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Dexibuprofen – a portrait

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Dexibuprofen, the pharmacologically active enantiomer of ibuprofen, shows good efficacy in both acute and chronic pain. The review summarises study results that confirm dexibuprofen as an effective and safe alternative compared to ibuprofen and other COX inhibitors.

Dexibuprofen, the active S(+)-enantiomer of ibuprofen, is the only enantiomer of ibuprofen with therapeutic activity. Following its recent introduction onto the market in four additional European countries, it is time to consider the advantages and particular features of this modern COX inhibitor in more detail.

Dexibuprofen: licensed as COX inhibitor in 23 countries

Stereoisomers are molecules with the same molecular formula and molecular mass, but which differ in the three-dimensional spatial arrangement of their atoms. If the stereoisomers behave as image and mirror image, they are known as enantiomers. Dexibuprofen is the active S(+)-enantiomer of ibuprofen and the only pharmacologically active enantiomer of racemic ibuprofen. The pure crystalline dexibuprofen is obtained from the racemic mixture through the innovative manufacturing process of differential crystallisation [1]. It differs from the racemate in several of its physicochemical properties and has been classified as a new chemical entity with a separate ATC code [2]. In the OTC setting, dexibuprofen is indicated for the treatment of symptomatic short-term treatment of acute mild to moderate pain and inflammation in adults (like muscular-skeletal pain, back pain, toothache, dental pain, pain after dental extraction, menstrual pain, headache, pain during cold and flu).

It is licensed in 23 countries worldwide. Market launches in Italy in April 2020, in the Czech Republic and Slovakia in November 2020 and in Hungary in April 2021 are the reason for an in-depth consideration of the particular features of dexibuprofen.

Tab. 1. Pharmacokinetic properties of ibuprofen enantiomers (according to Evans et al. 2001 [3])

	General properties	Pharmacokinetic data of the enantiomers
Absorption	Rapid and extensive absorption; moderately affected by simultaneous ingestion of food.	The bioavailability of the two enantiomers is approximately 100%; the absorption half-life of the usual dosage forms is about 30 minutes.
Distribution	The enantiomers undergo extravascular distribution, but their volumes of distribution are low because of strong plasma albumin binding. Slow distribution into and out of synovial and cerebrospinal fluids, partly due to the strong plasma protein binding.	Both enantiomers have a volume of distribution of about 10 to 12 l. The fraction not bound in plasma is 0.008 for S(+)-ibuprofen and 0.004 for R(–)-ibuprofen.
Clearance	Mainly hepatically cleared. Low hepatic extraction ratio and a clearance which is low relative to liver blood flow.	Plasma clearance is between 50 and 150 ml/min for both enantiomers.
Elimination	The metabolites are predominantly eliminated by the kidneys (90%), the remainder is eliminated in the bile.	Almost exclusively metabolic, through glucuronidation and oxidation. Only the R(–)-enantiomer undergoes a metabolic chiral inversion and incorporation into triglycerides.
Half-life	Short half-life (3–4 times daily administration required).	Both enantiomers have a half-life of 2 hrs in healthy adults. In some studies, the R(–)-enantiomer showed a shorter half-life than S(+)-ibuprofen.

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Pharmacokinetics

There are many similarities and a few important differences in the pharmacokinetic characteristics of the enantiomers of ibuprofen (see **Tab. 1**).

The most noticeable difference between the two enantiomers is their metabolism. Unlike S(+)-ibuprofen, R(–)-ibuprofen forms a thioester with coenzyme A. This intermediate product leads to the formation of hybrid triglycerides. S(+)-ibuprofen appears not to be subject to this unusual metabolic reaction, which is why S(+)-ibuprofen is regarded as metabolically "cleaner" than racemic ibuprofen [3].

On average, 50–60% of the R(–)-portion undergoes metabolic inversion and becomes S(+)-ibuprofen. Clinical studies suggest an equivalent dose of 0.5 : 1 [1].

A randomised double-blind study investigated the effectiveness of dexibuprofen in acute pain after dental extraction (n = 176) [4]. A single dose of dexibuprofen (200 mg or 400 mg) was compared with that of ibuprofen (400 mg). After one hour, dexibuprofen (200 mg, 400 mg) showed a significantly better analgesic effect than ibuprofen 400 mg or placebo. Even three hours after a single dose of 200 mg, dexibuprofen was still significantly more effective than ibuprofen, which confirmed the dose ratio of 0.5 : 1.

No special dosage modifications are required in the elderly. However, individual dose reduction and assessment has to be considered due to increased susceptibility to GI adverse reactions in the elderly. Dose reduction is required in patients with mild to moderate impairment of renal or hepatic function. Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with COX inhibition. The adverse drug reactions listed in the SmPC are similar compared to racemic ibuprofen [5].

