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Some Aspect of Bioavailability of Indomethacin in Untreated Rheumatoid Arthritis as a Anti Inflmatory Models

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Abstract

Aim: Turmeric and its active ingredients, curcuminoids, have long been used to treat inflammatory, bacterial, dermatological, and neurological diseases. However, they are constrained by their poor bioavailability as therapeutics. A new complex of curcumin and cyclodextrins has been formulated that has been shown to enhance the bioavailability of curcumin by about 50 times.

Methods: The biochemical parameters and methods to be used for their estimations were as follows. These parameters are compared with concentration of indomethacinum as reference parameter. Using the colorimetric method, we examined samples of 70 participants. (35 RA pts treated only with Indomethacinum, 35 RA pts treated with Turmeric), Rheumatoid factor (RF) is determined with the agglutination test (Lateks RF test) in the same participants.

Results: It is found that an antioxidant ceruloplasmin is increased significantly ($p<0.001$) in rheumatoid arthritis for scavenging the free radicals formed. Increased activity of indomethacinum ($p<0.001$) correlates with severity of rheumatoid arthritis.

Conclusion: Serum indomethascinum can be used as marker to detect inflamatory model in rheumatoid arthritis and also helps to know 10 severity of rheumatoid arthritis.

Keywords: Rheumathoid arthritis; Indomethacinum; Inflammatory diseases; Bioavailabilit

Introduction

The significance of turmeric in medicine has changed in modern times with the scientific observation of turmeric's therapeutic properties. Curcuminoids have scientifically documented anti-oxidant, anti-inflammatory, anti-bacterial, anti-fungal, anti-parasitic, anti-mutagen, anti-cancer properties. Significant data are available on the safety, toxicity, dose range, pharmacokinetics, and other biological properties of turmeric and its components, including curcuminoids and turmeric peptide. As detailed below, turmeric components are well tolerated while providing anti-oxidant benefits, inhibit microbial growth, inhibit several enzymes, and inhibit abnormal cell growth in studies of cells, animals, and humans [1-3].

Turmeric and turmeric extracts have long been active ingredients in compositions for oral and topical application to treat diseases and conditions. Curcuma long a (Fam. Zingiberaccae), or turmeric, is a spicy plant that is a common ingredient in curry powder. Turmeric is one of the oldest herbs in Ayurveda, the traditional Indian system of medicine. Turmeric has been applied topically to wounds to stop bleeding, speed healing and reduce scaring. Ground turmeric has been used as a topical salve to prevent and treat a variety of skin diseases and conditions [4,5].

Materials and Methods

The diagnosis of the patients included in the study is based on the revised diagnostic criteria for classification of Rheumatoid arthritis proposed in 1987 by the American Association for Rheumatism (ARA). In order to include the patient in the group with RA, he should fulfill at least 4 of the 7 criteria. Criteria 1-4 should persist at least 6 months.

In the study are included 70 patients with RA (20 women, 15 men), treated with Indomathacinum, and 35 patients with RA (22 women, 13 men) treated with Turmeric. Their average age is 53, 35 years (±10.12) range (44-64 years), in the group treated with Indomethacinum, while 54, 22 years (±11.26) range (26-

64 years) in the group treated with Turmeric. Mean disease duration from the begining is 41.11 months (±41.22 months), range (1-160 months). None of the patients has previous or current hystory of renal disease. None of the patients previously used NSAIDs. Other patients negated use of other drugs such as golden salts, antibiotics or diuretics.

Hydroxy Propyl β-cyclodextrin was obtained from Sigma Aldrich (catalogue number 332593) and a 20% solution created. Curcumin was obtained from Sigma Aldrich (catalogue number C7727) and a 15mg/ml curcumin stock solution created. Cyclodextrin Curcumin was created by mixing curcumin stock to cyclodextrin stock in a proprietary method.

Indomethacin (Sigma I8280, lot #098K1500) 10ml dosing solution was made by suspending 5mg in 10ml of sterile water with stirring, and then adding 0.1N $NaCO_3$ dropwise until pH was 7-8.

λCarrageenan 1% (Fluka 22049, lot #1408463) 2ml was made by dissolving 20mg in 2ml of saline at 4 °C and then vortexing, warming and sonicating. It was tested for injection resistance by 27G and 28G needles.

Inclusion criteria

In the study are included patients with RA, aged 18-65 years, not previously treated with NSAIDs or DMARDs.

Exclusion criteria

From the study are excluded patients with diseases or conditions that could influence results directly or indirectly:

a. Patient younger than 18 years.

b. Patients with previous history of disease of the spleen, thyroid gland, liver, kidneys, hematological, cardiovascular, neurological, autoimmune and lung diseases.

c. Patients with diabetes mellitus, febrile conditions, acute infections, neoplasms.

d. Patients with uric arthritis, SLE, mixed connective tissue disese, vasculitis.

e. Patients with history of blood transfusion and patients with body overweight.

f. All the patients took part in this study voluntarily, so the ethic criteria for this study are fulfuled.

