly used drugs from the profens group.

Key words: metabolic chiral inversion, ibuprofen, flurbiprofen, ketoprofen, naproxen, chiral drugs, enantiomers

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Introduction

Currently, according to data of the American Food and Drug Administration (FDA), optically pure compounds represent more than a half of the total investigational new drugs (INDs).

This quantity of tested drugs is reflected in the commercial availability of enantiomers. Eighty percent of the best-selling drugs in the United States are enantiomers of chiral compounds [1].

2-arylpropionic acid derivatives (profens) belong to nonsteroidal anti-inflammatory drugs (NSAID) and have a chiral centre (chiral carbon atom) within the propionic acid moiety, and therefore exist in two enantiomeric forms: (*R*)-enantiomer and (*S*)-enantiomer. Clinically used racemic mixture (racemate) consists of an equimolar mixture of two enantiomers ((*R*) and (*S*)). Profens are widely administered in the inflammatory conditions, to relieve pain and to reduce fever [2, 3]. Due to presence of the profen forms (*R*) and (*S*), a phenomenon called metabolic chiral inversion of these drugs can be observed in the human body. It occurs in the presence of enzymes that determine the change in enantiomeric composition of chiral drug and/or metabolites by inversion of one form to its antipode [4].

The aim of this mini-review is to demonstrate the phenomenon called metabolic chiral inversion of 2-arylpropionic acid derivatives (profens) and to indicate pharmacotherapeutic and toxicological consequences of profens administration in racemic form.

Metabolic chiral inversion of profens

It has been shown that (*R*)-enantiomers of profens in the presence of coenzyme A (CoA), adenosine triphosphate (ATP) and Mg²⁺ are transformed to active (*S*)-forms (Fig. 1). The pathway consists of three parts, beginning from the synthesis of (*R*)-profen thioester with the use of coenzyme A; racemisation of (*R*)-profen thioester and hydrolysis. The first step occurs when formation of thioester from (*R*)-profen and coenzyme A is started. This reaction is catalysed by acyl-CoA synthetase. The next step is racemisation (epimerisation) of the obtained (*R*)-thioester by the activity of epimerase 2-arylpropionic-CoA. Afterwards, newly created thioesters hydrolyse to (*R*)- and (*S*)-forms, with the use of hydrolase. The metabolic chiral inversion may lead to toxic effects, due to modulation of triglycerides and phospholipids structures by the acyl-CoA thioester (profenyl-CoA) [4, 5].

(R,S)-ibuprofen

Ibuprofen (2-[4-(isobutyl)phenyl]propionic acid) is a substance that belongs to nonsteroidal anti-inflammatory drug (NSAID) 2-arylopropionic acid derivatives. Due to the presence of the chiral α atom of carbon in its structure, it is defined as an optically active compound. Ibuprofen exists as a racemic mixture of two enantiomers: (*R*) and (*S*), which are characterised by different pharmacokinetic and pharmacodynamic profiles (Fig. 2) [6]. It has been proven in *in vitro* tests that (*S*) isomer shows about 160-times higher activity in prostaglandins inhibition compared to (*R*) enantiomer. (*S*)-enantiomer equally inhibits the activity of COX-1 and COX-2, while (*R*)-ibuprofen inhibits COX-1 less potently than (*S*)-form and demonstrates no inhibition of COX-2. It should be emphasised that (*R*)-ibuprofen increases the side effects caused by the intake of racemic mixture, mainly from the gastrointestinal tract [4].

Created thioesters from coenzyme A and ibuprofen can incorporate into triglycerides or phospholipids forming 'hybrids'. In adipose tissue, the estimated elimination half-life ($t_{1/2}$) of the 'hybrids' is about seven days. The data show that only (*R*)-enantiomer was detected in human adipose tissue, when both (*S*)- and (*R*)-enantiomers were used in experiment. No accumu-

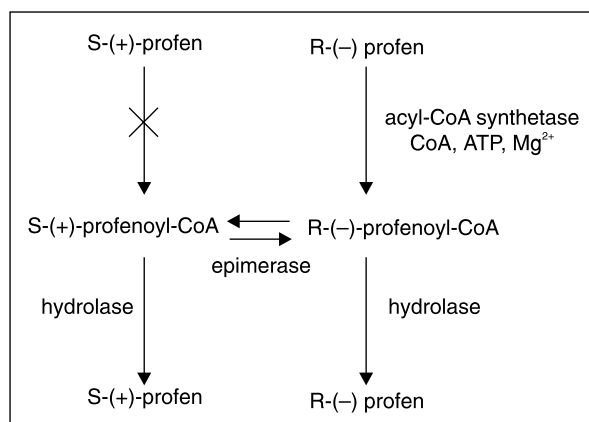


Figure 1. Mechanism of metabolic chiral inversion of profens [4]

lation of (*S*)-ibuprofen was noticed. Actually, studies on the effect of 'hybrids' in the adipose tissue and their long $t_{1/2}$ have been performed. It has been demonstrated that creation of 'hybrids' with phospholipids may have an influence on the function of the cell membranes. It is estimated that the values of metabolic chiral inversion of (*R*)-ibuprofen in humans are between 35 and 70%, depending on the condition of the liver and the intake of medicines [5, 7].