Efficacy and tolerability

The S(+)-enantiomer is capable of inhibiting cyclooxygenase (COX) 1 and 2 at clinically relevant concentrations, whereas the R(–)-ibuprofen enantiomer does not show any COX inhibition. The two enantiomers of ibuprofen therefore differ in relation to their pharmacological properties [3].

In three post-marketing studies (n = 7,133), dexibuprofen at half the dose of the racemate was at least equieffective to ibuprofen. 75 % of the maximum daily dose of dexibuprofen produced comparable analgesia to 100 % of the maximum daily dose of diclofenac, whilst adverse drug reactions were observed less often under dexibuprofen [6].

A meta-analysis of five randomised clinical studies (n = 1,330) investigated the prevalence of side effects of ibuprofen compared to dexibuprofen after 21 days of treatment. The dosages of dexibuprofen varied between 600 and 1200 mg and of racemic ibuprofen from 1200 to 2400 mg. Significantly fewer side effects occurred in the dexibuprofen group: dexibuprofen 15.66%, racemic ibuprofen 20.41% ($p < 0.05$). CNS side effects were also significantly less common, at 2.54 % vs. 4.63 % ($p < 0.05$). The author of the review article assessed dexibuprofen as a modern COX inhibitor that combines the high efficacy of diclofenac and the good tolerability of ibuprofen [6].

In an observer-blinded, multicenter, non-inferiority study, including 489 patients suffering from painful osteoarthritis of the hip or knee, gastrointestinal adverse drug reactions were reported in 8 patients (3.3%) in the dexibuprofen group and in 19 patients (7.8%) in the ibuprofen group. Also all other analyses of secondary tolerability parameters showed the same result of a significantly better safety profile in this therapy setting for dexibuprofen compared to ibuprofen [7]. To further decrease gastric side effects after oral administration of dexibuprofen, ongoing research aims to increase the water solubility of dexibuprofen in order to achieve higher plasmatic concentrations [8].

Summary

Dexibuprofen is the only pharmacologically active enantiomer of racemic ibuprofen.

Dexibuprofen is absorbed within about 30 minutes of oral administration. The simultaneous ingestion of food causes only a minimal reduction in absorption, so dexibuprofen can be taken with or after food – which is generally recommended to avoid side effects on the stomach [4].

With a dose ratio of 0.5 : 1 (dexibuprofen versus racemic ibuprofen) at least an equal efficacy has been demonstrated in models of acute mild to moderate somatic and visceral pain.

The recommended daily dose is up to 600 mg dexibuprofen per day, divided into three single doses of 200 mg. Due to the lower dosage, the load on the kidneys during elimination can be reduced. No accumulation in adipose tissue occurs and possible adverse drug reactions through additional metabolites such as thioesters are avoided. There is no individually variable fractionated inversion, making a more reliable dosage recommendation possible.

Dexibuprofen is a modern COX inhibitor obtained from racemic ibuprofen by the technologically innovative process of differential crystallisation. The results of clinical studies have confirmed its efficacy and safety of use compared to ibuprofen, diclofenac or celecoxib with similar or even lower incidence of side effects in patients who suffered predominantly from chronic pain.

Conclusions

Dexibuprofen is a suitable analgesic option for patients with either acute or chronic pain. It combines the high effectiveness of diclofenac and the good tolerability of racemic ibuprofen.

Dexibuprofen showed comparable efficacy to ibuprofen, diclofenac and celecoxib with similar or even favourable gastrointestinal tolerability.

Literature

1. Kähler S, et al. Dexibuprofen: pharmacology, therapeutic uses and safety. Inflammopharmacology 2003;11(4–6):371–383.
2. Trung TQ, Kim JM, Kim KH. Preparative method of R-(−)-ibuprofen by diastereomer crystallization. Arch Pharm Res 2006;29:108–111. https://doi.org/10.1007/BF02977477.
3. Evans AM. Comparative pharmacology of S(+)-ibuprofen and (RS)-ibuprofen. Clin Rheumatol 2001; 20(Suppl 1):9–14.
4. Dionne RA, McCullagh L. Enhanced analgesia and suppression of plasma β-endorphin by the S(+)-isomer of ibuprofen. Clin Pharmacol Ther. 1998;63:694–701.
5. Summary of Product Characteristics (SmPC) Ibolex, 07/2021.
6. Phleps W. Overview on clinical data of dexibuprofen. Clinical Rheumatology [online]. 2001;20(Suppl. 1):S15–S21. doi:10.1007/BF03342663.
7. Zamani O, Böttcher E, Rieger JD,Mitterhuber J, et al. Comparison of safety, efficacy and tolerability of dexibuprofen and ibuprofen in the treatment of osteoarthritis of the hip or knee. Wien Klin Wochenschr. 2014;126(11-12):368–75. doi: 10.1007/s00508-014-0544-2.
8. Gliszczyńska A, Sánchez-López E. Dexibuprofen therapeutic advances: Prodrugs and nanotechnological formulations. Pharmaceutics. 2021;13(3):414. doi: 10.3390/pharmaceutics13030414.

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