INVESTIGATIONS OF INTER- AND INTRA-INDIVIDUAL RELATIONSHIPS BETWEEN ABSORPTION OF ORAL SALMON CALCITONIN AND A SURROGATE MARKER OF PHARMACODYNAMIC EFFICACY

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Purpose: The aim of the study was to compare inter- and intra-individual bioavailability of 0.8 mg of oral salmon calcitonin (sCT) given once before or after food intake to assess the relationship between bioavailability and levels of the bone resorption biomarker, serum C-terminal telopeptide of collagen type I (CTX-I).

Methods: Participants were from two randomized, double-blind, placebo-controlled studies. Study I was a cross-over trial including healthy postmenopausal women receiving a single dose of 0.8 mg of oral sCT or placebo pre-breakfast at 08:00 (n=42), pre-dinner at 17:00 (n=20), or post-dinner at 22:00 (n=19). Blood samples were taken before drug intake, and at 5, 10, 15, 30, 45 minutes, 1, 1½, 2, 2½, 3 hours, and every subsequent hour until 24 hours after dosing. Study II investigated the pharmacokinetics and pharmacodynamics of oral sCT administered on days 1 and 14 to postmenopausal women and men (n=73) suffering from osteoarthritis (OA). In one treatment arm, 0.8 mg of oral sCT was given twice daily with one dose in the morning at 08:00 and one dose given pre-dinner at 17:00 (n=26). On treatment day 1 and day 14, blood samples were taken before drug intake, and at 10, 15, 30, 45 minutes, and 1, 2, and 4 hours post-dose. In both studies the absorption of calcitonin was assessed by plasma sCT concentrations, and bone resorption by the biochemical marker of serum CTX-I.

Results: Irrespective of dosing time, a single dose of 0.8 mg oral sCT was rapidly absorbed, reaching Cmax between 15 to 30 minutes in both low and high absorbers. Following Cmax, sCT was eliminated from plasma with a half-life of between 9 and 15 minutes. Overall, a single dose of 0.8 mg oral sCT resulted in significant suppression of serum CTX-I compared with placebo irrespective of the level of absorption of sCT. At all three dosing times a significantly higher suppression of sCTX-I was observed in subjects with the highest intestinal absorption of sCT. The effect of increased absorption of sCT was a marked prolongation of serum CTX-I suppression whereas acute suppression 1 to 2 hours after dosing was unaffected. A high degree of correlation between the level of absorption of sCT and the suppression of serum CTX-I was observed at all three dosing times, i.e. a Pearson correlation coefficient of \( r = -0.74 \), \( r = -0.94 \), and \( r = -0.78 \), was found at the dose times 08:00, 17:00, and 22:00. A weak association of borderline significance was found in the intra-individual absorption of sCT on dosing days 1 and 14 with \( r = 0.40 \) and \( r = 0.38 \) at the dose times 08:00 and 17:00. As expected, the intra-individual response in serum CTX-I levels was statistically non-significantly associated on dosing days 1 and 14 with \( r = 0.34 \) and \( r = 0.27 \) at the dose times 08:00 and 17:00.

Conclusions: Increased bioavailability of orally administered 0.8 mg sCT is highly correlated with suppression of the bone resorption marker, serum CTX-I. Moreover, the effect is highly controlled with a minimum of individual variability in serum CTX-I. The variable absorption of the drug demonstrates the importance of determining the optimal conditions for ensuring a most beneficial drug uptake.

EXTRACORPOREAL SHOCKWAVE SHOWS REGENERATION IN HIP NECROSIS

C.-J. Wang

Purpose: The effect of shockwave in osteonecrosis of the femoral head (ONFH) is poorly understood. The purpose of this study was to investigate the regeneration effects of shockwave in ONFH.

Methods: This study consisted of 14 femoral heads from 14 patients undergoing total hip arthroplasty for ONFH. Seven patients with seven hips who received shockwave prior to surgery were designated as the study group, whereas, seven patients with seven hips who did not receive shockwave were assigned to the control group. Both groups showed similar demographic characteristics. The femoral heads were investigated with histopathological examination and immunohistochemical analysis with von Willebrand factor (vWF), VEGF, platelet endotelial cell adhesion molecule-1 (PECAM-1) also referred to as CD31 and vascular cell adhesion molecule (VCAM) for angiogenesis, and with proliferation cell nuclear antigen (PCNA), Dckkopf-1 (DDK1) and Wnls 3a (Wnt 3) for bone remodelling and regeneration.

Results: In histopathological examination, the study group showed significantly more viable bone and less necrotic bone, higher cell concentration and more cell activities including phagocytosis than the control group. In immunohistochemical analysis, the study group showed significant increases in vWF (P<0.01), VEGF (P<0.0012) and CD 31 (P<0.0023), Wnt3 (P<0.008) and PCNA (P<0.0011), and decreases in VCAM (P<0.0013) and DDK1 (P<0.0007) than the control group.

