Antiinflammatory effect of tepoxalin

Blood and synovial tissue studied in patients with knee arthrosis

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Our aim was to determine the amounts of eicosanoids in blood and synovial tissue of patients with knee arthrosis and to examine the effects of 2 doses of tepoxalin (50 mg twice, 200 mg twice), administered p.o. for 3.5 days.

Concentrations of leukotriene B_4 (LTB_4), LTC_4, and thromboxane B_2 (TXB_2) were measured in blood before and after oral administration of tepoxalin and release of prostaglandin E_2 (PGE_2), 6-keto-PGF_{1alpha}, and LTC_4 was measured in incubation media of synovial tissue, taken at surgery from patients treated with tepoxalin. Radioimmunoassay (RIA) was used to determine the levels of the eicosanoids.

LT and TXB_2 release was reduced by tepoxalin in both doses used. Under these conditions, PGE_2, 6-keto-PGF_{1alpha}, and LTC_4 release from synovial tissue was detectable only after stimulation with calcium ionophore A23187. Washed synovial tissue, in which tepoxalin concentrations should be reduced, released higher amounts of all eicosanoids measured than directly incubated synovial tissue did. Pain after tepoxalin administration was significantly reduced. Relevant drug concentrations were detected in plasma and synovial fluid. Tepoxalin was well tolerated and had no marked adverse effects.

At 400 mg, tepoxalin is a dual inhibitor of cyclooxygenase (CO) and 5-lipoxygenase (5-LO) in blood and synovial tissue.

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2 major pathways of arachidonic acid (AA) metabolism are known. These are the cyclooxygenase (CO) and 5-lipoxygenase (5-LO) pathways which convert AA to prostaglandins (PG) and leukotrienes (LT) (Goldyne 1984, Stenson and Parker 1984, Kulkarni and Parale 1985). Both PG and LT are potent inflammatory mediators (Bray 1983, Stenson and Parker 1984, Higgs and Moncada 1985, Kulkarni and Parale 1985, Feuerstein and Hallenbeck 1987, Ford-Hutchinson 1990, Lewis et al. 1990). Elevated levels of LTB_4 (Klickstein et al. 1980, Davidson et al. 1982), TXB_2, PGE_2 and 6-keto-PGF_{1alpha} (the stable metabolite of PGI_2) have been detected in synovial fluid of patients with OA and RA (Trang et al. 1977, Brodie et al. 1980, Egg et al. 1980, Egg 1984).

Commonly used non-steroidal anti-inflammatory drugs (NSAIDs) are CO inhibitors. Since BW 755c, the first prototype (Blackwell and Flower 1978), the quest for 5-LO inhibitors, LT antagonists or biosynthesis inhibitors and dual inhibitors has been intense but, until recently, frustrating (Lewis et al. 1990, Ford-Hutchinson 1990). Tepoxalin [5-(4-chlorophenyl)-N-hydroxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-propanamide], a novel compound, is an orally active anti-inflammatory agent, which inhibits both CO and 5-LO activities (Depre et al. 1996). Tepoxalin also inhibits neutrophil migration, suppresses NF kappa B activation and inhibits T-cell proliferation (Zhou et al. 1994, Kazmi et al. 1995, Ritchie et al. 1995, Depre et al. 1996, Zhou et al. 1996).

We determined the clinical activity and biochemical profile of tepoxalin in blood and synovial tissue of patients with knee arthrosis.

Patients and methods

This study was approved by the local ethics committee. The patients gave informed consent and the study complied with the principles for the standard of good clinical practice for trials on medicinal products in human beings in the European Community (Pharmacol Toxicol 1990; 67: 361-72).

Patients

14 patients (10 women), mean age 67 (53–79) years, operated on with total knee replacement because of arthrosis, were examined in a clinical phase II study

Table 1. Study procedures

Procedures	Day 1	Day 2	Day 3	Day 4
Drug administration	07.00 19.00	07.00 19.00	07.00 19.00	2 hrs before surgery
Plasma (LTB_4/LTC_4)	7.00 19.00			2 hrs after drug
Serum (TXB_2)	7.00 19.00			2 hrs after drug
Synovial tissue (PG/LT)				X
Synovial fluid (tepoxalin)				X
Plasma (tepoxalin)				2 hrs after drug
Clinical assessment	X	X	X	

(double-blind, randomized, parallel, 2-dose levels). The oral dosage of tepoxalin was 200 mg twice daily (n 7) or 50 mg twice daily (n 7). Tepoxalin was administered for 3 days before surgery and on day 4, 2 hours before surgery (Table 1). Participating patients had no gastrointestinal disorder or hypersensitivity to aspirin.