It was proven that oral administration of pure (*S*)-ibuprofen allows a stronger analgesic effect in a shorter time, compared with racemic mixture that contained approximately the same amount of active (*S*)-form. Moreover, the research conducted on 1400 patients showed higher effectiveness of therapy and significantly reduced side effects, while only (*S*)-ibuprofen was used [8, 9]. Commercially available formulations of this medicine are racemic mixtures (Ibuprofen) or single (*S*)-enantiomer (Dexibuprofen).

(R,S)-flurbiprofen

Another one of the broadly applicable nonsteroidal anti-inflammatory drugs of 2-arylopropionic acid derivatives is (*R,S*)-flurbiprofen [2-(2-fluoro-4-biphenyl)-propionic acid]. This drug possesses a chiral centre and therefore exists in two enantiomeric forms: (*R*)- and (*S*)-flurbiprofen, which demonstrate various pharmacokinetic and pharmacodynamic activities (Fig. 3). Nevertheless, clinically (*R,S*)-flurbiprofen is used as a racemic mixture, not as an individual enantiomer [10–12]. (*S*)-enantiomer exhibits an inhibitory effect on cyclooxygenase (COX-2), thus anti-inflammatory action is determined. This enantiomer also shows activity towards cyclooxygenase-1 and thereby induces gastrointestinal side effects. Analysing the influence of (*R*)-form, it has been reported that this enantiomer has no effect on cyclooxygenase (alike COX-1 and COX-2) and is therefore less toxic to the kidneys and gastrointestinal tract, and what is important, *in vivo* in a small range it undergoes chiral metabolic inversion to its opposed form (*S*) [13, 14]. Currently, the mechanism of

