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RESEARCH ARTICLE

Effect of Betamethasone dipropionate, Betamethasone valerate and combination of Betamethasone valerate and Neomycin sulphate with Biopolymer on skin inflammatory model in Wistar rats

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Abstract

Topical anti-inflammatory agents are used to treat muscle pains, sprains, strains and arthritis. Topical anti-inflammatory agents are sometimes prescribed instead of oral anti-inflammatory agents because they have lesser side-effects. Hence there is always a need for better topical anti-inflammatory drugs. A study was undertaken to compare the efficacy of betamethasone dipropionate with biopolymer with betamethasone dipropionate (Betamil) and betamethasone valerate with biopolymer with betamethasone valerate (Betnovate) and combination of betamethasone valerate and neomycin sulphate with biopolymer with betamethasone valerate and neomycin sulphate (Betnovate N) in croton oil ear edema model in rats. There was significant reduction in edema for all the treatment groups when compared with the control group ($p < 0.001$).

Introduction

Inflammation is the body's attempt at self-protection; the aim being to remove harmful stimuli, including damaged cells, irritants, or pathogens and begin the healing process. To know the effect of drugs used in inflammation various animal models are used. Inflammatory changes can be induced in these animals by administration of various agents and anti-inflammatory effect of different drugs can be compared. Inflammation is a complex biological response of vascular tissues to harmful stimuli, pathogens or irritants [1]. Exposure to chemicals, irritants and allergens leads to various inflammatory disorders. The treatment for such disorder includes avoidance of allergens, irritants, adequate cutaneous hydration and judicious use of low to moderate potency corticosteroids. There is always a search for more efficacious preparations. Betamethasone dipropionate, betamethasone valerate and a combination of betamethasone valerate and neomycin sulphate are moderately potent glucocorticoids with anti-inflammatory and immunosuppressive properties. These drugs are available in various forms and one of them is betamethasone dipropionate marketed as Betamil, betamethasone valerate marketed as Betnovate and combination of betamethasone valerate and neomycin sulphate marketed as Betnovate N. Apex Laboratories Channai has come out with biopolymer based formulations of these steroids. There are three formulations of the same steroid(A,B and C) depending on the percent of biopolymer added to it. A study was undertaken to compare the anti-inflammatory effect of betamethasone dipropionate, betamethasone valerate and a combination of betamethasone valerate plus neomycin sulphate with their biopolymer based formulation respectively.

MATERIALS AND METHODS

Animals

Adult male Wistar rats weighing between 150-200 g were used. Animals were acclimatized to the laboratory environment for 5-7 days before entering in the study. They were allowed free access to water and were maintained on standard rat diet under laboratory conditions. 12- hour light/dark cycle was maintained. All procedures were carried with approval of Institutional Animal Ethics Committee of Kasturba Medical College, Manipal University, Manipal (India).

Drugs

Betamil (betamethasone dipropionate)**,** Betnovate (betamethasone valerate), Betnovate N (betamethasone valerate+ neomycin sulphate), betamethasone dipropionate, betamethasone valerate and a combination of betamethasone valerate and neomycin sulphate with biopolymer (Apex Laboratories Private Ltd., Chennai, India). The new formulations contain different percentage of biopolymer to study the effect

Induction of ear oedema by irritant solution of croton oil

The irritant croton oil solution was prepared by dissolving 4 parts of croton oil, 10 parts of ethanol, 20 parts of pyridine, and 66 parts of ethyl ether. The test compounds were dissolved (5 mg/ml strength) in the croton oil [2].

Experimental procedure

A total of 160 Wistar rats (male, pathogen free, 6-8 weeks old) were used in the experiment. All the rats were grouped into 16 groups each consisting 10 animals. The drug was applied once externally to the outer surface of right ear of each rat. The left ear of each rat was kept as control (untreated) with respect to the right ear.

Group 1- 0.02 ml of croton oil solution
Group 2- 0.02 ml of croton oil solution containing dissolved Betamil (5 mg/ml)
Group 3- 0.02 ml of croton oil solution containing betamethasone dipropionate A with biopolymer (5 mg/ml)
Group 4- 0.02 ml of croton oil solution containing betamethasone dipropionate B with biopolymer (5 mg/ml)
Group 5- 0.02 ml of croton oil solution containing betamethasone dipropionate C with biopolymer (5 mg/ml)
Group 6- 0.02 ml of croton oil solution containing Betnovate (5 mg/ml)
Group 7- 0.02 ml of croton oil solution containing betamethasone valerate A with biopolymer (5 mg/ml)
Group 8- 0.02 ml of croton oil solution containing betamethasone valerate B with biopolymer (5 mg/ml)
Group 9- 0.02 ml of croton oil solution containing betamethasone valerate C with biopolymer (5 mg/ml)
Group 10- 0.02 ml of croton oil solution containing Betnovate N (5 mg/ml)
Group 11- 0.02 ml of croton oil solution containing betamethasone valerate and neomycin sulphateA with biopolymer (5 mg/ml)
Group 12- 0.02 ml of croton oil solution containing betamethasone valerate and neomycin sulphateB with biopolymer (5 mg/ml)
Group 13- 0.02 ml of croton oil solution containing betamethasone valerate and neomycin sulphateC with biopolymer (5 mg/ml)
Group 14- 0.02 ml of croton oil solution containing betamethasone valerate and neomycin sulphateD with biopolymer (5 mg/ml)
Group 15- 0.02 ml of croton oil solution containing betamethasone valerate and neomycin sulphateE with biopolymer (5 mg/ml)
Group 16- 0.02 ml of croton oil solution containing betamethasone valerate and neomycin sulphateF with biopolymer (5 mg/ml)

