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

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Abstract

Objectives: To compare the analgesic activity of thiocolchicoside and ketoprofen alone and their combination with piroxicam 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 albino rats using the radiant heat method. For each test, five groups of six animals each were orally fed with a single dose of test drugs thiocolchicoside, ketoprofen, and combination of thiocolchicoside and ketoprofen, piroxicam as standard and normal saline as control, respectively.

Results: In all four 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 both drugs than that of individual drugs and more effective than the piroxicam, though this difference was statistically significant.

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

Keywords: Skeletal muscle relaxants, NSAIDs, analgesia and reaction time, piroxicam

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment in pain [1]. 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 [2]. So, some authors have claimed that the combination of thiocolchicoside and ketoprofen does offer advantage and is therefore rational. Thiocolchicoside is skeletal muscle relaxant and mode of action includes modulation of chemokine and prostanoid production. It is an analgesic and anti-inflammatory properties [3, 4]. In addition, thiocolchicoside does not have significant gastroduodenal side effects [5, 6]. Piroxicam and ketoprofen are NSAIDs with analgesic anti-inflammatory and antipyretic actions and mode of action is inhibitor of COX.

Materials and methods

Animals

Healthy male albino Wistar rats (3 months old) weighing 200-250 g were used for antinociceptive test. Animals were housed in appropriate cages in uniform hygienic conditions and fed with standard pellet diet (Lipton India Laboratories, Bangalore) and water ad libitum and were fasted overnight before the day of experiment. Animals were housed within the departmental animal house, and the room temperature was maintained at 27°C. The protocol was approved and carried out after the permission of Institutional Animal Ethics Committee. Animal house registration no-1392/ac/10/CPCSEA.

Investigational drugs and dosage preparation

Tablet piroxicam 20 mg (Glaxo-Smithkline, Dr. Annie Besent Road, Worli, Mumbai) was purchased from the hospital pharmacy counter.

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Tablet thiocolchicoside 4 mg (Emcure Pharmaceuticals Ltd., Dopadi, Pune). 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 0.50µg/250 g rat for piroxicam, 0.09µg/250 g rat for thiocolchicoside, ketoprofen 10µg/250 g rat and 10.38 µg/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 = 30) were allocated to five main groups (GI, GII, GIII, GIV and GV) 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 piroxicam (standard), group V 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 rat 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 the tail flick latency compared to control. The onset of action of thiocolchicoside [THC] and ketoprofen alone was slower than their combination and piroxicam, showing greater decrease in latency of tail flick response at 20 and 30 min than combination and piroxicam treated groups. Piroxicam treated group has shown continuous in latency with time when tested up to 60 min. 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 piroxicam, So this difference was statistically significant [8]. Figure 1

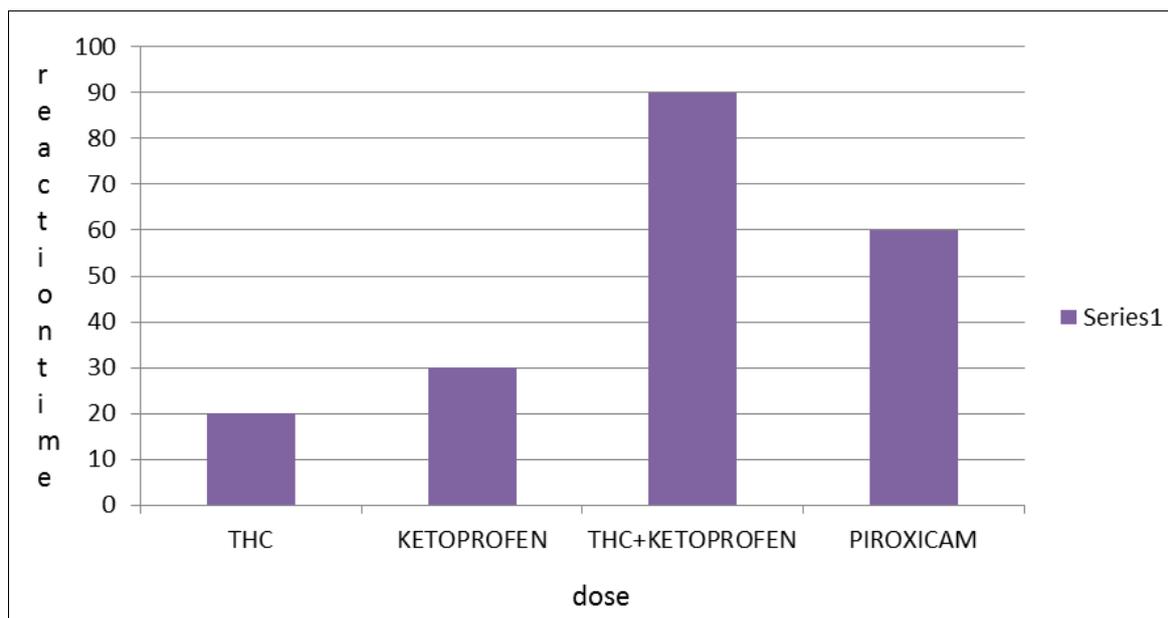


Fig 1

Discussion

This study was undertaken to compare the analgesic efficacy of thiocolchicoside, ketoprofen and combination of Thiocolchicoside and ketoprofen with piroxicam 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 an NSAIDs. It was presumed that their combination will have synergistic effects [9, 10, 11]. 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 and piroxicam with other NSAIDs; [12].

^{13, 14]} however, there is no such study, which compares thicolchicoside 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 ^[15]. Combinations of analgesics are more effective if they act through different analgesic mechanisms and act synergistically ^[16]. In similarly, the components of the fixed dose combination of thicolchicoside 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 ^[17]. It has been seen that ketoprofen is as good analgesic as any other NSAIDs, but its combination with thicolchicoside increases its hepatotoxic potential ^[18]. 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 thicolchicoside alone and ketoprofen alone are less efficacious analgesics as compared to the combination of thicolchicoside and ketoprofen. Both the drugs potentiate or synergize the action of the other and greater degree of analgesia than the piroxicam. Therefore, there is pharmacological rationale for the combined administration of thicolchicoside 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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