Methods Ambulatory patients with gonarthrosis grade 2 or 3 of Kellgren and Lawrence classification, 30 ± 60 years old, with body mass index (BMI) < 30 kg/m² were admitted to the study after comply with inclusion and exclusion criteria. After have been given their informed consent, patients were randomly allocated, in a double-blind way, into treatment groups – Loxoprofen 60 mg t.i.d. or diclofenac 50 mg t.i.d. Duration of treatment was four weeks, and patients were evaluated at pretreatment and every two weeks during therapy for: overall severity of symptoms; pain at rest, on pressure, on movement and nocturnal through a visual analogue scale (VAS); swelling of knee; functional disability; global improvement; side-effects. Laboratory tests were performed in all patients, pre and post treatment.

Results A total of 60 patients was treated ± 30 in each group. There was no significant difference between the groups; 87% of patients were >51 years old. Mean disease duration was 2655 ± 2168 days in LOX and 2086 ± 1333 days in DIC (n.s.). 23 patients in LOX and 24 in DIC reported previous treatments with NSAIDs, being diclofenac the most frequent prescribed drug. All parameters evaluated showed statistically significant improvements compared with baseline ($p < 0.0001$ ± chi square) with both treatments; there were no statistically significance differences between treatments groups. GI adverse events occurred in 3 patients (10%) of LOX and in 12 (40%) of DIC ($p < 0.01$). Epigastralgia was the most prevalent GI event reported (1 in LOX; 7 in DIC). One serious adverse event ± enterorrhagia ± was reported in the diclofenac group, with discontinuation of treatment. Tolerability assessments were classified as both very good and good in 90% in LOX and in 79% in DIC ($p < 0.05$). One patient in LOX discontinued therapy due to worsening of the disease, and 5 in DIC ± 4 due to adverse events and 1 worsening of the disease. About 80% of overall assessment were classified, by investigator and patient, as either very good or good in Loxoprofen group and 70% in the diclofenac group (n.s.).

Conclusion Loxoprofen 60 mg, t.i.d., showed good efficacy accompanied by excellent tolerability and safety in gonarthrosis, which was superior to that of an established NSAID, diclofenac 50 mg, t.i.d.

SAT0055 EFFECT OF ROFECOXIB, CELECOXIB, AND NAPROXEN ON BLOOD PRESSURE AND URINARY SODIUM EXCRETION IN ELDERLY VOLUNTEERS

¹JL Schwartz, ²MP Malice, ³KC Lasseter, ⁴GB Holmes, ¹KM Gottesdiener, ⁵K Brune. ¹Clinical Pharmacology, Merck & Co, Inc., Rahway; ²Biostatistics, Merck & Co, Inc., Brussels, Belgium; ³Clinical Research, Clinical Pharmacology Associates, Miami; ⁴Clinical Research, SFB International, Miami, USA; ⁵Clinical Pharmacology, University Erlangen, Erlangen, Germany

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Background Nonsteroidal anti-inflammatory drugs (NSAIDs) can affect sodium reabsorption by decreasing the synthesis of renal prostaglandins. Since COX-2 is constitutively expressed in the kidney, it is hypothesised that the effects of COX-2 inhibitors on sodium handling would be similar to non-selective NSAIDs. It is hypothesised moreover that the effects of the two COX-2 inhibitors on sodium handling would be similar.

Objectives This study evaluated the effects of two COX-2 inhibitors [rofecoxib, 25 mg QD and celecoxib, 200 mg BID], a non-selective NSAID [naproxen, 500 mg BID], and placebo on blood pressure (BP) and urinary sodium excretion during a 2-week in-house administration.

Methods 67 healthy elderly (60 to 80 years) subjects participated in a double-blind, placebo-controlled, parallel-group study. Subjects received a weight-maintaining isocaloric diet (200 mEq sodium, 0.8 g/kg protein, 80 to 120 mEq potassium daily), beginning 8–13 days prior to the first dose of study drug. After attaining sodium balance [based on stable weight (within 0.5 kg) and 24-hour urinary sodium between 180 to 220 mEq on 2 consecutive days], subjects were randomised to treatment. Daily 24-hour urine collections were obtained. Daily BP measurements were taken at 8AM and 8PM, and more often (8 AM, Noon, 4 PM, and 8 PM) on Days -1, 1, 7, and 14.

