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Dexibuprofen meets the recommendation criteria of the headache guideline

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Abstract: Dexibuprofen, the active enantiomer of ibuprofen, acts faster and causes less stress on the body compared to ibuprofen. It effectively relieves acute somatic and visceral pain. Thus, it meets the guideline criteria: good evidence, high safety profile and patient acceptance with minimized side effects.

S1 guideline tension-type headache strengthens the monotherapy with NSAIDs

In the previous guideline, combination preparations with active ingredients, such as ibuprofen (ibu), acetylsalicylic acid and caffeine, were recommended as first-line treatment for acute headache. These combinations are considered highly effective because caffeine can enhance the effect of painkillers [1].

The current S1 guideline for tension-type headache recommends single preparations such as ibu, acetylsalicylic acid and paracetamol as first-line treatment. Especially ibu has been shown to have a good analgesic effect in clinical studies. This change to monotherapy is based on the finding that the risk of medication-induced headache is increased with combination preparations. Therefore, combination preparations should be used for a maximum of 10 days per month, whereas single preparations can be used for up to 15 days per month. Furthermore, the addition of caffeine in painkillers leads to more side effects such as dizziness and nervousness [2].

A cautious and situation-appropriate use of painkillers is better for many patients in the long term and reduces the risk of overuse. Scientific and clinical findings indicate that dexibuprofen (dexibu), the active enantiomer of ibuprofen, exerts less strain on the body and also has a faster onset of action. Dexibu, a further development of ibu, is not explicitly mentioned in the S1 guideline for tension-type headache. However, based on its efficacy and safety data, the active ingredient meets all requirements of the guideline.

Dexibuprofen: The effective enantiomer of ibuprofen

In the production of ibu (racemic ibuprofen), the two enantiomers dexibuprofen (dexibu, S(+)-ibuprofen) and levibuprofen (levibu, R(–)-ibuprofen) occur in equal proportions. These differ in their pharmacodynamic, metabolic and physical properties. In a special filtration process, the non-effective enantiomer levibu can be removed to obtain the pain-relieving enantiomer dexibu [3].

Pharmacodynamics: While dexibu effectively inhibits the pain- and inflammation-causing enzyme cyclooxygenase 2 (COX-2), levibu shows no effect. Studies even suggest that levibu could, if anything, unfavourably influence the desired effects of dexibu on COX-2. In addition, compared to dexibu, levibu shows a significantly greater effect on cyclooxygenase 1 (COX-1), the enzyme that is, among other things, responsible for side effects in the gastrointestinal tract [3].

Metabolism: In contrast to dexibu, levibu is incorporated into fat metabolism. It forms triglycerides with fatty acids, so-called hybrid triglycerides. These accumulate in the adipose tissue and release the active ingredient slowly. The clinical consequences of this are not yet fully understood. Dexibu does not exhibit these metabolic pathways, thus also avoiding possible adverse drug reactions from additional metabolites such as thioesters. As a result, dexibu is considered to be metabolically "cleaner" [3].

Another difference is the metabolic inversion. After the intake of ibu, a certain amount of levibu is converted into dexibu. However, the conversion rate of levibu varies individually and its extent is not predictable. In contrast, dexibu is not converted in the body and thus enables a reliable dosage recommendation. Clinical studies verify that dexibu demonstrates the same efficacy at only half the dose of ibu [3].

In addition, the use of dexibu reduces the burden on the kidneys due to the lower dosage [3].

Physical properties: In-vitro studies, which simulate the physiological conditions of the stomach, showed that dexibu

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dissolves twice as fast as ibu. The authors of the study therefore conclude a high physiological availability for dexibu [4].

Dexibuprofen: Advantages in clinical studies

The guidelines of the European Medicines Agency (EMA) for the development of pain medications consider tooth extraction and menstrual pain as suitable study models for acute somatic and visceral pain [5]. The results obtained for dexibu in these studies are described below.

Dexibuprofen works more quickly than ibuprofen

Dexibu proved to be at least as clinically effective as ibu in studies on acute somatic and acute visceral pain despite the dose being halved and was also shown to be superior in terms of a rapid onset of action [6, 7].

