DOSE–RESPONSE RELATIONSHIP FOR THE ANTIPYRETIC EFFECT OF MELOXICAM IN AN ENDOTOXIN MODEL IN CATS

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ABSTRACT


The antipyretic efficacy of meloxicam was evaluated in a feline endotoxin model using a replicated change-over design. Twelve adult cats of both sexes were allocated at random to three experimental groups. At 30 min prior to the intravenous (i.v.) endotoxin challenge (0.5 μg/kg bodyweight(b.w.)), 2 animals in each group received an i.v. injection of 0.1, 0.3 or 0.5 mg meloxicam/kg b.w. and the two remaining animals in each group received physiological saline. In a second phase, 21 days later, the meloxicam/placebo treatment was exchanged within each group. The rectal temperature and scores for general demeanour were determined at 30-min intervals from before dosing to 300 min after the endotoxin challenge. Haematological parameters were analysed before and 60 min after administration of endotoxin. The results indicated a significant dose-dependent antipyretic response to meloxicam after endotoxin challenge. The antipyretic response in the medium- and high-dose meloxicam groups did not differ significantly, but both were significantly different from the low-dosage group. The individual effects of endotoxin on general demeanour were rather variable but meloxicam tended to have a beneficial effect. Endotoxin induced a reduction in the white blood cell count but this was not influenced by meloxicam. It was concluded that the pyretic endotoxin model is very suitable for studying new NSAIDs in cats and that the optimum single dose of meloxicam in this model was 0.3 mg/kg b.w.

Keywords: cat, demeanour, endotoxin, meloxicam, NSAID, pyrexia

Abbreviations: AUC, area under the curve; b.w., body weight; i.v., intravenous; LPS, lipopolysaccharide; MCV, mean corpuscular volume; NSAID, non-steroidal anti-inflammatory drug; WBC, white blood cell count

INTRODUCTION

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) belonging to the enolic group of these substances. It is a potent inhibitor of prostaglandin synthesis and exhibits antiphlogistic, analgesic, and antipyretic properties (Engelhardt, 1987). The compound has been developed for the treatment of acute and chronic locomotor disorders in dogs at a dosage of 0.2 mg/kg b.w. once daily, which can be reduced to 0.1 mg/kg for maintenance. Preliminary testing has indicated that meloxicam may also be effective for the treatment of similar clinical conditions in cats (Justus and Philipp, 1994). However, the optimum efficacious dosage for this species remains to be determined. For this purpose there is need for a practicable and reproducible experimental model.

Lipopolysaccharide (LPS) is a component of the surface of the outer membrane of all Gram-negative bacteria and affects a broad range of cellular and physiological
functions, referred to as the endotoxic response, which may be fatal within hours after administration of high dosages (Le Grand, 1990). After small doses of endotoxin only, a pyretic response and various minor changes in haematological or biochemical parameters are observed in some animal species (Morris et al., 1986a,b). The pyretic response is mediated by the central synthesis and release of eicosanoids in the brain and can be influenced by cyclooxygenase inhibitors (Parratt and Sturgess, 1973). Thus, the course of the rectal temperature following challenge with a low dosage of endotoxin may provide an objective and sensitive pharmacodynamic parameter. The purpose of this study was to investigate any dose-related effects of meloxicam on the pyretic response and haematological changes after the administration of a low dosage of endotoxin in experimental cats.

MATERIALS AND METHODS

Experimental animals

Twelve cats (6 non-pregnant females and 6 intact males) of various breeds and crosses, ranging in age from 8 to 42 months, were selected from a colony of experimental animals. The study was conducted in two phases. For each phase, the animals were removed from the colony and placed in individual cages for 3 days prior to the commencement of the experimental work. After completion of each phase, the cats were returned to the colony. The animals received a standard diet (Gilpa Bliss Cat Food; Gilbertson & Page, Welwyn Garden City, UK) once daily. Food was withdrawn 12 h prior to each experimental procedure and withheld until the observations were completed. Drinking water was available ad libitum throughout the study.

Experimental design

The study involved a replicated change-over design so that each cat acted as its own control, with the control (placebo) and treated states being repeated so as to avoid any confounding of effects associated with time (i.e. test sequence). At the start of the study, the animals were allocated at random to three groups, each consisting of 2 animals of each sex. At 30 min before endotoxin challenge, 2 animals in each group, one of each sex, received a single i.v. bolus administration of a 0.5% meloxicam injection solution (Metacam, Boehringer Ingelheim Vetmedica GmbH, Germany) in volumes which delivered dosages of 0.1, 0.3 and 0.5 mg meloxicam/kg body weight in the case of groups 1, 2 and 3, respectively. The remaining animals in each group received corresponding volumes of a similarly administered non-pyrogenic placebo injection (Physiological Saline Infusion, BP, Baxter Healthcare Ltd, Thetford, UK). In the second experimental phase of the study, which was conducted after a wash-out period of 21 days, the meloxicam and placebo treatments were exchanged between the animals within each of the three groups.

In both phases, all the animals received an i.v. challenge with endotoxin 30 min after the administration of meloxicam/placebo. Endotoxin prepared from E. coli serotype 005:B5 (Sigma Chemicals Co. Ltd, Dorset, UK) was dissolved in