

Safety and efficacy of flavocoxid compared with naproxen in subjects with osteoarthritis of the knee: a pilot study

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ABSTRACT

Purpose: The present study was designed to compare the effectiveness and safety of flavocoxid, a dual pathway inhibitor anti-inflammatory agent of botanical origin, to naproxen in a population of subjects with moderate-severe OA.

Methods and Materials: In this double blind study 103 Russian subjects were randomly assigned to receive either flavocoxid (500 mg BID) or naproxen (500 mg BID) for one month. Outcome measures included the short WOMAC scale (validated in Russian) subject VAS scales for discomfort and global response, investigator VAS for global response and fecal occult blood.

Results: Both groups noted significant reduction in the signs and symptoms of knee OA. There were no statistically detectable differences between the flavocoxid and naproxen groups with respect to any of the outcome variables ($p \leq 0.001$) nor with respect to any adverse event although there was a trend toward a higher incidence of edema in the naproxen group.

Conclusions: In this short term pilot study flavocoxid appeared to be as effective as naproxen in controlling the signs and symptoms of OA of the knee. A low incidence of adverse events was reported for both groups.

Key words: Osteoarthritis, Flavocoxid, Flavonoids, Medical Foods, Dual Pathway Anti-Inflammatory Agents.

MeSH: Osteoarthritis [C05.550.114.606]; Anti-Inflammatory Agents [D27.505.954.158]; Flavonoids [D03.438.150.266.450]

BACKGROUND

Osteoarthritis (OA) is the most common form of joint disease in adults worldwide affecting more than 40 million people in the United States alone.¹ In addition to physical therapy, analgesics and intra-articular injections of corticosteroids or hyaluronate preparations, NSAIDs and COX-2 inhibitors are the mainstay of chemical therapies. While effective at relieving pain and inflammation, their use is often limited by toxic effects on the gastrointestinal tract, kidneys, platelets, heart and liver. These adverse effects are mediated by molecules generated via the primary enzyme pathways involved in arachidonic acid metabolism, cyclooxygenase-1 and -2 and 5-lipoxygenase (Figure 1) all of which serve important physiologic functions.^{2,3} It is thought that imbalance in the levels of these end products from selective blocking of one or another metabolic pathway may account for much of the toxicity of anti-inflammatory agents.^{4,5}

Flavocoxid is a proprietary medical food product for the dietary management of the metabolic processes involved in the pathogenesis of OA. In pre-clinical

FLAVOCOXID'S DUAL INHIBITION OF COX & LOX

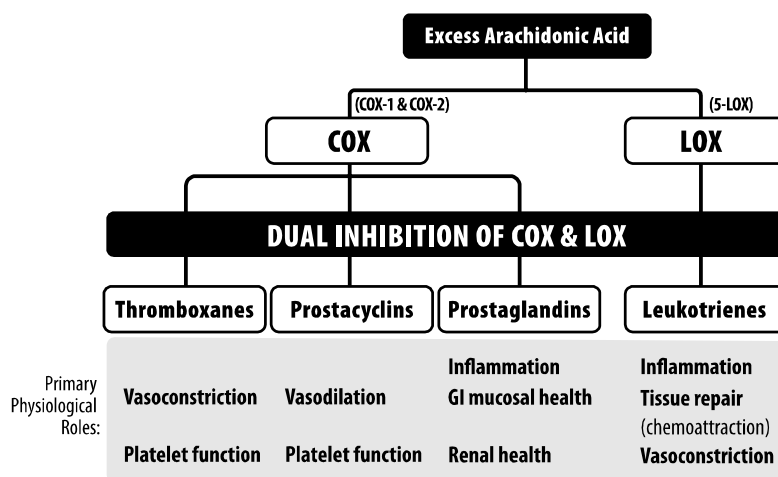


Figure 1. Dual Inhibition of COX & LOX mechanism of action regulates production of prostaglandins and leukotrienes to manage joint inflammation, without over-inhibition of either that is necessary for GI health and other physiological functions.⁶

biochemical assays the product has been shown to possess significant action against the primary enzyme pathways involved in arachidonic acid metabolism, cyclooxygenase-1 and 2 and 5-lipoxygenase.⁶ When compared with other anti-inflammatory agents, flavocoxid is a more balanced inhibitor of all major pathways. Dual pathway inhibition greatly reduces the downstream production of inflammatory mediators and results in an improved toxicity profile.⁷ Prior studies have suggested that flavocoxid may have a beneficial effect in the management of OA. This study is designed to compare the efficacy and safety of flavocoxid compared to naproxen in subjects with moderate-severe OA of the knee and to provide guidance for the development of future studies.

