AB1023

ENHANCED RENAL TRANSPORTER ACTIVITIES OF OAT1 AND OAT3 BY KEISHIBUKURYOGAN (K-06) AND IN VIVO URIC ACID MODULATING EFFECT AT POTASSIUM OXONATE-INDUCED MOUSE SETTING

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Background: Studies on renal solute carrier transporters have made the renal pathophysiology be in progress towards more mechanistic and the knowledge on renal drugs including drug-drug interaction be more evidentiary. Among the evidence, uricosuric phenomenon has been known that rodent experimental model is also useful for predicting human uricosuria.

Objectives: The aim of this study was to assess the substrate uptake at the over-expression of renal transporters, OAT1, OAT3 and URAT1 at kidney proximal tubular cell lines with or without a commercial herbal medicine, Keishibukuryogan (K-06) and to further measure serum and urinary uric acid concentrations in the setting of potassium oxonate (PO)-induced ICR mouse model with or without K-06.

Methods: The transporter-expressed HEK293-OAT1 and HEK293-OAT3 cells were seeded on BD poly-d-lysine microplates to uptake the [³H] estrone sulfate for 5 min in absence or presence of K-06. URAT1 was overexpressed using Xenopus oocytes being injected with *in vitro*-copied RNA of URAT1, and then to measure the uptake of [¹⁴C] uric acid with/without K-06. Total radioactivity was measured using a liquid scintillation counter. Serum and urinary uric acid was measured in PO ICR mice after three-day intake of K-06. They were assigned by 4 per each group; 1) control group, 2) PO-induced group, 3) PO-induced with allopurinol 50 mg/kg/day intake group and 4) PO-induced with allopurinol plus K-06 300 mg/kg/day intake group.

Results: To determine the kinetic parameters of concentration-dependent uptake of overexpressed OAT1 and OAT3 transporters in HEK293 cells, the K-06 inhibitory parameters on OAT1 and OAT3 were presented with the IC₅₀ values of 49.3 and 31.5 µg/mL, respectively. The K-06 inhibited URAT1 with IC₅₀ of 59.3 µg/mL. The K-06 (300 mg/kg) reduced serum levels of uric acid approximately 30% compared to that of PO-control group (p=0.039) and K-06 showed the slight elevation of urinary uric acid by 12% compared to that of PO-control group with no statistical significance.

Conclusions: The present findings demonstrated that the K-06 modulated basolateral and apical renal transporters and the K-06 showed the slight increased uric acid excretion and the uric acid lowering effect in experimental mouse setting.

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AB1024

RISK OF DRUG INDUCED LIVER INJURY FROM NSAIDS IN PATIENTS WITH GOUT

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Background: Drug Induced Liver Injury (DILI) in patients under nonsteroidal anti-inflammatory drugs (NSAIDs) is more frequently presented by hepatocellular damage when serum alanine aminotransferase (ALT) level exceeds 2 times (or more) the upper limits of norms.¹ The value of minimal hypertransaminasemia (MHTE) (when serum ALT exceeds the upper limit of normal up to twice) is still not clear today.

Objectives: To define the terms of DILI development and the value of MHTE in patients with gouty arthritis (GA) under NSAIDs.

Methods: 189 patients (25.6%) of 738 with GA^{ACR, 1977} were included in our retrospective study. At the onset of gout attack, all patients had normal basal serum ALT, which elevated after starting NSAIDs therapy. Pre-existing liver impairment was not registered. Patients were divided into 2 groups according to the changes in serum ALT after NSAIDs treatment: patients with MHTE (n=101) and those with

DILI (n=88). The mean age of 55^{49–60} years and 54^{44–59.5} years as well as the sex distribution (men 90.1% and 93.3%, respectively) were compatible in both the groups (p<0.05). In DILI group, elevated serum ALT exceeded 2–3 times the upper norms in 81.8% (n=72) of patients; 3–5 times in 14.8% (n=5); more than 5 times in 3.4% (n=3) with the mean serum ALT being of 89^{75–108.5} U/L. In MHTE group, serum ALT exceeded the upper norms by more than 50% in 50.5% (n=51) of cases. After NSAIDs therapy, the mean serum ALT of 51^(47–57) U/L was revealed.

Results: The mean duration of NSAIDs therapy in the groups made 8^{5–10} days in MHTE group and 10^{6–14} days in DILI group. Statistically significant difference (U=3236, p<0.001) was revealed between the groups when comparing the duration of NSAIDs treatment. In addition, in DILI group, 97.7% of patients received NSAIDs in high doses (χ²=19.4; p<0.001) during all period of treatment. ROC analysis showed that the probability of DILI development decreased in patients with GA taking NSAIDs in high doses during less than 11 days (AUC=0.64±0.04, p=0.010, S=47.7%, Sp=82.2%, OR=4.21, 95% CI – 3.38–5.24).

