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Note

Intranasal delivery of tenoxicam in rat

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Abstract

Intranasal delivery of tenoxicam was studied in male rats on single dose administration of 0.36 mg/rat and compared with intravenous administration. Tenoxicam plasma levels were determined by RP-HPLC method with UV detection that employed piroxicam as an electroactive internal standard in the analysis. Following intravenous administration the area under the plasma concentration curve was 2452.17 ± 86.49 ng h/ml as compared to 1357.69 ± 102.36 ng h/ml following intranasal dosing. This corresponds to a relative bioavailability of 55.36%.

Keywords: Tenoxicam; Nasal delivery; Bioavailability study; Rat

1. Introduction

Tenoxicam 4 hydroxy-2-methyl (N-C_2 pyridyl) 2H-thieno-(2-3e)- 1,2-thiazine carboxamide 1,1 dioxide is a new non-steroidal anti-inflammatory and analgesic agent of the oxicam class useful in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout (Thadikonda et al., 1995). Although this compound is rapidly and completely absorbed from the G.I tract following an oral dose this route causes gastric ulceration (Gonzalez and Todd, 1987). So by intranasal administration the drug circumvents the G.I tract and avoids the side effects frequently associated with oral administration. The present study was undertaken to (a) determine the suitability of the nasal mucos as a site for the administration of a non-steroidal anti-inflammatory agent tenoxicam; (b) compare the resulting plasma pharmacokinetic parameters with that follow intravenous (0.36 mg/rat) and intranasal (0.36 mg of tenoxicam in 0.2 ml of 2% methyl cellulose) administration. Previous studies in humans showed that on nasal administration propranolol (Hussain et al., 1979, 1980a,b), progesterone (Hussain et al., 1981), naloxone (Hussain et al., 1984a) and testosteron (Hussain et al., 1984b) achieved drug blood levels similar to that of intravenous administration.

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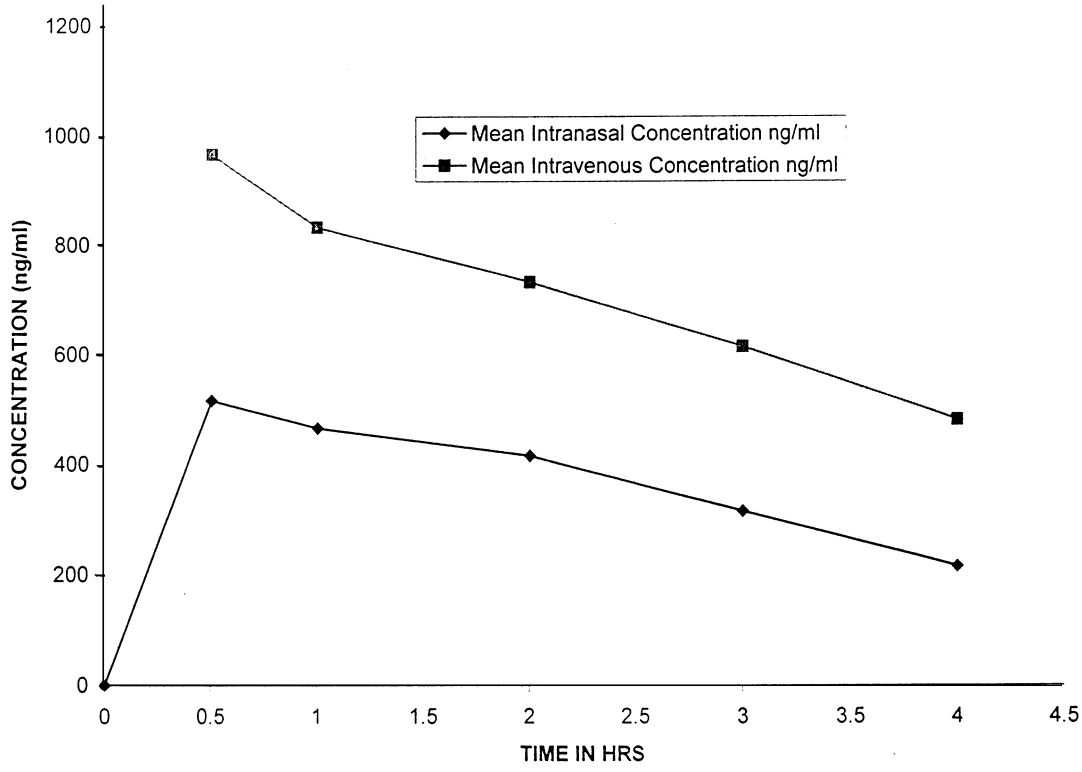

Fig. 1. Mean plasma tenoxicam concentration in three rats following intranasal and intravenous administration of 0.36 mg/rat.