In order to avoid effects of previously administered drugs on the results of this study, only patients who had received their last intraarticular corticosteroid injection at least 3 months before and who had stopped all corticosteroid medication at least 4 weeks before were included. All therapy with NSAIDs had to be terminated at least 8 days before tepoxalin treatment was commenced.

Clinical parameters were evaluated. Pain was assessed daily before surgery, using visual analogue scales (VAS) asking about pain during the previous night, the same day and intermittent pain induced by a specific activity, like sitting down or climbing stairs. The maximum flexion angle of both knees was determined on every day of the study.

Blood and synovial tissue samples

Blood taken from the cubital vein was used for the measurement of TXB_2 and heparinized blood for determination of LTB_4 and LTC_4. Synovial tissue and fluid were obtained during total knee replacement, avoiding blood contamination. 2 mL of whole blood was incubated for 30 min at 37 °C, as described by Patrono et al. (1980). 2 mL of heparinized blood was incubated for 15 min at 37 °C, thereafter the divalent cation ionophore A 23187 was added, resulting in a final concentration of 50 micromol/L. Ionophore A 23187 activates Ca^{2+}-dependent phospholipase and increases free AA (Borgeat and Samuelsson 1979). Incubations were then continued for an additional 30 min, as described by Carey and Forder (1986). After incubation, all samples were centrifuged at 1500 × g for 10 min at 4 °C and the serum/plasma kept frozen at –20 °C until eicosanoid RIAs were performed.

The synovial tissue was cut into fragments of about 3 × 3 mm, divided into portions of 150 mg wet weight (ww), and placed in plastic tubes. 2 portions were washed once with ice-cold Tyrode's solution to eliminate blood traces. Another 2 portions were washed 5 times over a period of 20 min with ice-cold Tyrode's solution. Thereafter, the synovial tissue was incubated in oxygenated prewarmed (37 °C) Tyrode's solution for 5 min and then for an additional 20 min in Tyrode's solution, containing 5 microg/mL ionophore A23187. After incubation, the supernatant was removed and the samples were either immediately analyzed for PG and LT or stored at –20 °C. Storage under these conditions has been shown not to affect significantly the amounts of eicosanoids detected over a period of up to 2 months.

Analysis of PG, LT and TXB_2

Levels of PG and LT in the supernatants of tissue incubates, TXB_2 in serum and of LTB_4 and cysteinyl-LT in heparinized plasma samples were determined radioimmunologically, as described previously (Peskar et al. 1979, Patrono et al. 1980, Aehringhaus et al. 1982). LTB_4 and cysteinyl-LT in plasma were determined by RIA, after Sep-Pac-purification (Dreyling et al. 1986). The validity of the radioimmunoassay (RIA) measurements was verified by high-pressure liquid chromatography (HPLC) and bioassay. HPLC analysis followed by RIA measurement of eluted fractions showed that immunoreactive LTB_4 co-chromatographed exclusively with authentic LTB_4, whereas immunoreactive LTC_4 consisted of a mixture of cysteinyl-leukotrienes C_4, D_4 and E_4 in approximately equal amounts. Release of cysteinyl-LT was calculated, using standard curves for LTC_4 and was expressed in terms of LTC_4. The details of these measurement techniques and their accuracy have been described elsewhere (Dreyling et al. 1986, Simmet et al. 1988).

Measurement of tepoxalin

The concentrations of tepoxalin and its carboxylic acid metabolite in plasma and synovial fluid were determined according to Seidemann et al. (1994) and Depre et al. (1993).

Statistics

Incubations were performed in duplicate and the means and SD values for eicosanoid release were calculated. Statistical analysis was performed using the Student's t-test. P-values less than 0.05 were consid-

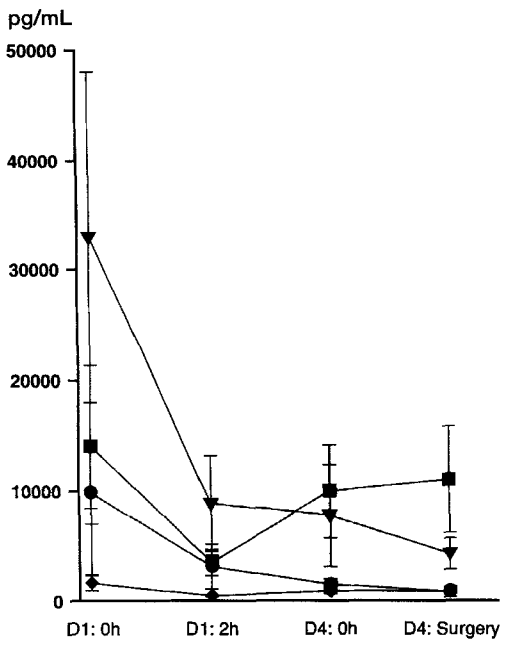

Figure 1. LTB_4 and LTC_4 levels in heparinized ionophore A 23187-stimulated blood of patients with OA, before and after oral administration of tepoxalin. (▼) 400 mg tepoxalin LTB_4, (■) 100 mg tepoxalin LTB_4, (●) 400 mg tepoxalin LTC_4, (◆) 100 mg tepoxalin LTC_4. D1: 0h – blood sample before first administration of tepoxalin, D1: 2h – blood sample 2 hours after first drug intake, D4: 0h – blood sample before administration of tepoxalin on day 4, D4: Surgery – blood sample 2 hours after drug intake during surgery (n 7 respectively, for 400 mg tepoxalin LTB4 and LTC4 $p<0.05$).