In a study with 176 patients after tooth extraction, the analgesic properties of 200 mg of dexibu, amongst other things, were compared with those of 400 mg of ibu and placebo. An initial pain relief occurred for dexibu 15 minutes after intake (measured on the basis of the pain relief achieved at defined measurement points). The onset of significant pain relief with 200 mg dexibu, measured using a stopwatch, was observed at 22 minutes and was therefore significantly faster compared to ibu (400 mg: onset of significant pain relief after 35 minutes). After 30 minutes, dexibu achieved a level of pain relief that not attained by ibu until after one hour. Dexibu demonstrated significantly stronger analgesic properties within the first three hours than ibu in the same duration of action (see **Fig. 1**) [6].

A significantly faster onset of action was also seen in a randomized, double-blind, crossover study with 77 patients with menstrual pain, who received, among other things, dexibu 200 mg and ibu 400 mg over three cycles. Dexibu 200 mg led to a significantly faster onset of action ($p = 0.035$) without shortening the overall duration of pain relief. The time to maximum pain relief was comparable in all groups and correlated with the plasma peak levels [7].

Dexibuprofen shows less strain on the body

A comparable tolerability of ibu and dexibu is generally assumed. However, clinical studies indicate a better tolerability of dexibu [8, 9].

A meta-analysis examined five GCP-compliant studies regarding the reported side effects of higher dosed dexibu and ibu. 1330 patients were included in the analysis, who were treated for up to 21 days with dexibu 600–1200 mg or with ibu 1200–2400 mg per day (ratio 0.5 : 1).

In the dexibu group, fewer side effects occurred per organ system. CNS reactions occurred significantly less frequently (2.54% vs 4.63%, $p < 0.05$). Common side effects of both medications were stomach complaints, nausea and vomiting. The overall incidence of side effects was significantly lower with dexibu (15.66% vs 20.41%, $p < 0.05$). There were no serious adverse events and the study withdrawal rate was comparable (2.40% vs 3.25%) (see **Table 1**) [8].

Tab. 1. Meta-analysis of side effects of dexibu and ibu in five randomized, double-blind clinical studies [8]

System	Adverse events [%][1]	
	Dexibu (n = 747)	Ibu (n = 583)
Gastrointestinal tract	9.37%	9.78%
Central nervous system	2.54%*	4.63%
Skin	0.67%	0.86%
Cardiovascular	0.00%	0.00%
Others	0.54%	0.69%
Changes in blood count	1.34%	2.92%
Changes in laboratory values	1.20%	1.54%
Total	15.66%*	20.41%
Study withdrawals	2.40%	3.25%

[1]multiple selections possible if there is more than one symptom or if more than one system is affected; *$p < 0.05$

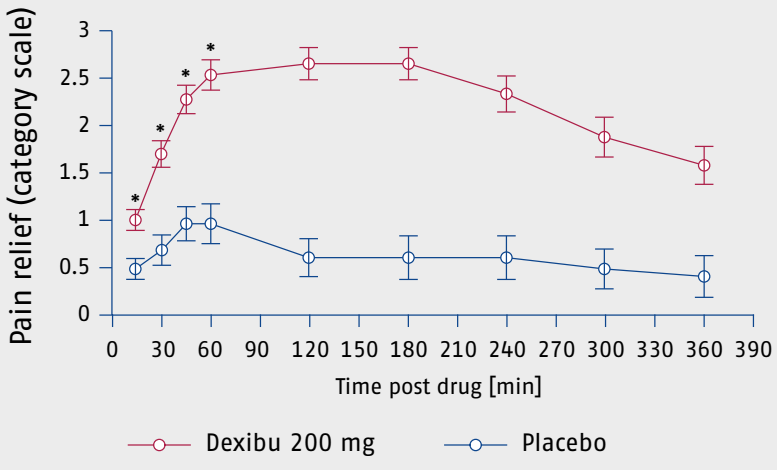

Fig. 1. Pain relief attained by Dexibu, Ibu and Placebo after tooth extraction in the first 360 minutes after intake; *$p < 0.05$ versus Ibu 400 mg [6]