2. Experimental section

2.1. Chemicals and reagents

Tenoxicam and piroxicam were donated by Cipla, Cipla Ltd, Mumbai, India. Acetonitrile (HPLC grade) was obtained from Ranbaxy Laboratories Ltd, New Delhi, India; Dichloromethane (HPLC grade) was obtained from S.D fine chemicals Ltd. All other reagents and solvents were of analytical grade.

3. Method (Hirai et al., 1981)

Six male albino wistar rats weighing 200–220 g were fasted for 16 h prior to study, however drinking water was given. They were divided into two groups containing three rats each. For nasal administration the rats were anaesthetized with an intraperitoneal injection of thiopentone sodium (40 mg/kg). The nasal absorption studies were performed according to the procedure described by Hirai et al. (1981). An incision was made in the

Table 1
Mean pharmacokinetic parameters of tenoxicam in rats following intranasal administration of 0.36 mg/rat and intravenous administration of 0.36 mg/rat

Parameters	Intranasal	Intravenous
C_{max}[a]	516.66 ± 26.35 ng/ml	966.67 ± 28.86 ng/ml
T_{max}[b]	30 min	30 min
Kel	0.3 8 ± 0.03/h	0.24 ± 0.05/h
Bio-half life	1.82 ± 0.20 h	2.94 ± 0.74 h
AUCo-t*[c]	1357.69 ± 102.36 ng h/ml	2452.17 ± 86.49 ng h/ml

[a] Maximum plasma tenoxicam level.
[b] Time required to reach the maximum plasma tenoxicam level.
[c] Area under the plasma tenoxicam level–time curve up to 4 h post-administration.

neck and the trachea was cannulated with a polyethylene tube. Another tube was inserted from the oesophagus to the posterior part of nasal cavity. The nasopalatine was closed with an adhesive agent to prevent the drainage of the drug from the nasal cavity to the mouth. The nasal preparation (0.36 mg/rat) was administered to the nasal cavity through the tube by means of a micropipet. Blood 0.8 ml was sampled from the femoral aorta periodically and analysed using RP-HPLC method with UV detection (Tamhankar et al., 1995). For intravenous administration the rats were anaesthetized using thiopentone (40 mg/kg). Then 0.36 mg/rat of drug in 0.2 ml of pH 7.6 buffer was injected through the femoral vein. After intravenous administration blood samples 0.8 ml were collected periodically from femoral aorta and analysed as above.

4. Results and discussion

The mean plasma levels of tenoxicam following nasal and intravenous administraion are shown in Fig. 1. The time course of these profiles revealed that significant blood levels were attained with intranasal delivery within 30 min. Table 1 summarises the pharmacokinetic parameters C_{max}, T_{max}, Kel, Bio-half life, AUCo-t* calculated for (0–4 h) nasal and intravenous administration of tenoxicam. The area under the curve was calculated using the trapezoidal method (Cribaldi et al., 1982). The fraction of drug absorbed after nasal administration was 55% of that obtained by the intravenous route (AUC_{nasal} 1357.69 ± 102.36 vs. 2452.176 ± 86.49 ng h/ml). The result of this study suggest that tenoxicam is efficiently absorbed through the nasal mucosa into the systemic circulation of the rat. Because the nasal route circumvents the gastro intestinal tract, this route may be of practical value for administration of tcnoxicam to avoid gastric ulceration frequently associated with oral administration of this drug. Furthermore, the bioavailability of this compound can be improved by coadministering with absorption enhancers. A study is underway on the bioavailability of tenoxicam from nasal dosage forms in humans.

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