Potassium Humate Reduces Inflammation and Clinically Improves the Outcomes of Patients with Osteoarthritis of the Knee

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Abstract: A pilot study was done to determine if potassium humate, a natural substance derived from brown coal, with known anti-inflammatory properties, is safe and effective in reducing pain and inflammation in osteoarthritis of the knee. This was conducted as a randomized, double-blind, placebo-controlled, single centre, cross-over. Participants were enrolled for a total of 14 weeks, starting with an initial 1-week washout period, after which they were randomly assigned to either potassium humate or lactose, administered orally for 6 weeks at a dosage of 600mg three times daily. Following another 1-week washout period, participants were crossed over to the other treatment for another 6 weeks. Participants were not permitted the use of anti-inflammatory medications. Paracetamol was allowed as rescue medication for the duration of the trial. The primary efficacy variable were the WOMAC™ scores (visual analogue version) for pain, stiffness, physical function and total score and health related issues using the RAND 36 levels, rescue medication use, adverse effects and tolerability.

28 participants were enrolled and 21 participants successfully completed the protocol. A carry-over effect in the stiffness subscale was observed. There was a significantly greater clinical benefit with potassium humate over placebo with reduction in all the WOMAC subscale scores for pain. After adjusting for baseline, potassium humate showed a greater reduction in hs-CRP levels when compared to placebo. Tolerability was good for all groups. Safety parameters remained unchanged, except for an increase in the GGT-levels (n=4 in potassium humate group, n=2 in the placebo group). Levels of GGT returned to baseline within 2 weeks of discontinuation of therapy. In conclusion, potassium humate showed possible benefit over placebo in patients with OA of the knee, with a statistically significant reduction in hs-CRP levels. The small sample size and the carry-over effect limited further interpretation of data.

Keywords: Potassium humate, inflammation, osteoarthritis of the knee.

INTRODUCTION

Osteoarthritis is one of the most common forms of arthritis, and is a progressive, debilitating disease that affects mainly elderly people [1]. It remains a difficult disorder to treat as there is no cure, and current regimes to treat pain and maintain joint function, all have long-term risks for the patients. Paracetamol is not an anti-inflammatory drug, but is however regarded as a safe and effective analgesic with a favourable side effect profile, as it causes less gastrointestinal and renal side effects than NSAIDs (non-steroidal anti-inflammatory drugs). It has however demonstrated less symptomatic efficacy than NSAIDs in some clinical trials [2] whereas NSAIDs provide relief of pain and inflammation in osteoarthritis. Both paracetamol and NSAIDs are also associated with adverse effects, such as gastrointestinal toxicity, renal function impairment [3] and increased cardiovascular risk [4, 5].

Inflammation is increasingly recognized as a factor contributing to the symptoms and progression of osteoarthritis (OA), even in the absence of acute inflammatory flares [2]. Inflammatory infiltrates can be found in the synovial membrane of osteoarthritic joints, and there is serological and histological evidence of synovitis, even though osteoarthritis is not associated with specific immune markers [6].

High sensitivity C reactive protein (hs CRP) is a sensitive marker of low grade systemic inflammation and serum levels of CRP correlates well with CRP levels in the synovial fluid of patients with osteoarthritis and rheumatoid arthritis. Increased synovial turnover markers are associated with increased WOMAC™ scores as well as increased serum CRP [7].

Humic acids are formed during the decomposition of organic matter and can therefore be found in practically all natural environments in which organic materials and micro-organisms are, or have been present [8]. Peat extracts have been used in therapeutic baths for the treatment of rheumatic conditions during the 19th century [9]. It was shown in two recent studies that potassium humate, derived from brown coal, suppresses (i) ear swelling in a contact hypersensitivity animal model, (ii) an increase in paw volume of carrageenan-induced oedema in rats and (iii) a graft-versus-host reaction induced in normal and immune incompetent rats [10, 11]. It was also found that this product had no effects on the safety parameters tested at 1000mg/kg body weight per day when administered to rats by gavage for one month, nor did 500mg/kg body weight have any effect on pups after oral administration of the product to pregnant female rats, indicating the safety profile of this compound.

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The aim of this research was to establish the safety and efficacy (using clinical and laboratory markers) of potassium humate in a pilot study in patients suffering from osteoarthritis of the knee.