The animals were sacrificed by cervical dislocation after four hours. Both ears were removed and discs of 8 mm diameter were punched with a cork borer. Each ear disc was weighed immediately and the difference in weight between the treated and the untreated ear indicated the degree of inflammatory oedema. The percentage increase in the oedema of the treated ear was calculated by the following formula:

% ear oedema = Wt. of Right ear disc (test) – Wt. of Left ear disc (control) x 100/ Wt. of Left ear disc

Statistical analysis

Data were expressed as mean ± SEM and were analyzed statistically by one way analysis of variance (ANOVA) followed by post hoc Tukey test. The data was considered statistically significant for the p value < 0.05.

RESULTS

Topical application of croton oil induced cutaneous inflammation which caused a significant increase in ear plug weight. There was significant reduction in edema for all the treatment groups when compared with the control group ($p < 0.001$). Both the formulations of Betamethasone dipropionate B and C (with biopolymer) significantly decreased the edema in comparison with the Betamil treatment group ($p < 0.05$). However, the formulations of

betamethasone valerate and its combination with neomycin were not superior to standard marketed product used in this study.

Table 1- Percentage inhibition of ear skin edema:

Groups (n=10)	Mean ± SEM
Control	70.84 ± 3.41
Betamil	24.66 ± 2.08^{***a}
Betamethasone dipropionate A	27.74 ±4.10^{***a}
Betamethasone dipropionate B	15.50 ± 2.54$^{***a, *b}$
Betamethasone dipropionate C	16.24 ± 3.37$^{***a, *b}$
Betnovate	23.52 ± 4.02^{***a}
Betamethasone valerate A	23.27 ± 5.17^{***a}
Betamethasone valerate B	26.12 ± 3.30^{***a}
Betamethasone valerate C	38.24 ± 7.54^{***a}
Betnovate N	13.98 ± 2.51^{***a}
(Betamethasone valerate + neomycin sulphate) A	23.04 ± 3.62^{***a}
(Betamethasone valerate + neomycin sulphate) B	25.41 ± 6.17^{***a}
(Betamethasone valerate + neomycin sulphate) C	17.83 ± 1.63^{***a}
(Betamethasone valerate + neomycin sulphate) D	17.51 ± 2.40^{***a}
(Betamethasone valerate + neomycin sulphate) E	28.78 ± 4.34^{***a}
(Betamethasone valerate + neomycin sulphate) F	17.20 ± 0.96^{***a}

^{***a} $p < 0.001$; compared to control group, ^{*b} $p<0.05$; compared to Betamil treatment group.

DISCUSSION

All the formulations used in this study have demonstrated their potential therapeutic action against croton oil-induced ear edema in Wistar rats. It has been established that inflammation induced by croton oil is related to the activation of phopholipase A2, which releases arachidonic acid from the cell membrane. Arachidonic acid, in turn, is metabolized to prostaglandins (PG's) and leukotrienes. Substances able to inhibit edema could be inhibitors of cyclooxygenase (COX) and/or 5-lipoxygenase [3]. The anti-inflammatory action of glucocorticoids is mediated mainly by lipocortin 1, which inhibits phospholipase A2 on the arachidonic acid cascade resulting in decreased synthesis of prostaglandins [4]. Many topical anti-inflammatory drugs have limited efficacy because of sub-optimal pharmacokinetics and advances in drug delivery are needed to improve the pharmacokinetics of such drug [5]. Biopolymer based drugs play an important role in development of drug formulations as they have specific advantages [6]. Biopolymers are generally nontoxic and biocompatible. It is most probably the better pharmacokinetics of the biopolymers that gives them an advantage over the conventional preparations. In conclusion, advances in drug delivery improve the pharmacokinetics of promising drugs for many diseases and biopolymers have great potential for delivery of pharmaceuticals. Biopolymer based formulations can be promising candidates for various types of inflammation in which conventional preparations have shown less efficacy. This may result in better anti-inflammatory profile of the topical preparations.

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