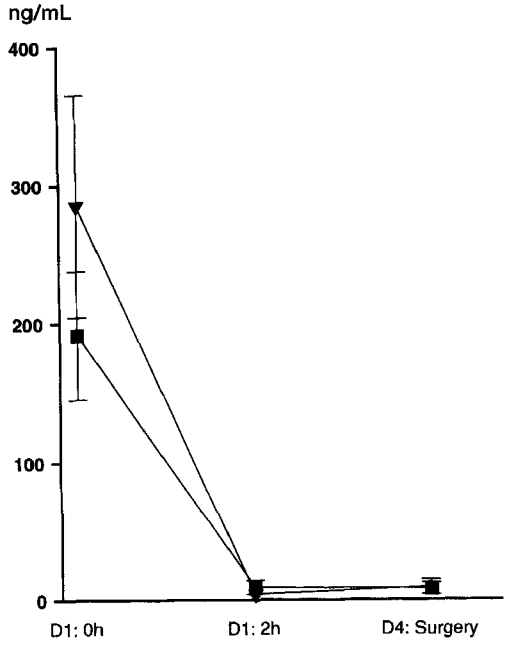

Figure 2. TXB_2 levels in serum after clotting of whole blood of patients with knee arthrosis, before and after oral administration of tepoxalin. For the abbreviations, see Figure 1 (n 7 respectively, for 400 mg and 100 mg $p<0.01$).

ered significant.

VAS scores were transformed, using logit transformation, i.e., logit (x) = log (x/(100-x)). Due to variations in baseline values (assessment of clinical data on the day before the first dose of tepoxalin), changes from baseline were analyzed for all parameters. For these data, the method of summary measures, in accordance with Matthews et al. (1990), was used.

Results

The oral administration of 100 mg tepoxalin reduced and of 400 mg tepoxalin significantly inhibited LTB_4 and LTC_4 release from ionophore A 23187-stimulated heparinized whole blood (Figure 1).

TXB_2 release into serum from whole blood during clotting was very significantly inhibited by both concentrations of tepoxalin (Figure 2).

Release of PGE_2, 6-keto-PGF_{1alpha} and LTC_4 from synovial tissue in the absence of ionophore A 23187 was below the detection limits of the RIAs used after administration of either dose of tepoxalin. After stimulation with ionophore A23187, LTC_4 release was easily detectable, while PGE_2 and 6-keto-PGF_{1alpha} release was still close to the detection limits of the RIAs used. After washing the synovial tissues 5 times, the release of all eicosanoids measured increased, as compared to the release from the tissues incubated immediately after one brief washing (Table 2).

Table 2. Eicosanoid release from synovial tissue (n 7 in each group). Mean (SD)

Synovial tissue	Tepoxalin	PGE_2 (pg/mg ww)	6-keto-$PGF_{1\alpha}$ (pg/mg ww)	LTC_4 (pg/mg ww)
Intact	400 mg	0.3 (0.3)	0.2 (0.2)	252 (51)
Washed	400 mg	1.6 (1.4)	2.0 (1.1)	407 (100)
Intact	100 mg	1.1 (0.8)	0.8 (0.5)	226 (68)
Washed	100 mg	5.7 (2.8)	6.8 (2.8)	298 (61)

Drug concentrations in plasma and synovial fluid (day 4, 2hrs after drug administration) are shown in Table 3.

Pain was significantly reduced with both concentrations from study start to surgery (Table 4).

No significant increase in maximum knee flexion was detectable.