PRODUCT

Under U.S. FDA law, flavocoxid is classified as a medical food, a category distinct from drugs and supplements. Flavocoxid is a blend of B-ring flavonoids and flavans extracted from two botanical sources, *Scutellaria baicalensis* and *Acacia catechu*, concentrated and standardized to approximately 98% purity. In Asia, these compounds have been used for more than 1000 years for treatment of a variety of inflammatory conditions. Recently, this action has been shown to be related to inhibition of COX-1, COX-2 and 5-LOX, the major pathways of arachidonic acid metabolism in joints. Thus, flavocoxid is the first so-called dual pathway inhibitor to reach market.

PURPOSE

This study was designed to compare the effectiveness and safety of full therapeutic doses of flavocoxid and naproxen in subjects with osteoarthritis (OA) of the knee using conventional efficacy and safety endpoint parameters.

STUDY DESIGN

This was a 4 week, multi-center, double-blind, active comparator controlled study performed in the Russian Republic. Subjects were chosen from investigators' hospital clinic practices and were required to have Kellgren-Lawrence grade 2-3 osteoarthritis of a knee

Table 1. Baseline Characteristics

	Flavocoxid 500 mg BID	Naproxen 500 mg BID
N per group	52	51
Age: Mean (sd)	60.3 (9.7)	57.5 (14.4)
Sex: (N male; N female)	7 M; 45 F	6 M; 45 F
Weight (KG): Mean (sd)	82.3 (14.1)	83.0 (15.8)
BMI: Mean (sd)	30.4 (6.3)	30.7 (5.1)
WOMAC (composite score): Mean (sd)	55.3 (17.0)	55.8 (15.1)
PGAD (mm on VAS): Mean (sd)	57.1 (16.7)	57.7 (14.2)
SGAD (mm on VAS): Mean (sd)	33.2 (16.1)	36.3 (15.2)
SGADc (mm on VAS): Mean (sd)	56.8 (19.4)	58.2 (18.2)

Table 1. Baseline characteristics of subjects in both flavocoxid and naproxen groups were similar. WOMAC = Western Ontario and McMaster's University (WOMAC) Osteoarthritis; PGAD = Physician's Global Assessment of Disease; SGAD = Subject's Global Assessment of Disease; SGADc = Subject's Global Assessment of Discomfort.

in need of anti-inflammatory therapy. Subjects were required to discontinue taking NSAIDs (including selective COX-2 inhibitors) at least 2 weeks prior to the screening visit. Acetaminophen was provided for rescue analgesia.

Efficacy parameters included subject VAS for discomfort and global disease activity, investigator global assessment of disease activity and short WOMAC (validated in Russian). The short form WOMAC has been validated as a surrogate for the full WOMAC.⁸

Major inclusion criteria are:

1. Grade 2-3 K-L OA in at least one knee
2. Age 35 to 85, inclusive
3. In general good health
4. Not pregnant or breast feeding

Major exclusion criteria are:

1. Grade 1 or 4 OA in target knee
2. Grade 4 OA in any knee or hip
3. Any form of arthropathy other than OA
4. Any musculoskeletal or neurologic condition that might alter gait or confound evaluation of discomfort in the target knee
5. Use of NSAIDs (including selective COX-2) inhibitors within 2 weeks of the screening visit
6. Use of any gastroprotective medication whether by prescription or OTC within 2 weeks of the screening visit
7. Intra-articular corticosteroids within 3 months or hyaluronate preparations within 6 months of the screening visit

Table 2. Improvements in WOMAC and VAS

	Flavocoxid 500 mg BID (N = 52)		Naproxen 500 mg BID (N = 51)		Within-group p-value	Between-group p-value
	Patients with Improvement N (%)	Improvement Mean (sd)	Patients with Improvement N (%)	Improvement Mean (sd)		
WOMAC	41 (79%)	32% (33)	45 (88%)	36% (36)	<.001	.67
PGAD	43 (83%)	31% (32)	38 (75%)	38% (35)	<.001	.34
SGAD	45 (87%)	162% (249)	45 (88%)	130% (188)	<.001	.46
SGADc	45 (87%)	28% (39)	45 (88%)	38% (39)	≤.001	.20

Table 2. Fisher’s Exact Test: Over 75% of both flavocoxid and naproxen groups showed improvement. Within group improvements were statistically significant. Differences between groups were not statistically significant. WOMAC = Western Ontario and McMaster’s University (WOMAC) Osteoarthritis; PGAD = Physician’s Global Assessment of Disease; SGAD = Subject’s Global Assessment of Disease; SGADc = Subject’s Global Assessment of Discomfort.