Results Least-Squares mean changes from baseline (SE) for average daily BP on Day 14 (prespecified primary endpoint for BP) are shown in the Table 1 below. There was no significant difference between the active treatment groups in daily average sodium excretion during the first 3 days or over 2 weeks of treatment ($p > 0.05$). No incidence of peripheral oedema occurred during the 2 week treatment. Two subjects experienced elevated systolic BP during the course of the trial (one on each COX-2 inhibitor).

Abstract SAT0055 Table 1

	Rofecoxib N = 17	Celecoxib N = 17	Naproxen N = 17	Placebo N = 16
Systolic BP(mm Hg)	3.4 (2.0)	4.3 (2.0)	3.1 (2.0)	-1.4 (2.0)
Diastolic BP(mm Hg)	0.3 (1.0)	0.8 (1.0)	-0.4 (1.0)	-1.4 (1.0)

Least-Squares Mean Changes from Baseline (SE) for Average Daily BP on Day 14.

Conclusion These results, obtained under well-controlled conditions for two weeks, suggest that the COX-2 selective agents, rofecoxib and celecoxib, have similar effects on BP and urinary sodium excretion; their effect is similar also to that of non-selective NSAIDs.

SAT0056 BISPHOSPHONATE MODULATES ECTOPIC BONE FORMATION AFTER HIP ARTHROPLASTY -WITH JAPANESE CASES-

Y Yutani, Y Yamano. Department of Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan

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Background Ectopic bone formation has been reported as the complication after hip arthroplasty, at the time of paralysis of extremities and cerebral trauma, and in the presence of congenital diseases such as progressive osteosis. Bisphosphonates have been developed as the agent for improving bone metabolism, and are currently used as 1) a derivative in making a radioisotope diagnosis, 2) an inhibitor of bone resorption, 3) a preventive agent for ossification, and 4) an inhibitor of calculus formation in dentistry.

Objectives We have investigated the therapeutic effects of etidronate disodium (EHDP) as a bisphosphonate on ectopic bone formation developing after hip arthroplasty and the indications for administration of EHDP. The patients who had received implant arthroplasty 8 years ago were clinically evaluated, and the influence of EHDP on the prostheses was investigated.

Methods The subjects were the patients who had undergone total hip replacement or hip prosthesis replacement. They consisted of 40 women, and the ages at the time of operation

ranged from 50 to 82 years, with a mean of 63.9. Twenty (mean age at operation, 62.6 years) of them were administered EHDP, and the rest 20 (mean age at operation, 65.1 years) were not administered the agent. The administration was initiated within 2 weeks postoperatively at a daily dose of 600–1000 mg, and continued for 12 weeks. The patients were clinically evaluated 4, 8, 12, 24, and 96 weeks and 8 years after the start of administration. The Finermann's classification was used for radiological evaluation of ectopic bone formation.

Results The incidences of ectopic bone formation 24, 96 weeks and 8 years after the start of administration in the group administered EHDP (EHDP group) were 15%, 25%, and 30%, respectively, while the corresponding values in the non-administration (control) group were 30%, 40%, and 45%, respectively. Within 12 weeks after operation, the ectopic bone formation occurred in 33% of all patients with the ectopic bone formation and 17% of the patients administered EHDP. According to the Finermann's classification, grade 1 was observed in 67%, grade 2 in 22%, and grade 3 in 11% of all patients with the ectopic bone formation 24 weeks postoperatively, while grade 1 was observed in 73% and grade 2 in 13% grade 3 in 14% 8 years postoperatively.

Conclusion The incidence of ectopic bone formation has been reported to range from 15% to 90% in Western countries. In contrast, the incidence in Japan is 15.7–38.5%, being lower than in Western countries. The severity has also been reported to be mild in Japan, as compared to cases in Western countries. In our data, the incidences were 20% and 30% in the control and EHDP groups, respectively, 24 weeks postoperatively, and the mildest grade 1 accounted for 67%. The ectopic bone formation manifested within 12 weeks after operation in 13% of the patients who had the condition, showing that the occurrence was suppressed during this period. These results suggest that the administration is efficacious for postoperatively early prevention of ectopic bone formation and that the indications for the administration must be taken into much consideration.