Conclusions: Shockwave treatment significantly promotes angiogenesis and bone remodelling than the control. It appears that application of shockwave results in regeneration effects in hips with ONFH.
and those without night pain (WN-group) and core temperature of theirs was compared. Statistical analysis was performed using repeated measures ANOVA and p value less than 0.05 was considered as statistically significant.

**Results:** Core temperature of both the knee and the sternum decreased at around 5 am according to circadian rhythm. Core temperature of the knee was significantly lower than that of the sternum in KOA. On the other hand, such difference was not seen in control knees.

Core temperature of the knee between N-group and WN-group was not different.

**Conclusions:** We revealed the lower core temperature of the knee in end-stage KOA. This indicated existence of blood flow disturbance in OA knees. Our data supports decreased bone perfusion in KOA exhibited with perfusion MRI. Elevated bone marrow pressure measured with invasive technique was also reported as one possible mechanisms of KOA pain and it might related to blood flow disturbance, though inconsistent results was reported about bone marrow pressure.

In the present study, we firstly reported blood flow disturbance in KOA by measuring core temperature. We only dealt end-stage OA patients in this study, but this non-invasive method might be useful in monitoring KOA status.

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**Purpose:** This was a randomized controlled trial (RCT) with extension and open-label re-treatment phases to determine if single or repeated intra-articular injections of Gel-200 are safe and effective in subjects with symptomatic knee osteoarthritis.

**Methods:** Subjects completing Week 13 in SI-6606/01 RCT were eligible for re-treatment based on WOMAC pain subscore ≥40 mm; and those without night pain (WN-group) and core temperature of theirs was compared. Statistical analysis was performed using repeated measures ANOVA and p value less than 0.05 was considered as statistically significant.

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**DOSE STABILITY OF TAPENTADOL EXTENDED RELEASE AND OXYCODONE CONTROLLED RELEASE IN A ONE-YEAR, RANDOMIZED, OPEN-LABEL, PHASE 3 SAFETY TRIAL IN PATIENTS WITH CHRONIC LOW BACK OR OSTEOARTHRITIS PAIN**

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**Purpose:** To assess the long-term safety and effectiveness of tapentadol extended release (ER), a novel centrally acting analgesic in development for the management of moderate to severe back or osteoarthritis pain.

**Methods:** Patients were randomized 4:1 to receive controlled, adjustable, oral bid doses of tapentadol ER 100-250 mg or oxycodeone HCl controlled release (CR) 20-50 mg. In order to establish an optimal therapeutic dose, defined as a dose providing a balance of efficacy and tolerability, patients could titrate their doses in increments of 50-mg bid tapentadol ER or 10-mg bid oxycodeone HCl CR during a 51-week maintenance period. Safety was assessed for all patients who received at least 1 dose of study medication.

**Results:** Patients received tapentadol ER (N = 894) or oxycodeone CR (N = 224). The mean (standard deviation) and median most frequently used daily doses were 352.2 (132.43) mg and 400 mg with tapentadol ER and 56.8 (30.07) mg and 40 mg with oxycodeone HCl CR. Patients who received tapentadol ER and oxycodeone CR took the most frequently used dose for a median duration of 133.5 and 45.0 consecutive days, respectively. Patients in the oxycodeone CR group discontinued treatment earlier than patients in the tapentadol ER group; in the first 4 weeks of the study, approximately 20% of patients in the oxycodeone CR group discontinued treatment compared with approximately 20% of patients in the tapentadol ER group. The percentage of patients who discontinued because of adverse events (AEs) during the

<table>
<thead>
<tr>
<th>Weeks post injection</th>
<th>Endpoint A (p=0.049)</th>
<th>Endpoint B (p=0.034)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel-200 (N=247)</td>
<td>PBS (N=128)</td>
<td>Gel-200 (N=247)</td>
</tr>
<tr>
<td>Week 1</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Week 3</td>
<td>0.952</td>
<td>0.941</td>
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<td>Week 6</td>
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<td>Week 9</td>
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<tr>
<td>Week 13</td>
<td>0.419</td>
<td>0.346</td>
</tr>
<tr>
<td>Week 16 (Week 3 in Extension phase)</td>
<td>0.292</td>
<td>0.264</td>
</tr>
<tr>
<td>Week 19 (Week 6 in Extension phase)</td>
<td>0.292</td>
<td>0.264</td>
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<tr>
<td>Week 22 (Week 9 in Extension phase)</td>
<td>0.280</td>
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<tr>
<td>Week 26 (Week 13 in Extension phase)</td>
<td>0.280</td>
<td>0.237</td>
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</table>

**Conclusions:** Together, these data support the efficacy and durability of response of a single intraarticular injection of Gel-200 over 13 weeks as treatment for knee osteoarthritis. This study also demonstrated that repeat treatment of Gel-200 was well tolerated.