MATERIALS AND METHODS

Study Design

In this randomized, double-blind, placebo-controlled, cross-over single-centre clinical trial (Fig. (**1**)), volunteers were enrolled, after signing an informed consent, for a 14 week study period. This study was reviewed and approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria. The study started with a 7-day washout period of all anti-inflammatory agents, followed by treatment with either potassium humate or placebo, in a randomized order in two successive treatment periods of six weeks each, separated by another 7-day washout period. Participants were not permitted the use of anti-inflammatory medications such as NSAIDs, cartilage supplements, steroids, or any other agents that may affect the outcomes of the study other than the rescue medication. Any medication taken by the subjects for two months prior to the inclusion of the study, and whose intake was stabilized, was permitted and monitored. The dosing of these medications was not changed for the duration of the investigation.

Paracetamol and tramadol were provided as rescue medication in the first washout period, and paracetamol for the rest of the duration of the trial. Participants completed medication diaries to indicate the use of all concomitant and rescue medication.

Screening included clinical assessment, radiographic assessment, laboratory tests and the disease-specific questionnaire, WOMAC™ (Western Ontario and McMaster Universities Osteoarthritis Index questionnaire) [12] as well as the RAND 36-Item Health Survey [13]. Clinical assessment consisted of an interview and examination by a clinician, and the supervised self-administration of the questionnaire, and a visual analogue scale (VAS) for pain to ensure that patients scored at least 40mm on a 100mm scale for pain. Radiographic assessment was performed in patients who have not had X-rays previous to the trial. It was done using standard antero-posterior weight-bearing X-ray films of the knees to determine the presence of osteophytes.

Study Procedure

After the initial screening visit, the participants had 4 scheduled visits to the investigator (randomization visit, after first 6-week treatment period, after second washout period, when the treatments were crossed over and after the second 6-week treatment period). Identical maroon capsules contained 600mg of either potassium humate or lactose was supplied by Unique Health Trust. All subjects took one capsule of either potassium humate or lactose, three times daily, and were allowed paracetamol 2 tablets 4 times daily (a total maximum of 8 tablets daily) as rescue medication. Compliance was assessed by a pill count at each study visit.

The primary efficacy outcome measure were the WOMAC™ that measured pain stiffness and function as well as the RAND 36-Item Health Survey measured on a 100mm scale which was completed at baseline and at the end of each 6-week treatment period. The study was designed to detect a MClD (minimal clinically important difference) of a reduction of -9.1mm to -7.9mm in the 100mm visual analogue scale of the WOMAC™ subscale scores. Secondary efficacy outcome measures included serum hs-CRP (high sensitivity C-reactive protein) assays, tolerability, compliance, reduced use of rescue medication and adverse event reporting. The hs-CRP values were determined at baseline (after both wash-out periods) and repeated after each 6-week treatment period.

Use of rescue medication, i.e. paracetamol, was documented as a measure of both pain management and efficacy. The amount of rescue medication was only assessed in terms of total use at the conclusion of the study period. Rescue medication use was assessed sequentially along with other variables. Safety outcome measures included the recording of vital signs at each visit and laboratory tests (full blood count, sedimentation rate, creatinine and liver function tests, i.e. ALT and GGT, which

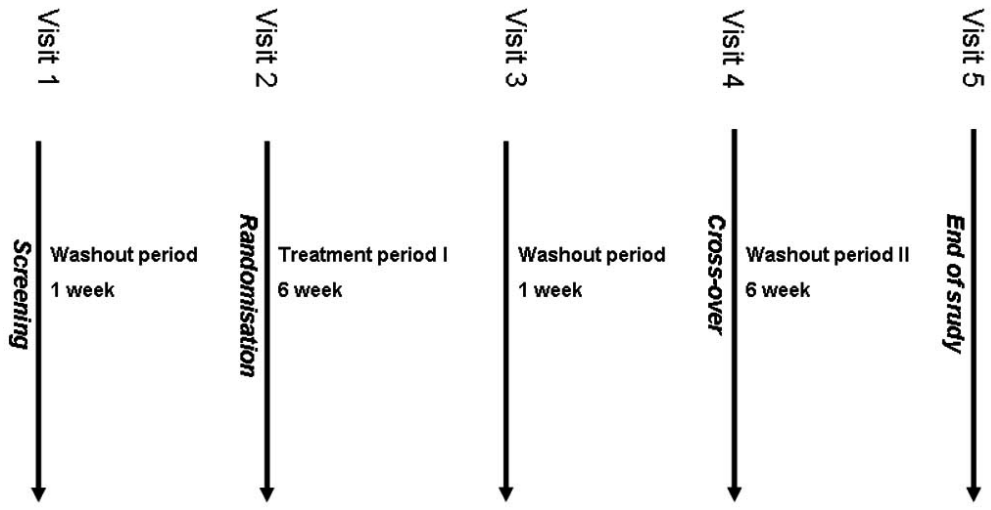

Fig. (1). The trial was done in a cross-over fashion. Participants were enrolled for 14 weeks, starting with a 7-day washout period of all anti-inflammatory agents, followed by treatment with either potassium humate or placebo, in two successive treatment periods of six weeks each, separated by another 7-day washout period.

were done at screening and repeated at the end of each 6-week treatment period.

