SAT0063 BLEEDING TIME AND PLATELET FUNCTION IN NORMAL VOLUNTEERS RECEIVING MELOXICAM

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Background Traditional NSAIDs relieve the inflammation and pain of arthritis through inhibition of cyclooxygenase (COX)-2, but adverse gastrointestinal and platelet side effects are common with inhibition of COX-1. Because meloxicam inhibits COX-2 to a greater degree than COX-1, it may therefore have inflammatory efficacy without adverse effects on platelet function.

Objectives This study assessed the effects of once daily meloxicam (7.5, 15, and 30 mg) on bleeding time and platelet function in healthy subjects as compared to placebo or extended-release indomethacin capsules (75 mg) as an active control.

Methods In this double-blind study, healthy male and female subjects were randomised to received 8 days of a single dose of meloxicam 7.5 mg (N = 16), 15 mg (N = 16), or 30 mg (N = 16), placebo (N = 16), or indomethacin ER 75 mg (N = 15). Subjects were serially evaluated with bleeding times (simplat method), platelet aggregation to Arachidonic acid (AA) and ADP, and serum thromboxane B₂ (TXB₂) levels. Changes from the pre-drug baseline were evaluated on Day 8 prior to drug dosing and at 3 and 6 h after dosing.

Results None of the meloxicam doses prolonged the bleeding time, either chronically (Day 8 predose) or acutely (Day 8, 3 and 6 hrs post-dose) in comparison with placebo. By contrast, indomethacin significantly prolonged the bleeding time 6 hrs after dosing on Day 8. Similar to the bleeding time results, there was no inhibitory effect of meloxicam at any dose on either ADP- or AA-induced platelet aggregation when compared with placebo; whereas indomethacin significantly inhibited platelet aggregation to ADP (Day 8, 3 and 6 hrs post-dose) and to AA (Day 8, pre-dose and 3 and 6 hrs post-dose (p < 0.05).

Abstract SAT0063 Table 1

	Bleeding Time (mean ± SE)	Platelet Aggregation (mean ± SE)
Placebo	0.2 ± 0.4 min	-1.3 ± 3.1%
Meloxicam 7.5	0.4 ± 0.3 min	0.9 ± 5.6%
Meloxicam 15	-0.2 ± 0.5 min	-2.3 ± 3.8%
Meloxicam 30	0.7 ± 0.5 min	2.4 ± 3.6%
Indomethacin ER 75	1.6 ± 0.5 min*	-69.3 ± 3.6%*

*P < 0.05 vs placebo.

Conclusion Meloxicam at higher than recommended doses had no acute or chronic effect on bleeding times and did not inhibit either AA or ADP induced platelet aggregation in healthy volunteers.

By contrast indomethacin ER 75 mg significantly reduced platelet aggregation and increased bleeding times.

SAT0064 TREATMENT WITH ETORICOXIB (MK-0663), A COX-2 SELECTIVE INHIBITOR, RESULTED IN CLINICAL IMPROVEMENT IN KNEE OSTEOARTHRITIS (OA) OVER 52 WEEKS

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Background Prostanoid synthesis is catalysed by two distinct cyclooxygenase (COX) isoforms; COX-1 (constitutive) and COX-2 (inducible). NSAIDs such as aspirin and ibuprofen inhibit both COX isoforms. Etoricoxib has been characterised as a COX-2 selective inhibitor with doses up to 150 mg QD (~100-fold selective in human whole blood assay).

Objectives Evaluate long-term efficacy following dose range finding of etoricoxib in knee OA.

Methods Double-blind, randomised, placebo-controlled, multi-center study conducted in 617 knee OA patients. Patients with increased pain after NSAID withdrawal were allocated to qd oral etoricoxib 5 mg (N = 117), 10 mg (N = 114), 30 mg (N = 102), 60 mg (N = 112), 90 mg (N = 112) or placebo (N = 60). Following Part I (6 weeks), patients continued in double-blind continuation studies (total treatment 52 weeks). Patients receiving placebo, etoricoxib 5 and 10 mg in Part I were reallocated to etoricoxib 30-, 60-, 90 mg, or diclofenac 150 mg in the continuation studies. Etoricoxib 30-, 60-, and 90 mg remained constant over 52 weeks.

Results In Part I, etoricoxib 5-, 10-, 30-, 60-, and 90 mg demonstrated significantly greater efficacy than placebo for the primary endpoints (p < 0.05), with effect sizes exhibiting a strong, dose-related trend. For the subset of patients remaining in the etoricoxib 30-, 60-, 90 mg groups over 52 weeks, the treatment effect was generally maintained. Similar to the results in Part I, the 60- and 90-mg treatments were shown to be more effective than the 30-mg dose with respect to each of the 3 primary efficacy endpoints (WOMAC VA 3.0 pain subscale, patient and investigator global assessment of disease status).

Etoricoxib was generally well tolerated over 52-weeks. In Part I, the incidence of patient discontinuation due to adverse events (AEs) was not significantly different between MK-663 and placebo. There were no clinically significant dose-related trends across treatments with ≥ 1 AEs, drug-related AEs, serious AEs, or drug-related serious AEs. The safety results through 52 weeks were consistent with those in Part I, with no evidence of new types of AEs arising.

Conclusion Etoricoxib was generally well tolerated in doses up to 90 mg in patients with OA for up to 52 weeks, and resulted in sustained clinical efficacy.

SAT0065 META-ANALYSIS OF NSAID-INDUCED GASTROINTESTINAL (GI) SIDE EFFECTS IN OA PATIENTS IN JAPAN

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Background GI intolerance is one of the major causes of failure of NSAID treatment for arthritis patients. There has been a large number of studies to examine the risk of NSAID-induced GI side effects in US and Europe, but few studies in Japan.