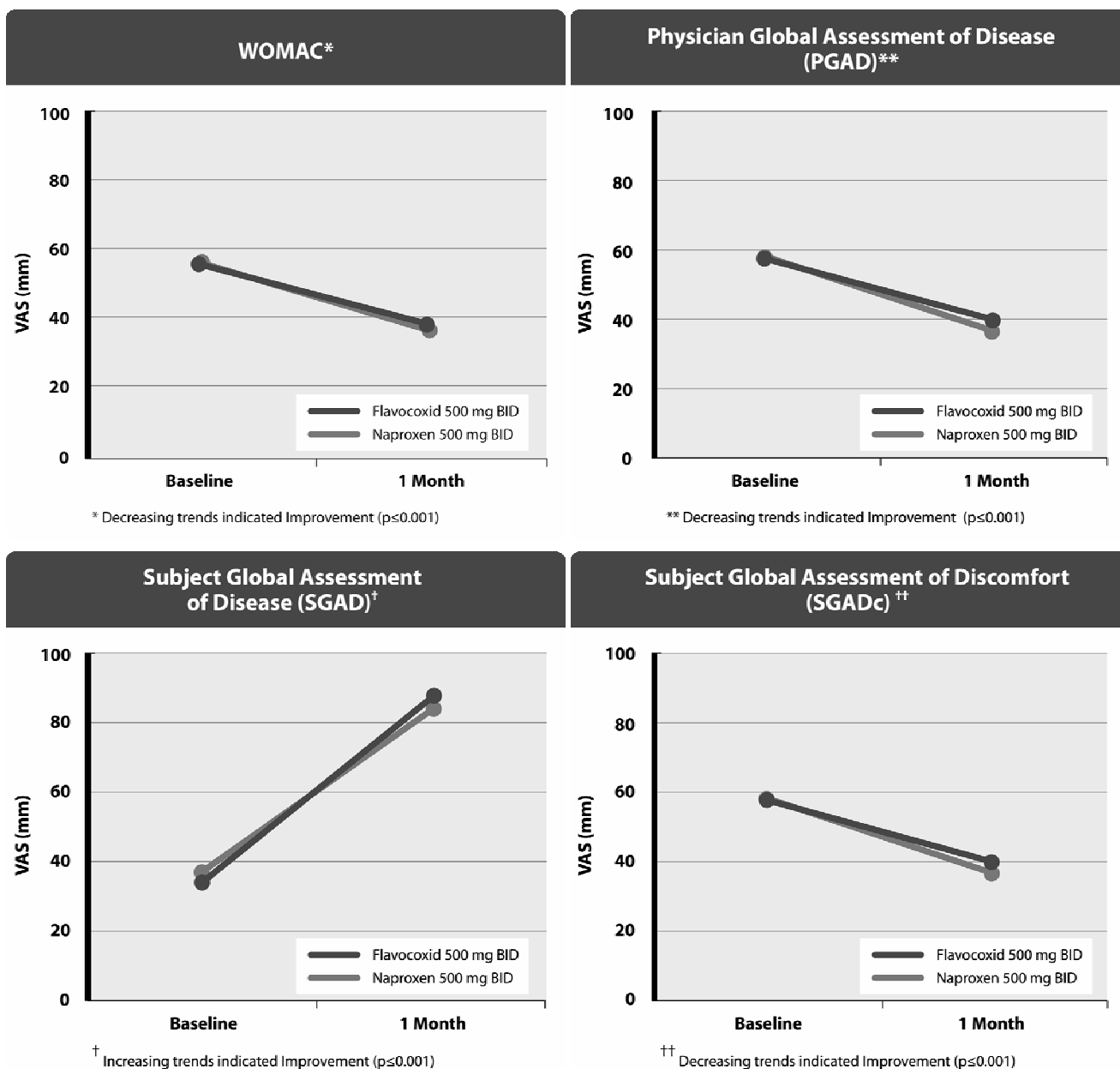


Figure 2. Efficacy endpoints. Within group improvements were all significant for both flavocoxid and naproxen groups ($p \leq 0.001$). Differences between groups were not statistically significant ($p > 0.2$).

