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A comparative study of analgesic effect of thiocolchicoside, ketoprofen and their combination in rats, using digital Analgesiometer

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Abstract

Objectives: To compare the analgesic effect of thiocolchicoside and ketoprofen alone and their combination in male albino wistar rats by using digital analgesiometer for the degree of analgesia and the time course of action.

Materials and Methods: Analgesia was studied in male albino wistar rats using the radiant heat method. For each test, four groups of six animals each were orally fed with a single dose of thiocolchicoside, ketoprofen, and combination of thiocolchicoside and ketoprofen and normal saline as control, respectively.

Results: In all three drug treatments showed significant analgesia ($P < 0.001$) as compared to control, but there was significant difference in the analgesia produced by drugs in combination. The radiant heat method demonstrated a quicker onset of action with thiocolchicoside and ketoprofen, whereas greater degree of analgesia was seen with the combination of thiocolchicoside and ketoprofen than the individual drug, though this difference was statistically significant.

Conclusions: Thiocolchicoside and ketoprofen combination offers advantage over thiocolchicoside and ketoprofen alone, in terms of degree of analgesia or onset of action. Therefore, our study supports the reports claiming the efficacy of the fixed dose combination of thiocolchicoside and ketoprofen greater than individual drug alone.

Keywords: skeletal muscle relaxants, thiocolchicoside, ketoprofen efficacy, analgesia, radiant heat and reaction time

Introduction

Drugs commonly used in modern medicine for suppression of pain and inflammation like non-steroidal anti-inflammatory drugs and corticosteroids provide only symptomatic relief. Long-term use of these drugs is associated with serious adverse effects. Hence, the search for a new, safe analgesic and anti-inflammatory drug is on-going. Skeletal muscle relaxant like thiocolchicoside is widely used for the prevention of treatment of orthopaedic, traumatic and rheumatologic disorders. Mode of action includes modulation of chemokine and prostanoid production and inhibition of neutrophil and endothelial cell adhesion molecules by which it interferes with the initiation and amplification of the joint inflammation and thiocolchicoside have also been shown to possess analgesic and anti-inflammatory effects [1, 2, 3]. Ketoprofen is a NSAID with analgesic, anti-inflammatory and antipyretic actions and it inhibits the COX enzyme which is partake for the synthesis of prostaglandins. Various fixed dose combinations of NSAIDs and skeletal muscle relaxants are available in the market, particularly those of thiocolchicoside and ketoprofen. Following this trend, many drug companies have introduced thiocolchicoside and ketoprofen combination and claim that it has faster onset and longer duration of analgesic and anti-inflammatory effects than either drug alone [4]. So, some authors have claimed that the combination of thiocolchicoside and ketoprofen does offer advantage and is therefore rational. In addition, thiocolchicoside does not have significant gastro duodenal side effects [5, 6].

Materials and Methods

Animals

Adult male wistar albino rats (*Rattus norvegicus*, weighing between 200 -250 g) were used. Animals were kept in cages in temperature-regulated rooms with air-cooling and 12 hours light and dark cycle, and had free access to water and standard laboratory diet.

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They were allowed to acclimatize to the laboratory conditions for a period of one week, and kept fasting overnight prior to the experiment. The study was approved by the Institutional Animal Ethics Committee and all the experiments were performed as per the Committee for the purpose of control and supervision on experiments on animals (CPCSEA) guidelines. Animal house registration No-1392/ac/10/CPCSEA.

Investigational drugs and dosage preparation

Tablet thiocolchicoside 4 mg (Glaxo-Smithkline, Dr. Annie Besant Road, Worli, Mumbai) was purchased from the hospital pharmacy counter. Ketoprofen 400 mg and thiocolchicoside and ketoprofen combination 404 mg (Emcure Pharmaceuticals Ltd., Dopadi, Pune) were also procured from the same hospital outlet. The appropriate body weight adjusted doses of test drugs as extrapolated from doses used in similar studies conducted previously to be 0.09 μ g/250 g rat for thiocolchicoside, ketoprofen 10 μ g/250 g rat and 10.38 μ g/250 g rat for thiocolchicoside and ketoprofen combination were used [5, 6].

Formulations were made as suspension prepared in 10 ml of DMSO uniformly mixed. The formulations were fed to the animals through gastric tube (9 mm) for rat. The normal saline alone was used as a control group.

Experimental protocol

Animals (n = 24) were allocated to four main groups (GI, GII, GIII and GIV) of 6 animals each. Depending on the treatment design, each receiving group I(test I) thiocolchicoside, group

II (test II) ketoprofen, group III combination of thiocolchicoside and ketoprofen, group IV normal saline as the control, respectively.

Radiant heat method

Prior to subjecting rats to their individual analgesic response to test drugs, animals were subjected to a preliminary screening and rats showing tail flick response in 10 s were selected. Test drugs were administered. Each rat was restrained, and radiant heat was applied to a portion of tail (about 5 cm from the tip) placed 2 mm above (5A) heating wire of Digital Analgesiometer (INCO). The current was allowed to flow through heating wire and the time taken for the mouse to show tail flick response was recorded every 30 min up to 90 min maximum [7].