Objectives In order to evaluate the GI tolerability of NSAIDs in OA patients in Japan, a systematic review of Japanese randomised controlled trials was performed.

Methods This meta-analysis consisted of double blind randomised controlled trials with 4-weeks NSAID treatment in OA patients in Japan. The analysis was composed of 25 trials with 26 types of NSAIDs, among which 6 types were used in more than two trials. The endpoints evaluated in the meta-analysis included incidence of any side effects, any digestive side effects and symptoms indicative of upper GI symptoms such as abdominal pain, nausea and dyspepsia. The general variance-based method was used to estimate the risk of these endpoints. Additionally, to evaluate the effect of risk factors for GI discomfort, odds ratios (ORs) of side effects by sex and age were estimated for individual treatment arms and then combined.

Results The analysis included a total of 4,725 patients. On average, cumulative incidences of patients who had experienced any side effects and any digestive side effects were 14.3% (95% CI: 13.3–15.3%) and 10.4% (95% CI: 9.4–11.4%), respectively. Incidence of any side effects by type of NSAID were as follows: diclofenac 75 mg/day, 19.9% (10 trials), indomethacin 75 mg/day, 16.2% (12 trials), acetaminophen 90 mg/day, 12.6% (2 trials), nabumetone 800 mg/day, 9.2% (2 trials), fenbufen 600 mg/day 8.8% (2 trials), and ibuprofen 900 mg/day, 7.8% (2 trials). Incidence of any digestive side effects were as follows: diclofenac, 16.6%, indomethacin, 10.2%, nabumetone, 8.3%, fenbufen, 6.9%, and ibuprofen 900 mg/day, 6.4%. Abdominal pain, nausea/vomiting and dyspepsia were the three most common digestive side effects. The cumulative incidence for the upper GI symptoms was estimated to be approximately 10.9%. Comparing the risk of upper GI symptoms between male and female, the summary OR was 1.71 (95% CI: 1.11–2.65). Females were at significantly higher risk than males in the incidence of upper GI symptoms. Comparing the risk of upper GI symptoms between patients under 59 years and above 60 years old, the summary OR was 1.07 (95% CI: 0.75–1.52).

Conclusion Despite the incidence of side effects varying across the different types of NSAIDs being used, there was an obvious increased risk of GI symptoms. Abdominal pain, nausea/vomiting and dyspepsia were the three most common GI discomforts and this trend is similar to the evidence in US and Europe. Females show a higher risk of side effects and are approximately 50% more likely to have side effects compared to males. Older patients tend to have a higher risk of side effects, but this is not statistically significant.

SAT0066 STUDYING OF THE EFFICIENCY OF THE SYNVIK IN OSTEOARTROSIS

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Background At present for improvement of life quality in patients with osteoarthritis is necessary to solve some problems: precluding of development of degenerative process in cartilage of affected joint, relieving of pain and improvement of the function of the joint.

Objectives

Methods For these aims we studied the efficiency of the chondroprotective drug Synvisk by Boehringer Ingelheim in 25 patients with arthrosis of the knee in medium age of 61.2 ± 1.7 years, 16 women and 8 men, with duration of the disease 5.8 ± 0.9 years.

Results Conform X-ray data the distribution of the patients by stages of the disease was as follow: I grade ? 20%, II grade ? 64%, and III grade ? 16%. In experimental group the drug was administered intraarticular by blind method in dose of 2,0 ml one time in a week, 3 injections for the course, which were repeated after 6 and 12 months. The control group was matched by gender, duration of disease and X-ray date; in this group was administered placebo conforming same scheme.

Evaluation of the effectiveness and tolerability of compared drugs was carried out in evolution of clinical (pain, functional index by Lesquesne, volume of movement on affected joints), X-ray parameters and functional methods (ultrasonography, scintigraphy with ^{99m}Tc).

In the basic group were mentioned decreasing of the pain intensity and improvement of the joint functions after single injection in one third of the patients, while in control groups similar cases were absent. After 3 courses of the treatment in the basic group the effects were obtained in 86,7% of the patients, including 33,3% very good effect, in 53,4% moderate effect and only in 13,3% the effects were absent. In control group there were no effect in 80% of the patients, and in 20% of the patients there were mentioned moderate effects; good effects were not observed.

Conclusion Thus, a presented result suggests that administration of Synvisk lead to significant improvement of the life quality in the patients with arthrosis of the knee.

SAT0067 SERUM CARTILAGE OLIGOMERIC MATRIX PROTEIN (COMP) AS A PROGNOSTIC MARKER IN KNEE OSTEOARTHRITIS

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Background Three previously published studies aimed to relate radiographic disease progression in OA to baseline serum COMP levels (1–3). In two studies, the authors found no correlation between baseline serum COMP levels and subsequent progression of knee osteoarthritis (OA).^{1,2} In the study of hip OA, however, the authors found significant correlation between baseline serum COMP levels and yearly mean narrowing of joint space width.³

Objectives To evaluate serum COMP level measured at baseline with a new sandwich ELISA as a predictor of disease progression of knee OA.

Methods Patients with established OA (n = 54) represented placebo-taking group from finished and now opened 3-years long double-blind drug trial. Standing antero-posterior radiographs of both knees were taken at the beginning and at the end of the study and used to measure joint space width at the medial compartment. COMP was quantified by newly developed sandwich ELISA with monoclonal antibodies 16-F12 and 17-C10.

Results The increased serum COMP level at baseline correlated with 3-years change of joint space width (expressed as the sum