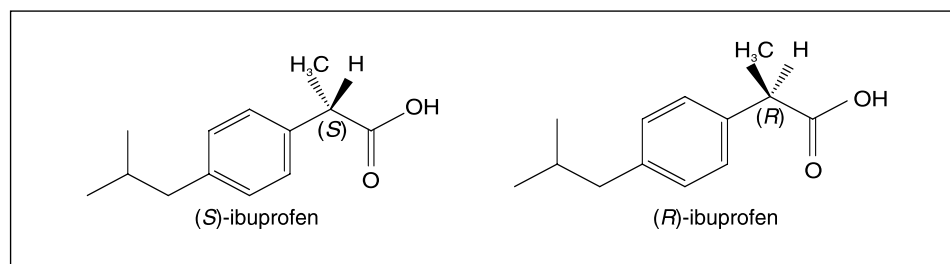


Figure 2. Molecular structures of (*S*)- and (*R*)-ibuprofen

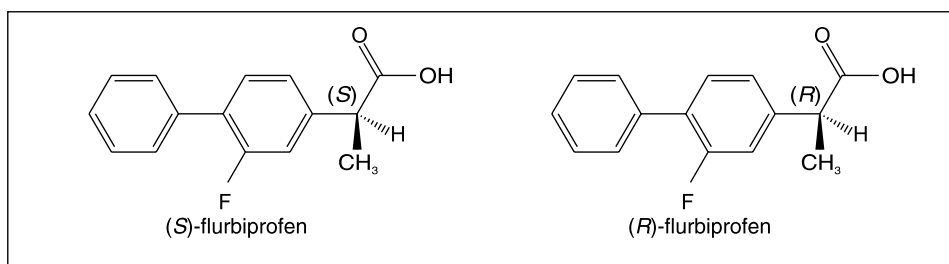


Figure 3. Molecular structures of (S)- and (R)-flurbiprofen

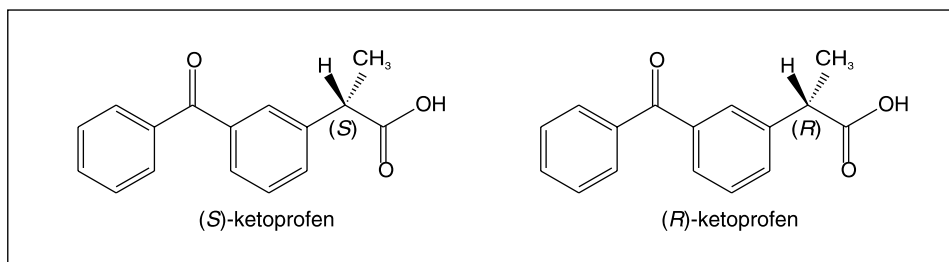


Figure 4. Molecular structures of (S)- and (R)-ketoprofen

molecular action of (R)-flurbiprofen is being investigated and it seems to be not related with COX inhibition. It has been proven in cell lines and animal models that (R)-enantiomer might be useful in oncology in treatment of colon and prostate cancers [15–19].

(R,S)-ketoprofen

The next representative of 2-arylpropionic acids derivatives is ketoprofen (2-(3-benzoylphenyl)-propionic acid) [20, 21]. The pharmacological actions of ketoprofen are similar to other NSAIDs, so the anti-inflammatory and analgesic effects are observed due to the inhibition of cyclooxygenase-2 (COX-2). The drug also expresses COX-1 inhibiting activity, and this is the reason why it enhances the risk of gastrointestinal side effects while repeatedly taken orally [22]. The particle is also a chiral compound since it possesses a centre of asymmetry. Ketoprofen, analogically as all 2-arylpropionic acid derivatives, exists in two forms: (S)- and (R)-enantiomer (Fig. 4). What is important, only (S)-enantiomer of ketoprofen possesses the pharmacological activity, while (R)-enantiomer is either completely inactive or possesses low activity [23, 24].

It was confirmed that the chiral metabolic inversion of (R) to (S)-ketoprofen is limited to around 10% [25]. Other authors claim that no relevant enantiomeric inversion of (R)- to (S)-form has been registered [4, 26, 27].

Commercially available formulations of this drug are racemic mixtures (ketoprofen) or single (S)-enantiomer (dexketoprofen).

(S)-naproxen

The last described drug from 2-arylpropionic acid derivatives is naproxen (2-[6-methoxy-2-naphthyl]-propionic acid) (Fig. 5). Due to the well documented hepatotoxicity and the effect of increasing the burden on renal clearance of (R)-naproxen, it is the only NSAID that is administrated as a stereochemically pure (S)-enantiomer. Similarly to other NSAIDs, naproxen is used as a treatment of arthritis, febrile syndrome, and pain because of its analgesic, antipyretic, and anti-inflammatory activity. Naproxen is a nonselective COX inhibitor with a balanced inhibitory effect on both COX-isozymes (COX-1 and COX-2) [28–30]. This drug possesses also a chiral centre, and it was observed in *in vitro* tests concerning inhibition of prostaglandin synthesis that the activity resides mostly in the (S)-enantiomer. The (S)-naproxen is 28-times more active than the corresponding (R)-enantiomer [31]. Jackson et al. claim that the (S) form has approximately 150-times higher activity than the (R) form [32]. Most of the NSAIDs are available at the market as racemates or single enantiomers, as was mentioned before, but naproxen is an exception because it is sold only as an (S)-enantiomer and not as a racemic mixture.

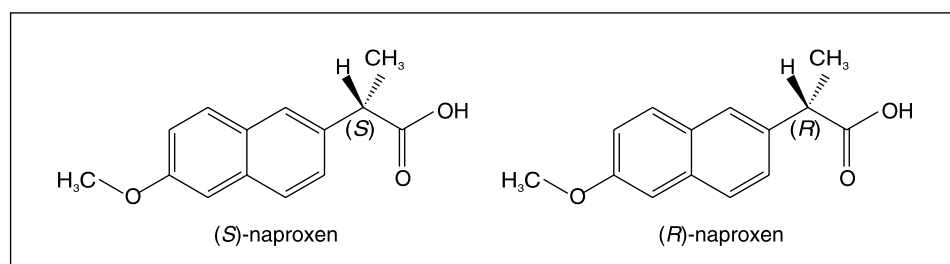


Figure 5. Molecular structures of (S)- and (R)-naproxen

Conclusions

The phenomenon of metabolic chiral inversion occurs in humans and is associated with potentially important pharmacotherapeutic and toxicological consequences. Enantiomers of chiral drugs are often characterised by different pharmacological activity. Therefore, because of these effects and the considerable popularity of these drugs, in clinical practice administration only of (S)-enantiomers of profens (including dexibuprofen and dexketoprofen) should be considered. Further studies on metabolic chiral inversion of enantiomers in terms of pharmacovigilance are needed.

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