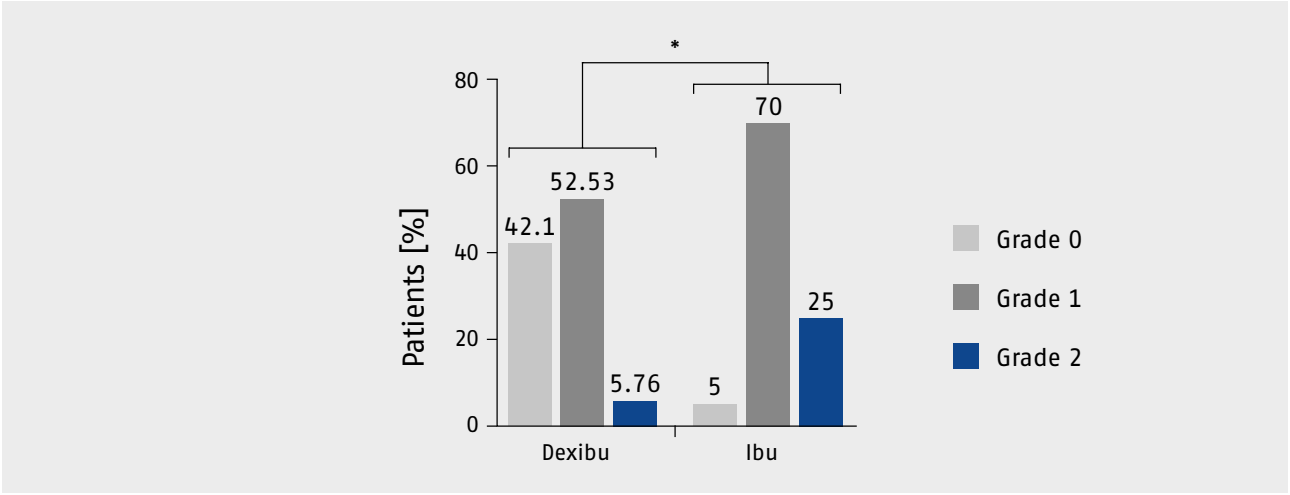

Fig. 2. Extent of gastroduodenal damage after dexibu and ibu have been taken for 14 days: *p = 0.003 [9]. Grade 0: normal mucosa, Grade 1: erosions, Grade 2: ulcers or active bleeding

With a special focus on gastrointestinal adverse drug reactions, a 2-week study examined the effects of higher dosed dexibu and ibu on the gastrointestinal mucosa in patients (n = 60) undergoing a chronic NSAID-therapy due to a rheumatological disease. Dexibu led to significantly less damage to the gastroduodenal mucosa. In 42.1% of the patients treated with dexibu, no damage occurred, whereas damage was evident in 95% of the patients in the ibu group (p = 0.003) (see **Fig. 2**).

The intestinal mucosa was also less affected in the dexibu group: 42.86% of the patients showed no damage, compared to 14.29% in the ibu group (p = 0.0175). The overall incidence of side effects was lower in the dexibu group with 28% compared to 38% in the ibu group [9].

Summary

The current guideline for the diagnosis and treatment of tension-type headaches recommends a monotherapy such as ibu because of its well-documented analgesic efficacy and high safety profile [2]. With dexibu, the effective enantiomer of ibu, only half of the ibu dosage is required to achieve at least an equally strong effect in the case of acute somatic and visceral pain [6, 7]. Therefore, the use of dexibu results in a lower active ingredient load and reduced metabolic burden for the body [3, 8, 9]. The undesirable effects that are associated with levibu are avoided [3]. Another advantage of dexibu is the faster onset of action compared to ibu [6, 7]. This is likely due to the fact that dexibu dissolves twice as quickly in the stomach [4]. Although dexibu, the further development of ibu, is not explicitly mentioned in the guideline on tension-type headaches, it fulfils all criteria of the current recommendation [2]. Additionally, the reduced amount of active ingredient leads to a smaller tablet. This could further increase patient acceptance.

Literature

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Gender note: All personal terms apply equally to all genders. For reasons of better readability, the language forms male, female and diverse (m/f/d) are not used simultaneously.

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