8. Use of mechanical ambulation aids
9. History of bleeding disorder or use of anticoagulant medications
10. History of chronic upper gastrointestinal disease or upper GI bleeding within 3 years of screening
11. Positive fecal occult at screening
12. Significant renal, cardiovascular or neoplastic disease or any other disease that, in the opinion of the investigator might put the subject at undue risk during the study
13. History of allergy to aspirin, NSAIDs or flavonoids
14. Current substance abuse including consumption of >1 unit of alcohol daily
15. Participation in another clinical trial within 30 days or 7 half lives of the prior study product, whichever is longer

RESULTS

One hundred three (103) subjects were randomized to the trial. Two (2) subjects, both in the naproxen arm, failed to complete the full month of study product, one for increasing upper GI discomfort, the other for personal reasons unrelated to the trial. Both, however, completed three (3) weeks of therapy and were included in the efficacy and safety analyses. The baseline characteristics of the two groups are shown in **Table 1**. There were no differences in demography or in WOMAC or VAS scores between the two groups.

Fisher's exact test was computed for Improved vs. Not Improved (sum of unchanged and worsened) for all parameters (**Table 2**). Both groups improved significantly in all parameters (75% – 88%) showing within group *p* values ≤ 0.001 . No significant differences were found between groups for any of the four efficacy parameters measured, although there was a slight trend toward greater improvement in PGAD in the flavocoxid group and WOMAC in the naproxen group.

Both flavocoxid and naproxen groups improved significantly on all efficacy primary endpoints ($p \leq 0.001$ within groups), as shown in **Figure 2**. The flavocoxid and naproxen groups performed nearly identically, and the between group differences were not statistically significant for all efficacy endpoints.

The overall adverse event (AE) rate was about the same for both groups, 46% for flavocoxid group and 51% for naproxen group (**Table 3**). Neither the

numbers nor kinds of AEs differed statistically between the groups, with the exception of a slight but not statistically significant trend toward more frequent edema and nonspecific musculoskeletal events in the naproxen group. No significant changes were observed within or between groups for weight, systolic blood pressure, or diastolic blood pressure. No positive fecal occult bloods were recorded.

Table 3. Adverse Events

	Flavocoxid 500 mg BID (N = 52)	Naproxen 500 mg BID (N = 51)
Cardiovascular	4 (8%)	6 (12%)
Worsening Hypertension	2	2
Edema	2	4
Dermal (itching)	1 (2%)	0 (0%)
Dizziness/Insomnia	1 (2%)	1 (2%)
Vertigo	1	0
Insomnia	0	1
Gastrointestinal	11 (21%)	11 (22%)
Abdominal pain	3	4
Constipation	0	1
Diarrhea	3	2
Heartburn	2	1
Nausea	1	3
Vomiting	2	0
Musculoskeletal (Increased knee pain)	3 (6%)	6 (12%)
Respiratory (Cold, URI)	3 (6%)	0 (0%)
Other (Facial swelling)	1 (2%)	2 (4%)
TOTAL	24 (46%)	26 (51%)

DISCUSSION

Flavocoxid is a proprietary blend of botanical extracts containing primarily baicalin and catechin, concentrated and standardized to approximately 98% purity. These compounds have been extracted from plants that have been used medicinally as anti-inflammatory agents in Asia for more than 1000 years.

In the present study, flavocoxid was shown to be as effective as naproxen in controlling the signs and symptoms of moderate-severe knee OA. Response rates are consistent with those reported in many other NSAID efficacy studies in OA, although the SGAD may be somewhat exaggerated compared to that seen in American and European trials. The length of the study was probably too short to demonstrate differences in safety between the two products. The complete absence of positive fecal occult blood tests is consistent with this hypothesis.

The data support the need to perform additional clinical studies to further evaluate both the safety and

efficacy of flavocoxid in larger populations over longer time courses.

CONCLUSION

Flavocoxid and naproxen appear to be equally effective therapies for symptomatic osteoarthritis of the knee. Except for a trend toward increased edema and nonspecific musculoskeletal discomfort in the naproxen group, flavocoxid and naproxen appear to be equally safe when administered in full therapeutic doses for the short term of this study.

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