Clinical estimation of disease activity

Clinical estimation is made by subspecialist in the fild. Disease activity is estimated using DAS 28 index (Disease Activity Score - DAS 28). The index uses mathematical formula to obtain unique composite quantitative score, which consists of: palpabile painful joints (maximal niumber 28), swallen joints (maximal niumber 28), Erythrocyte sedimentation rate (ESR) and patient's estimation for disease activity (0-100mm). Visual Analogue Scale - VAS) and morning stiffness (minutes). DAS 28 index ranges from 0 to 10 and score <3.2 qualifies the disease as low active.

Laboratory estimation

For clinical estimation of the disease it is necessary to examine following laboratory variables: complete blood count and differencial, reactants of the acute phase, ACPA-antibodies, C-reactive protein (CRP), Rheumatoid factor (RF) and Erythrocyte sedimentation rate (ESR), alcaline phosphatase (AP), aspartat aminotransferase (AST), alanin aminotransferase (ALT), creatin kinase (CK), laktat dehydrogenase (LDH), serum urea, serum creatinin.

Statistical analysis

To test the significance of the differences between two aritmetical means i.e. proportions is used the Student t-test. To compare the mean values of certain numerical parameters between two groups was used Wilcoxon-matched test for independent species. Sensitivity and predictivity for positive and negative test of the examined markers is determined with the sensitivity and specificity test. P-value between 0.05 and 0.1 is considered statistically significant. Data analysis is performed with statistical package Statistica 7.0.

Results

In patients treated with Indomethacinum, M+SD was in range 0.53±0.48, while in patients treated with Thurmeric is 0.67±0.57. So, Indomethacinum has identical values of in comparison with Thurmeric. Pearsons$\chi 2$ test shows that there is moderate correlation (r=0.28) between the increase of the values in the samples in the group of patients treated only with Indomethacinum.

Analysis with the Pearsons$\chi 2$ test shows that there is statistical significant correlation (r=0.16) between the increase of the values in the group of patients treated only Indomethacinum (Table 1).

Table 1: Laboratory values in group of patients with Indomethacinum and Turmeric.

Group Indomethacinum N=35		Group Turmeric N=35
	(M ± SD)	(M ± SD)
0 sample	1.22±0.45	0.13±0.27
1 week	1.26±0.56	1.16±0.36
8 week	1.28±0.56	1.47±1.44
12 week	1.11±1.23	1.71±0.23

Discussion

Turmeric reduces arachidonic acid-induced rat paw and mouse skin edema and markedly inhibits epidermal lipoxygenase and cyclooxygenase activity in vitro. Phosphorylation events

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can also be influenced by curcumin, as it has been reported that curcuminoids inhibit protein kinase C activity induced by 12-O-tetradecanoyl-phorbol-13-acetate in NIH 3T3 cells [4].

Turmeric can fight against microbial infections and parasitic infestations. In humans, ingestion of turmeric has been used to treat biliary infections where it demonstrates bacteriostatic or bactericidal effects against organisms involved in cholecystitis [6]. Topical application of a turmeric paste for the treatment of scabies has also shown good results [7,8]. The potential use of turmeric and turmeric extracts in the prevention of cancer are the subject of intensive laboratory and clinical research. The addition of turmeric to the diet has been shown to inhibit azoxymethanol-induced colonic epithelial cell proliferation and focal areas of dysplasia [8]. It has also been shown to interfere with the formation of covalent carcinogen-DNA adducts [9].

Curcumin can moderate the immune system as well as smooth muscle cell proliferation. Curcuminoids had a greater inhibitory effect on platelet derived growth factor-stimulated proliferation than on serum-stimulated proliferation [10].

Curcuminoids were shown to inhibit the 5-lipoxygenase activity in rat peritoneal neutrophils as well as the 12-lipoxygenase and the cyclooxygenase activities in human platelets [11]. Curcuminoids had no significant effect on quercetin-induced nuclear DNA damage, lipid peroxidation and protein degradation, and thus has the unique potential of acting as both pro- and antioxidants, depending on the redox state of their biological environment [12]. Administration of curcuminoids in mice exhibited antioxidant properties by significantly reducing the scavenging of peroxides and other activated oxygen species [13].

The complex of curcumin and cyclodextrin is a new way to increase the absorption of curcumin. A recent paper has shown that the complex of curcumin to cyclodextrin increases human PK of curcumin by a factor of almost 40 over native curcumin, better than any other approach to deliver curcumin [14]. In the present paper, it is shown that the complex of curcumin with cyclodextrin is also associated with better efficacy. In the carrageenan mouse foot paw model, a commonly used model for inflammation, VOLT03 was superior to both the active control, indomethacin, which behaved as expected, but also native curcumin. VOLT03 thus has the rare advantage of being not only the most potent curcumin formulation but also the one that has the best PK coverage. It can be used not only as a nutritional supplement for neurological and oncology prophylaxis, but also in the clinic for inflammatory diseases such as Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriasis.

Conclusion

The complex is superior to curcumin and positive control, indomethacin, in an inflammatory model. This is the only complex to show both a superior bioavailability as well as efficacy and thus could be a new therapeutic to treat inflammatory diseases such as Rheumatoid Arthritis.

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