Conclusions: 25.6% of patients with GA have demonstrated elevated serum ALT after NSAIDs therapy: MHTE developed in 13.7% of cases, DILI in 11.9%. Our study showed that MHTE developed in the period less than 11 days of high dose NSAIDs treatment with DILI being likely to occur during more prolonged treatment. MHTE group may be considered as a risk group for DILI development.

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AB1025

MONOSODIUM URATE CRYSTAL FORMATIONS FROM TOPHI IN SYNOVIAL FLUID

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Background: At the joints MSU crystals form primarily at the cartilage surface; on occasions also tophi form at joint margins. Most often monosodium urate (MSU) crystals at the synovial fluid (SF) are found isolated. In tophi MSU crystals often show as spherulitic formations, fanning away from a central point¹ (Figure 1, 200x, polarised light). We have detected in synovial fluid formations of MSU crystals with an organisation indicative that they formed in tophi, draining later to the fluid. The formations also help to understand how crystals formed in tophi.

Methods: Our photographic archive of SF have been reviewed.

Results: Two types of formations are found. A) A spherulitic formation where the crystals fan radially as in the segment of a sphere (Figure, middle, 600x, polarised light). B) Paired crystals bound longitudinally to each other (Figure, right, 600x, phase contrast).

Abstract AB1025 – Figure 1

Conclusions: At tophi spherulitic crystal formations are usual (figure 1) in which MSU crystals radiate as in a fan. A) Pieces of these same formations, seen as the segment of a sphere, are occasionally seen in SF (Figure 2), usually containing a large number of crystals and suggesting that they have drained from a tophus. Likely to build these formations, the initial crystals served as a template on which successive crystals formed by epitaxia, – the crystal formation method of least energy requirement –, explaining the rapid growth that tophi can present. Their unimpeded migration to the joint cavity suggest that they formed freely and unconnected to any organic structure within the tophus. B) In SF containing large numbers of crystals, paired crystals – two crystals lying side by side and usually of similar length and width – are also found. Their paired position likely indicates that one served as template to the other, or that they grew together sharing a crystal net – twin crystals. In all, these MSU crystal formations appear to indicate that besides the crystals formed in the surface of joint cartilages, the content of tophi can drain into the joint fluid, also contributing to the presence of crystals in it; the

periarticular tophi frequently seen in ultrasound appear as the likely source for these formations.

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AB1026 CLINICAL CHARACTERISTICS AND RISK FACTORS FOR GOUT ATTACK DURING THE POSTSURGICAL PERIOD

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Objectives: To evaluate the clinical features and risk factors for gout attack during the postsurgical period in patients with gout.

Methods: Seventy patients who had histories of gout and had been consulted to rheumatologic clinic before surgery under general anaesthesia at a single tertiary hospital were included. Clinical characteristics of patients who developed postsurgical gout attack were compared with patients who did not developed gout attack.

Results: Among 70 patients, 31 (44.3%) patients developed gout attack during postsurgical period. Mean time of gout attack after surgery was 3.7±4.9 days. Most of attacks involved lower extremity joints (83.9%) and tended to monoarticular involvement (61.3%). Knee joint (26%) and foot except 1st metatarsophalangeal (MTP) joint (26%) were more frequently involved than 1st MTP joint (13%). Uric acid levels before surgery (OR 1.46, 95% CI 1.13–1.88, p=0.004) and amount of uric acid changes between before and after surgery (OR 1.62, 95% CI 1.21–2.18, p=0.001) were risk factors for postsurgical gout attack. Taking medications for gout including uric acid lowering agents and/or colchicine reduced the risk of postsurgical gout attack (OR 0.11, 95% CI 0.04–0.32, p<0.001). Operation time, amount of blood loss during surgery, amount of fluid administration during surgery, and surgery site were not significantly associated with postsurgical gout attack.

Conclusions: Adequate uric acid control and taking medications for gout could prevent the postsurgical gout attack.

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AB1027 THE PREDICTIVE VALUE OF CYSTATIN C FOR GOUTY NEPHROPATHY

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Background: Gout is the most common cause of an inflammatory arthritis in men elder than 30 years, varies up to 1,7% of the total morbidity. One of the most common complication of chronic gout is gouty nephropathy with the morphological signs of kidney damage, even in the early stages.¹

It's well known, that urine albumin and glomerular filtration rate (GFR) are the generally accepted markers of nephropathy. But, recent data has shown, that the informative and obtainable new biomarkers of the kidney function are still needed. Thus, evaluation of the pathogenic role in the renal failure of cystatin C could be a "clue". The dozen trials have shown that an increasing of ranges cystatin C in serum could be tested at the stage of subclinical reduction of GFR with normal level of creatinine.^{2;3}

Objectives: To determine the serum ranges of cystatin C and creatinine as the markers of nephropathy in patients with gout.