Results

Pain induced by application of heat (Digital Analgesiometer) in male albino wistar rats

The drug treatments have shown significant increase in tail latency compared to control. The onset of action of thiocolchicoside [THC] and ketoprofen alone was slower than their combination, showing greater decrease in latency of tail flick response at 20 and 30 min than combination treated group. While in thiocolchicoside and ketoprofen combination treated group latency of response has increased at 90 min. So the onset of action of thiocolchicoside and ketoprofen combination was more than their individual drug action alone, so this difference was statistically significant [8]. Figure 1

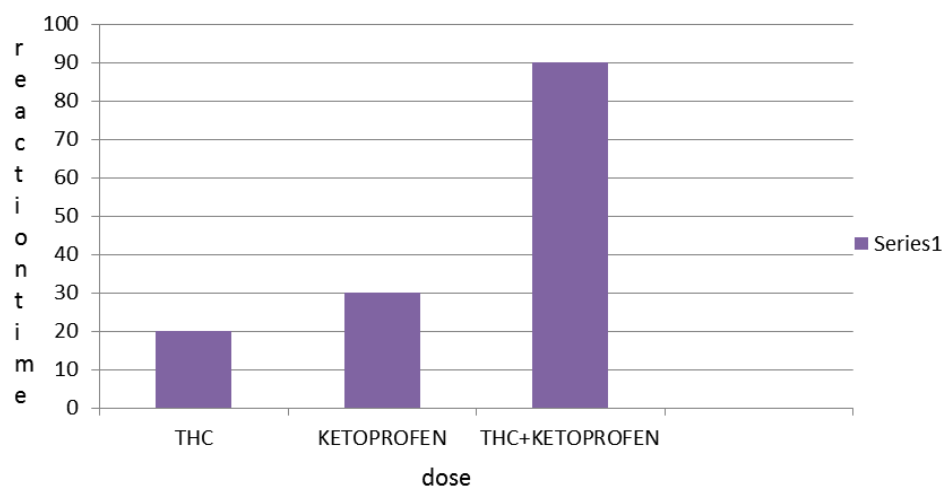


Fig 1

Discussion

This study was undertaken to compare the analgesic effect of thiocolchicoside, ketoprofen and the combination of Thiocolchicoside and ketoprofen in rats by using digital Analgesiometer. The comparison was done in terms of degree of analgesia and time course of action. The combination had been introduced in the market on the pretext that it will have the benefits of thiocolchicoside and ketoprofen. As Thiocolchicoside is a skeletal muscle relaxant and ketoprofen is a NSAIDs. It was presumed that their combination will have synergistic effects [9, 10]. However, our study showed that in radiant heat method, thiocolchicoside showed the fastest onset of action. But the combination of Thiocolchicoside and ketoprofen is definitely greater than either drug used alone. Hence, the popular belief that combining the two drugs would

give a greater onset does seem to be substantiated. However, since our observation period was only 90 min, we cannot make any comment about the other advantages of longer duration claimed by the combination. Further studies with longer periods of observation would probably throw more light on the validity of this combination. In addition, pain is a symptom with substantial subjective component as well. It is, therefore, difficult to comment on the effectiveness of an analgesic purely on the basis of animal studies. Hence, it would also be necessary to test the combination on human subjects, both on experimental pain in healthy volunteers as well as clinical pain, before commenting on the appropriateness of this combination. Many studies have compared the analgesic efficacy of ketoprofen with other NSAIDs; [11, 12, 13] however, there is no such study, which

compares thiocolchicoside with ketoprofen combination. Usually, the fixed dose combinations are introduced in the market to generate prescriptions and make profit with no consideration of the rationality ^[14]. Combinations of analgesics are more effective if they act through different analgesic mechanisms and act synergistically ^[15]. In similarly, the components of the fixed dose combination of thiocolchicoside and ketoprofen act by the different mechanism of inhibition of prostaglandin biosynthesis. The most important concern with irrational fixed dose combinations is that they expose patients to unnecessary adverse effects ^[16]. It has been seen that ketoprofen is as good analgesic as any other NSAIDs, but its combination with thiocolchicoside increases its hepatotoxic potential ^[17]. Usage of many available fixed dose combinations is controversial, and it is the need of hour to sensitize all practitioners and consumers against this practice.

Conclusion

Our study shows that thiocolchicoside alone and ketoprofen alone are less efficacious analgesics as compared to the combination of thiocolchicoside and ketoprofen. Both the drugs potentiate or synergize the action of the other and greater degree of analgesia than the individual effect. Therefore, there is pharmacological rationale for the combined administration of thiocolchicoside and ketoprofen. However, further studies with longer periods of observation are warranted to evaluate the validity of the combination. In addition, studies of the combination on human subjects are necessary to assess the subjective degree of pain and appropriateness of the combination.

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