Table 3. Drug concentrations (ng/mL). Mean (SD)

Variable	Group	n	Conc.
Tepoxalin plasma	100 mg	7	0.26 (0.19)
Tepoxalin plasma	400 mg	7	0.42 (0.20)
Tepoxalin syn. fluid	100 mg	7	0.21 (0.14)
Tepoxalin syn. fluid	400 mg	7	0.39 (0.23)
Metabolite plasma	100 mg	7	1.03 (0.31)
Metabolite plasma	400 mg	7	4.05 (2.48)
Metabolite syn. fluid	100 mg	7	0.46 (0.14)
Metabolite syn. fluid	400 mg	7	1.98 (0.98)

Table 4. Pain evaluation. Mean (SD)

Variable	Group	n	Day 0	Day 3	P-value
Previous night	100 mg	7	29 (28)	15 (11)	0.05
Previous night	400 mg	7	30 (34)	14 (20)	0.05
On same day	100 mg	7	45 (34)	22 (23)	0.05
On same day	400 mg	7	35 (31)	17 (22)	0.05
Intermittent	100 mg	7	54 (34)	31 (21)	0.05
Intermittent	400 mg	7	61 (34)	31 (37)	0.05

Tepoxalin caused no clinical side-effect that required treatment or any recurring abnormal laboratory adverse effects. The most serious findings were mild diarrhea and transiently elevated liver enzymes after surgery, each in 1 case.

Discussion

As in other studies and biological systems, high inter-individual variations of inflammatory mediator release were found. This resulted in a wide range of eicosanoid release levels and accounts for the very disparate baseline values. Nevertheless, release of TXB2 in clotting whole blood was significantly decreased as early as 2 hours after the first intake of tepoxalin, at either dose. There was no significant difference between the high and low doses of tepoxalin. Previous results have demonstrated CO inhibition at doses of 5–25 mg tepoxalin (Depre et al. 1993). The almost complete CO inhibition at the doses tested here was, therefore, to be expected. The higher values of LTB_4 in comparison to LTC_4 are in accordance with previous findings (Verpooten et al. 1993). Release of LTB_4 and LTC_4 in whole blood incubates was significantly decreased after oral intake of 400 mg tepoxalin, while 100 mg tepoxalin had no uniform effect and, therefore, caused no significant decrease in LT release.

Thus, our results prove that low concentrations of tepoxalin can inhibit CO, but 100 mg tepoxalin seems to be insufficient for 5-LO inhibition in blood.

Other reports have shown that the synovial tissue of patients with OA releases significant amounts of PGE_2, 6-keto-PGF_{1alpha}, and LTC_4 after stimulation with ionophore A23187 (Wittenberg et al. 1993). Our previous findings demonstrated inhibition of PG release by diclofenac and indomethacin but no inhibition of LT release. The inhibition of both CO and 5-LO by tepoxalin was demonstrated in this study.

Eicosanoid release from extensively washed synovial tissue was significantly higher than release from briefly washed synovial tissue. This is probably due to wash out of the drug, which is a reversible enzyme inhibitor, resulting in less inhibition of CO and 5-LO.

Gastric and intestinal ulcerations are significant side-effects of CO inhibitors. It has been stated that a possible mechanism for such effects is a substrate shift by CO inhibitors. The additional effect of 5-LO inhibition might be important, as it has been suggested that the enhancement of LTs observed with NSAIDs may be due to diversion of AA to the 5-LO pathway (Szabo and Goldberg 1979, Walker et al. 1980). The formation of these LTs might be responsible for events associated with NSAID-induced gastrointestinal inflammation. The data of Kirchner et al. (1997) suggest that 5-LO inhibition may play a role in the prevention of NSAID-induced gastric inflammation. Such inflammation is characterized by the migration of polymorphonuclear leukocytes. Immunohistochemical analysis has indicated that tepoxalin inhibits this neutrophil migration (Zhou et al. 1996). LTs have been proposed as culprits in mucosal damage (Morales et al. 1992). A dual inhibitor of CO and 5-LO like tepoxalin might prevent or reduce this mechanism (Wallace et al. 1991, Wallace et al. 1993). Another point is the existence of constitutive CO (COX-1) and inducible CO (COX-2). COX-1 is present in cells under physiological conditions, whereas COX-2 is induced in pathological conditions, like inflammation (Mitchell et al. 1993). COX-1 is probably involved in production of PG in cellular "housekeeping" functions, such as coordinating the actions of circulating hormones and regulating vascular homeostasis (Meade et al. 1993). COX-2 may produce PG involved in inflammation and/or mitogenesis. Selective COX-2 inhibitors may protect cellular functions and reduce proinflammatory symptoms. To what extent tepoxalin might specifically inhibit one CO isozyme is not yet clear.

Clinically, tepoxalin caused no severe adverse reactions. It was well tolerated and pain scores were reduced. 8 of 14 patients reported better alleviation of pain with tepoxalin than with different NSAIDs they had taken before the study. Therefore, tepoxalin might be a safe and potent alternative to known

NSAIDs. This is even more likely because of the dual inhibition of CO and 5-LO of arachidonic acid metabolism. Our results indicate sufficient accumulation of tepoxalin in synovial tissue. This might explain the good clinical results, with reduction of pain. In our opinion, tepoxalin should be studied further and it may find a place in the therapy of inflammatory joint diseases.

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