Patients

Patients, aged over 45 years of both male and female gender, with unilaterally symptomatic idiopathic OA of the knee were recruited. To be considered for the study, patients had to meet clinical and radiographic enrolment criteria.

The clinical criteria included the American College of Rheumatologist (ACR) Classification Criteria for Idiopathic Osteoarthritis of the Knee [14] and the presence of pre-enrolment ambulatory pain (defined as a score of at least 40units on a 100unit mm visual analogue scale (VAS) for pain. The radiographic criteria consisted of the presence of radiographic OA (Kellgren-Lawrence grade 2 or 3) [15, 16].

Participants were selected according to standardized inclusion and exclusion criteria. Except for OA of the knee patients had to be otherwise healthy. Recent use of non steroidal anti-inflammatory drugs (NSAIDS) and systemic corticosteroids required a 3 month washout period.

Treatments

Potassium humate (Zymate™) was supplied by Unique Health Trust, Milnerton, South Africa. The product is marketed as a food supplement. Lactose was used as the placebo.

All treatment capsules were uniform in size, colour, bottle filling, labelling, and packaging. Treatments were packaged in maroon gelatine capsules (size 0) containing 600mg of potassium humate or lactose and packed in wide mouthed white opaque plastic bottles with screw caps in a clean room.

Statistical Methods

In this study the RAND 36-Item Health Survey as described by Garratt *et al.* [13], as well as the WOMAC score [15] were used as primary outcome.

Differences in WOMAC scores and health survey parameters were used in treatment groups at baseline, 7 weeks, and 14 weeks, and group wise changes between baseline, 7 weeks and 14 weeks. Outcome scores were analyzed for variation in effect for Sequence, Treatment, Period and Carryover. Results for the WOMAC score were analysed using an ANOVA and the health survey results were analysed using the Wilcoxon test for paired values. A p value of <0.05 was regarded as significant.

Bonferoni test for multiple comparisons was used to compare differences in hs-CRP values, measured at the onset as well as at the end of each treatment period (week 2 and week 7; week 8 and week 15). Statistical significance was taken at the 95% level ($p < 0.05$). Results are expressed as the mean ± SD.

All participants lost to follow-up had been accounted for.

RESULTS

Subject Characteristics and Study Flow

Of the 55 patients screened, 28 patients met the clinical and radiographic criteria at enrolment and were randomized. The characteristics of the subjects at enrolment and randomization are given in Table **1**. 21 Participants successfully completed the protocol. A summary of patient disposition can be seen in Fig. (**2**).

Table 1. Baseline Characteristics of Patients on Trial

Age (mean in years)	**63.46±9.48**
Body Mass Index (BMI) (kg/m2) (mean)	31±5.13
Gender: Female	n=21
Male	n=7
Knee affected: Right	n=16
Left	n=12
Duration of OA: 1-5 years	n=12
5-10 years	n=10
>10 years	n=6
Pre-study pain medication: Paracetamol	n=1
NSAID/ high dose aspirin	n=7
NSAID & paracetamol	n=5
None	n=15

