EM 405: A new substance with an uncommon profile of anti-inflammatory activity

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Introduction

The search for drugs that are able to suppress inflammation with good efficacy but avoid the ulcerogenic effects of NSAIDs or avoid the severe side effects of steroids is pursued by many research groups.

Such drugs must show a pharmacological profile quite different from that of common antiphlogistic drugs and could be of great interest for long term therapy of chronic inflammatory diseases. EM 405 [1-p-chlorbenzyl-2-dimethyl-amino-methyl-cyclohexen-1,2] is a new substance with non-opioid antinociceptive and antitussive properties that could represent such a drug. It showed efficacy in different analgesic test models such as writhing, hot plate, electrical tail stimulation, tail pressure test and also in NH3 vapour induced cough reaction, but was ineffective in tail flick reaction. In vitro studies showed that these pharmacological actions are not mediated by opioid receptors but may be caused by norepinephrine uptake inhibition and local anesthetic effects of EM 405 [1].

In this report some antiphlogistic properties of EM 405 rather different from that of common NSAIDs or steroids are presented.

Materials and methods

Rat paw oedemas were induced by subplantar injection of 0.1 ml a) 0.05% Carrageenan solution (Carrageenan-oedema), b) 8 μg/ml Serotonin-Kreatinin-Sulfat-solution (Serotonin-oedema), c) 100 μg/ml Histamine-solution (Histamine-oedema), d) 0.5 mg/ml Anti-Ovalbumin-solution (+0.5 mg Ovalbumin in 1 ml 0.9% NaCl i.v.) (PRAR-oedema).

Paw volume was measured 3 or 5 hours after oedema induction plethysmographically. EM 405 (10–100 mg/kg) was given orally 1 h before oedema induction.

UV-erythema was induced by a UV light beam [33 mW/0.5 cm2, 80% UV-A (320–400 nm), 20% UV-B (280–320 nm)] directly onto the shaved back of mice for 15 s. Erythema-development was subjectively determined by a scoring system range 0 to 5 per animal at 2, 4, 6, 24 hours after UV-irradiation. Substances were applied in a water in oil ointment in concentrations from 0.01 to 10.0 w/w% 0.1 ml/animal, viz 0.01 to 10 mg/animal.

Allergic conjunctivitis was induced by local eye application of 1 μl Ovalbumin solution (0.1 mg/ml) to anesthetized animals, that were sensitized to ovalbumin [2]. Conjunctivitis development was subjectively determined by a scoring system range 0 to 5 per eye at 5, 10, 15 and 30 min after conjunctivitis induction. Substances were either given i.p. 0.5 h before or locally 2 min after conjunctivitis induction.

Pyrifer fever was induced by i.v. injection of 1000 U/ml/kg Pyrifer. 0.5, 1, 1.5, 2, 2.5, 3 h after fever induction body temperature of rabbits was measured with a rectal bimetal thermometer. EM 405 (10, 21.5, 46.4, 68.1 mg/kg) was applied orally 1 h before fever induction.
Granuloma was induced in rats by subcutaneous implantation of a perforated plastic tube (~1 cm³ size) into the right flank of the animals. 7 days later exudate volume, exudate leucocyte count, granuloma weight, different organ weights and weight of left side axillary lymphatic node were determined. EM 405 (10, 21.5, 46.4, 68.1 mg/kg) was orally applied twice daily starting 4 days before granuloma induction.

Adjuvant arthritis in rats was induced according to Rosenthale [3] with a scoring system range 0–13 per animal (3 paws, snout, penis). Weight of different organs (thymus, spleen, adrenals), count of different blood cells (erythrocytes, leucocytes, platelets) and weight of paws were determined on day 25. EM 405 (10, 21.5, 46.4 mg/kg) was orally applied twice daily starting the day of arthritis induction.

Results

EM 405 showed good efficacy in acute inflammatory rat paw oedema models. ED₅₀-values lay in the range of 13.6 to 29.4 mg/kg p.o. in carrageenan, histamine or RPAR-induced oedema. The anti-oedema effect of EM 405 seems to be long lasting as seen by 5 h values of RPAR-oedema. EM 405 showed only weak efficacy in serotonin-induced oedema.

EM 405 topically applied showed only weak efficacy in UV-induced erythema reaction in mice. Systemic prophylactically i.p. applied 21.5 mg/kg EM 405 showed an antiallergic effect of about 70% in Ovalbumin-induced allergic conjunctivitis of the mouse.

Topic eye application of 1 μl of a 10 w/w % saline solution of EM 405 showed no significant antiallergic effect.

EM 405 was not effective in pyrifer-induced fever reaction of the rabbit up to a dose of 68.1 mg/kg prophylactically p.o. applied.

EM 405 showed no effect in a model of chronic proliferative inflammation. Neither weight of granuloma nor exudate volume or leucocyte count of exudate were significantly changed by EM 405. The highest dose of EM 405 showed 60% reduc-