Methods: The main group was the 80 males with primary gout (average age – 53,4±8,2 years), with the disease duration from 3 up to 25 years. The second group – 20 healthy men (49,5±4,5). We determined the concentration of serum uric acid, serum cystatin C, creatinine, calculate the GFR using CKD-epi formula. For urine albumin evaluation we used the albumin/creatinine ratio in the morning urine portion.

Results: e determined that the main group identified by more significant violations of renal function. In the main group was found the statistically significant increase of the serum creatinine (97±18 µmol/l) and decrease of GFR (73^{64; 94} ml/min².

The serum cystatin C concentration in the main group was (1,7^{1,4; 1,9} mg/l) which was the significantly larger than in the comparison group (0,8 [0,7; 0,92] mg/l, p<0,001).

The albumin/creatinine ratio was statistically higher in the main group (26^{14; 56} mg/g) than in comparison (0,8 [0,7; 0,92] mg/l, p<0,001). Also the patients with gout are characterised by the larger concentration of uric acid in the serum (530±74) µmol/l than healthy men (347±75) µmol/l and negative correlation between uric

acid level and GFR (r=-0,4, p<0,05) which explain the increase of uric acid concentration in the serum.

We determined the correlation between level of urine albumin and creatinine concentration (r=+0,5, p<0,05) in the main group, but concentration between albuminuria and cystatin C was stronger (r=+0,6, p<0,05). We detected that cystatin C level had a greater accuracy for the diagnosis of albuminuria than creatinine according to the ROC-analysis. These facts show that serum concentration of cystatin C more closely connected with the renal function than creatinine.

Conclusions: 1. The increase of serum cystatin C level can be identified before the clinical manifestation of renal dysfunction while the serum creatinine remain relatively normal.

2. Serum ranges of cystatin C more closely correlate with elevation of urine albumin than creatinine.

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AB1028 ACTH VS BETAMETHASONE FOR THE TREATMENT OF ACUTE GOUT IN HOSPITALISED PATIENTS

AN OPEN LABEL, COMPARATIVE STUDY

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Background: The management of gout can be problematic in the hospital setting; hospitalised patients usually have significant comorbidities and receive multiple medications which leads to a high frequency of contraindications to established gout therapies. We have previously shown the ACTH is a safe and fast acting therapeutic option for acute gout in hospitalised patients in a large scale retrospective study.¹

Objectives: To directly compare the efficacy of ACTH vs betamethasone for the treatment of acute gout in hospitalised patients in a prospective manner.

Methods: Hospitalised patients with acute gout, fulfilling the ACR criteria, were treated with an IM injection of either 100 IU of ACTH (Synacthen Depot) or 6 mg of betamethasone (Celestone Chronodose-the most widely use IM steroid formulation in our country) on an alternate 1/1 basis. Clinical efficacy was assessed at 24, 48, 72 hour and 5 days as follows: a) Intensity of pain using a Visual Analogue Scale (VAS 0–10), b) physician global assessment (0–10) and c) swelling, redness and warmth (0–3 scale). Pain VAS was also self reported by the patient at 6 and 12 hour. Comorbidities representing contraindications to established gout therapies were recorded. Primary outcome of the study was the change in pain VAS at 24 and 48 hour. Secondary outcomes were changes in physician global assessment and changes in objective signs of inflammation.

Results: This is a 6 month interim analysis of an ongoing investigator initiated clinical study. Twelve patients (8 male) with a mean ±SD of 66.9±12.3 years were recruited and treated with ACTH or betamethasone on an alternate basis (6 in each treatment group). In most cases (n=11) the attack was monoarticular. The majority of patients had multiple comorbidities with the commonest being hypertension (9/12). Both treatments were effective. ACTH led to a significant decline in pain VAS at 24 hour compared to baseline (mean ±SEM: 2.33±1.21 vs 7.66 ±0.81 respectively, p=0.0002) and at 48 hour (1.40±1.14, p=0.0011 compared to baseline). Betamethasone was also effective with an improvement in pain VAS at 24 hour compared to baseline (mean ±SEM: 1.83±0.98 vs 5.33±2.16 respectively, p=0.0024) and at 48 hour (0.75±0.95, p=0.02 compared to baseline). However, direct comparison between treatment arms showed that ACTH treated patients exhibited a higher change in pain VAS at 24 hour compared to betamethasone treated patients (mean ±SEM: 5.5±0.5 vs 3.5±0.61 respectively, p=0.03). At the 48 hour time point ACTH treated patients still showed a higher change in pain VAS (mean ±SEM: 6.4±0.6 vs 4±0.91 respectively, p=0.056). A trend favouring ACTH was already evident at the 12 hour time point; the change in pain VAS was 4±1.54 vs 3.1±1.47 for ACTH vs betamethasone, respectively, p=ns). No changes in physician global assessment and objective signs of