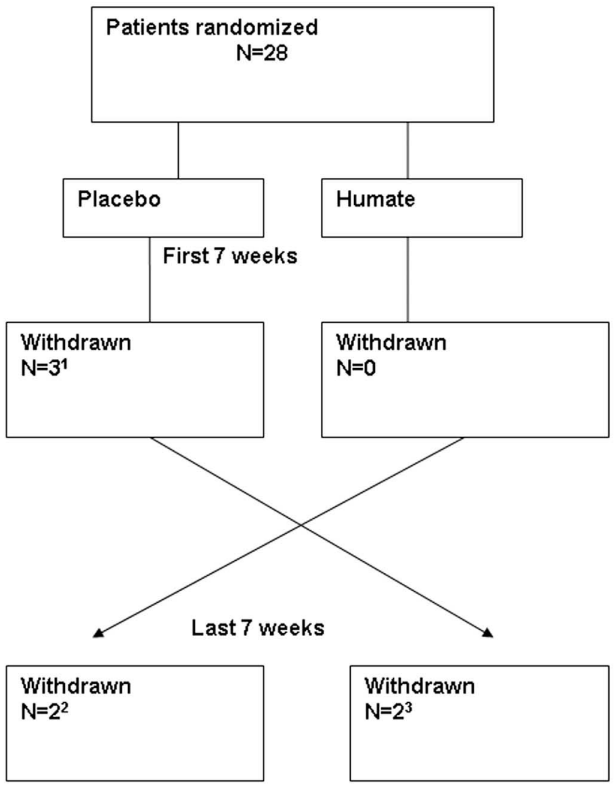

Fig. (2). Patient disposition in the double blind cross-over trial.

[1]One patient withdrawn due to lack of efficacy and two patients due to adverse effects.

[2]One patient withdrawn due to an unrelated adverse event and one patient due to an unrelated reason.

[3]One patient withdrawn due to lack of efficacy and the second patient due to an unrelated reason.

Table 2. Effect of Potassium Humate *vs* Placebo on the WOMAC™ Scores with Respect to Baseline with Order Placebo Cross Over to Potassium Humate

	Visual Analogue Scale (min=0, max=100)						
	Baseline		Placebo		Washout/Cross-over	Potassium Humate	
	Mean	±SD	Mean	±SD		Mean	±SD
Pain Dimension	45.667	16.948	30.089	19.781		29.533	26.745
Stiffness Dimension	52.333	16.145	42.611	26.726		*28.611	26.871
Physical Function	42.781	14.677	35.653	25.215		27.134	26.579
Global Score	140.781	39.756	108.353	68.230		*85.279	79.836
Mean Score	46.927	13.252	36.118	22.743		*28.426	26.612

*Indicating statistical significant difference from baseline ($p < 0.05$).

Table 3. Effect of Potassium Humate *vs* Placebo on the WOMAC™ Scores with Order Potassium Humate Cross Over to Placebo

	Visual Analogue Scale (min=0, max=100)						
	Baseline		Potassium humate		Washout/Cross-over	Placebo	
	Mean	±SD	Mean	±SD		Mean	±SD
Pain Dimension	46.217	28.480	44.177	20.870		35.358	23.123
Stiffness Dimension	64.000	25.733	64.892	32.479		58.667	31.186
Physical Function	54.001	22.834	48.136	21.153		46.649	27.356
Global Score	161.917	66.660	157.204	64.710		140.674	78.814
Mean Score	53.972	22.220	52.401	21.570		46.891	26.271

*Indicating statistical significant difference from baseline ($p < 0.05$).

Clinical Response

Primary Efficacy Variable

The primary efficacy variable was a clinically significant reduction on a 100 mm visual analogue scale (VAS) in the WOMAC scores for stiffness, global score and mean score in the group with order placebo cross over to potassium humate (Table **2**). This was not the case in the group with order potassium humate cross over to placebo (Table **3**) or when grouped together, indicating a carry-over effect. The high SD values could be due to the differences in individuals' response to the active ingredient, but overall when the patients where on the active, they responded significantly better than when on placebo.

The health survey parameters were tested using a Wilcoxon Rank test to test for significant variances within each group. The only significant difference obtained in the health survey was between the combined placebo groups and the treatment groups regarding physical functioning, where an increase of 12.86 on the VAS scale was documented vs 6.52 for the placebo group (Table **4**).

Secondary Efficacy Variables

hs-CRP

Potassium humate treated participants, using the combined placebo groups and the treatment group results, had a significant reduction ($p<0.5$) in hs-CRP from a mean value of 14.4 to 6.6 mg/L (Fig. (**3**)).

Patient Disposition and Consumption of Rescue Medication and

There were no significant differences in patient disposition or the use of paracetamol in both groups.

Tolerability

Tolerability was good for all groups. Pill counts performed at each study visit demonstrated greater than 90% compliance in both groups (results not shown).

Safety Measures

Safety parameters remained unchanged, except for an increase in the GGT-levels (n=4 in potassium humate group, n=2 in the placebo group). Increased levels of GGT were still within normal limits and returned to baseline values within 2 weeks of discontinuation of therapy.

Adverse Events

No serious adverse events were noted. Patients receiving potassium humate experienced black stools (n=3) and headache (n=2), while patients on placebo complained of headache (n=2), nausea (n=2), diarrhoea (n=2), flatulence (n=1) and loss of libido (n=1). Black stools could be explained by the black nature of the product.