SAT0057 A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFECTS OF VALDECOXIB, A NOVEL COX-2 SPECIFIC INHIBITOR, ON PLATELET FUNCTION IN THE ELDERLY

¹PT Leese, ²D Recker, ²ME Kuss. ¹Medical Scientific Services, Quintiles Phase I Services, Lenexa; ²Research and Development, Pharmacia Corporation, Skokie, USA

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Background Valdecoxib is a novel oral COX-2 specific inhibitor. COX-2 specific inhibitors effectively treat pain and inflammation without causing many of the side effects commonly associated with conventional NSAIDs.

Objectives The purpose of this study was to compare the effects of valdecoxib to ibuprofen on platelet function in healthy subjects, > = 65 years of age.

Methods In this single-centre, double-blind, placebo-controlled, parallel-group study, 65 healthy adults, aged 65–95 years, were randomised to receive valdecoxib 40 mg BID, ibuprofen 800 mg TID, or placebo for 7.5 days. Platelet aggregation in response to arachidonate (AA), adenosine diphosphate (ADP), or collagen; serum thromboxane B₂ (TxB₂) concentrations; and Simplate II bleeding times were assessed at 2, 4, and 8 h after dosing on Days 1 and 8. Vital signs and adverse events were monitored throughout the study.

Results Platelet aggregation responses to AA, collagen, and ADP were not affected by treatment with valdecoxib 40 mg BID. In contrast, ibuprofen resulted in marked decreases in AA-induced platelet aggregation at the 2 h and 4 h assessments on Days 1 and 8. The effects of ibuprofen on platelet aggregation in response to collagen and ADP were not as great as seen with AA. However, for all three stimuli, ibuprofen demonstrated significantly greater decreases in platelet aggregation compared to placebo and valdecoxib at several time points. Valdecoxib 40 mg BID had no effect on bleeding times or serum TxB₂ concentrations compared to placebo. Bleeding times were significantly prolonged ($p < 0.013$) and serum TxB₂ concentrations significantly reduced ($p < 0.026$) in ibuprofen-treated subjects.

Abstract SAT0057 Table 1

	Placebo	Valdecoxib 40 mg BID	Ibuprofen 800 mg TID
Med. change 30 min	-3.0	-2.0	-1.0
Med. change 2 h	-2.0	1.0*	-70.0**
Med. change 4 h	-1.0	0.0*	-60.0**
Med. change 8 h	-2.0	-2.0	-1.0

Platelet Aggregation Response to Arachidonate (%), Median Change From Baseline After Final Dose on Day 8 (* $p \leq 0.05$ vs ibuprofen, ** $p < 0.05$ vs placebo).

Conclusion Valdecoxib 40 mg BID does not affect platelet function, serum TxB₂ levels or bleeding times, and is well tolerated in healthy elderly subjects. However, ibuprofen significantly alters hemostasis. These findings suggest that valdecoxib can provide its previously demonstrated analgesic and anti-inflammatory therapeutic benefits without negatively influencing platelet function in subjects > = 65 years.

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SAT0058 THE NOVEL COX-2 SPECIFIC INHIBITOR, VALDECOXIB, DOES NOT AFFECT PLATELET FUNCTION IN HEALTHY ADULTS

¹PT Leese, ²D Recker, ²ME Kuss. ¹Medical Scientific Services, Quintiles Phase I Services, Lenexa; ²Research and Development, Pharmacia Corporation, Skokie, USA

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Background Conventional NSAIDs have traditionally been used to manage pain and inflammation; however, as nonspecific inhibitors of cyclooxygenase (COX-1 and COX-2), they are associated with significant adverse events, including impaired platelet function.

Objectives The purpose of this study was to compare the effect of valdecoxib, a new COX-2 specific inhibitor, on platelet aggregation and bleeding time to that of the conventional NSAIDs, naproxen and diclofenac.

Methods This was a single-centre, double-blind, randomised comparison of valdecoxib 40 mg BID, naproxen 500 mg BID, diclofenac 75 mg BID, and placebo in healthy adult subjects. Sixty-two subjects received active medication or placebo for 7.5 days. Platelet aggregation responses to arachidonate (AA), collagen, and adenosine diphosphate (ADP); Simplate II bleeding times; and serum thromboxane (Tx) B₂ concentrations were measured at baseline; 30 min predose, 2, 4, and 8 h postdose on Day 1; and 2, 4, and 8 h after the final dose on Day 8.