Table 4. Effect of Potassium Humate *vs* Placebo on the 8 Divisions of the Health Survey; Combined SF-36 Results

	Health Survey (%)					
	Baseline		Placebo		Potassium Humate	
Division	Mean	±SD	Mean	±SD	Mean	±SD
Physical functioning	39.306	18.726	45.826	22.171	*52.222	26.113
Bodily pain	46.944	17.722	55.625	25.760	60.104	23.135
Role limitations due to physical health problems	48.958	35.341	46.181	44.881	57.292	43.276
Role limitations due to personal or emotional problems	66.667	42.559	66.667	42.886	64.352	45.097
Emotional well-being	73.875	66.833	75.056	19.441	74.958	19.266
Social functioning	76.042	23.720	75.521	22.165	78.472	15.965
Energy/fatigue	54.236	14.593	60.208	23.941	55.556	17.341
General health	74.514	17.990	70.694	17.141	70.486	19.307

*Indicating statistical significant difference from baseline ($p<0.05$).

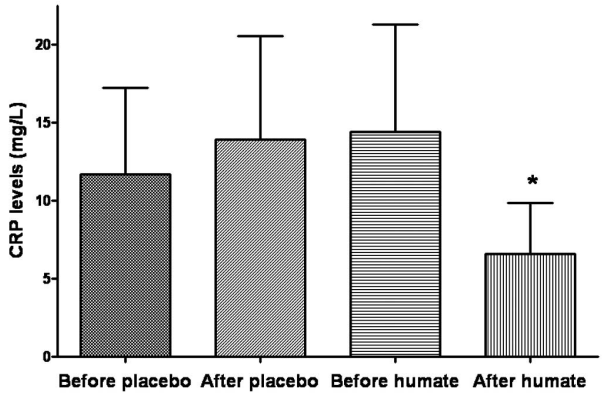

Fig. (3).

DISCUSSION

This is the first study to demonstrate the safety profile of potassium humate, at a daily dose of 1.8g in humans, which was consistent with the preclinical results obtained in a study done in rats [10]. Patients were selected with unilaterally symptomatic idiopathic OA of the knee. All haematology and biochemical parameters stayed within normal ranges during the study. Potassium humate treatment caused a reduction in inflammation in these patients as seen in a reduction in hs-CRP levels as well as clinically significant improvement of patients on the treatment drug compared to the placebo group.

Mechanistic studies done by Joone *et al.* on oxihumate, a water-soluble humate obtained through a wet oxidation of bituminous coal [17], decreases the expression of complement receptor 3 (CR3) by phorbol-12-myristate-13-acetate (PMA) stimulated human neutrophils as well as the adhesion of these cells to a baby hamster kidney cell line expressing intracellular adhesion molecule-1 (ICAM-1) [18], possibly contributing to its anti-inflammatory effects. An *in vitro* finding has recently been documented [19] indicating that brown coal derived potassium humate inhibits the activation of both the classical and alternative pathways of complement activation. It was also shown, in the same study, that potassium humate inhibits the release of the inflammatory related cytokines TNF-α, IL-1β and IL-6 *in vitro*. In the case of arthritis complement activation of both these pathways have been associated with the presence of auto-antibodies against joint components such as type II collagen [20]. Controlling complement activation with monoclonal anti-C5 antibodies has been proven to be effective in decreasing inflammation in animal models of experimental lupus erythematosus, rheumatoid arthritis and septic shock [21]. Regarding the blocking of cytokines, it has been shown that Anakinra, an interleukin-1 (IL-1) receptor antagonist, can be used successfully in the treatment of inflammation and bone destruction in rheumatoid arthritis [22]. Similar results were obtained with infliximab, an anti TNF α therapy when combined with methotrexate [23]. Further studies need to be done to confirm the mechanism of action of potassium humate plus efficacy studies in other inflammatory diseases such as rheumatoid arthritis.

Studies with bigger sample sizes than this one will have to be done in order to determine whether the results can be replicated. A washout period of more than one week is also recommended.

The identification of a naturally occurring compound that is safe and effective in reducing a serological marker of inflammation in an autoimmune disease such as OA of the knee, merits further evaluation in the treatment of patients suffering from other inflammatory arthropathies such as rheumatoid arthritis.

ABBREVIATIONS

OA = osteoarthritis

CRP = C-reactive protein

NSAIDs = non-steroidal anti-inflammatory drugs

WOMAC™ = Western Ontario and McMaster Universities Osteoarthritis Index questionnaire)

VAS = visual analogue scale

ICAM-1 = intracellular adhesion molecule-1

MClD = minimal clinically important difference

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