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The effect of cigarette smoke on the plasma piroxicam concentrations in rats

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Abstract—The plasma concentration of unchanged piroxicam has been determined at 15, 30, 60 and 90 min after 10 mg kg^{-1} oral administration of the drug to rats exposed to cigarette smoke or pretreated with phenobarbitone, 3,4-benzpyrene or ethanol. Plasma piroxicam concentrations decreased in rats pretreated with phenobarbitone, 3,4-benzpyrene and ethanol and in rats 24 h after exposure to cigarette smoke.

Cigarette smoke alters the kinetics of various drugs in man (Jusco 1979) and laboratory animals (Bilimoria et al 1977; Berkan et al 1989) by enzyme induction. Phenobarbitone represents a class of enzyme inducers that stimulate the metabolism of a wide variety of drugs whereas 3,4-benzpyrene is more specific (Remmer 1972). Acute or chronic intake of ethanol also alters the rate of elimination of some drugs taken subsequently, at a time when ethanol is absent (Liv et al 1975).

Piroxicam is a structurally distinct potent nonsteroidal anti-inflammatory drug which after single doses shows linear pharmacokinetics. Maximum plasma concentrations are usually attained in about 2 h, but this may vary between 1 and 6 h. After repeated doses of 20 mg once daily, steady-state concentrations are generally achieved in 7 to 12 days (Brogden et al 1984). Metabolism is probably the main mode of elimination of the drug (Schiantarelli et al 1981).

The metabolic fate of piroxicam is similar in man and rat (Wiseman & Hobbs 1982) with hydroxylation of the pyridyl ring being more prominent in man (about 50% of the dose) (Hobbs & Twomey 1981). Pharmacokinetics are not age related and renal function has a limited influence on the elimination of the drug, but plasma concentrations are increased in patients with severe liver insufficiency (Brogden et al 1984). Since piroxicam is used in the treatment of rheumatic diseases and musculoskeletal disorders, it may be helpful to obtain information concerning the effect of cigarette smoking on its plasma concentrations.

Materials and methods

Materials. Piroxicam was a gift from DEVA Drug Industry, Istanbul, Turkey. 3,4-Benzpyrene and urethane were purchased from Sigma Chemical Company (St. Louis, MO, USA). Sodium phenobarbitone was purchased from Merck (Darmstadt, Germany). Other chemicals were of analytical or reagent grade. The cigarettes used contained approximately 1·22 mg nicotine and 27·0 mg tar per cigarette.

Piroxicam was dissolved in 1% carboxymethylcellulose and dilute sodium hydroxide was added as necessary to ensure solution. 3,4-Benzpyrene was dissolved in corn oil. All other drugs were dissolved in 0·9% NaCl (saline).

Experimental procedures. Adult male Swiss albino rats, 200 to 300 g, were housed in stainless steel cages and were maintained under a 12 h light/dark cycle throughout the experiments. The rats were arranged in six groups. The first group served as control. The second, third and fourth groups, respectively received intraperitoneally, sodium phenobarbitone (80 mg kg^{-1}) daily for three consecutive days, a single dose of 3,4-benzpyrene (50 mg kg^{-1}), or a single dose of 96% ethanol (4 g kg^{-1}) as a 20% (w/v) solution in saline. Blood sampling was initiated 24 h after the last injection.

Rats in the fifth and sixth groups were placed one at a time into a stainless steel and Pyrex glass respiration-metabolism cage (Harvard Bioscience) (vol 1650 cc) with fresh air ventilation (about 300 mL min^{-1}) and were exposed to cigarette smoke once, as described by Raunio et al (1983). Blood sampling from the rats in the fifth group was initiated just after the smoking session and that from the rats in the sixth group 24 h after.

All rats were fasted for 17 h before surgery for which they were anaesthetized with urethane (1·5 g kg^{-1} i.p.) dissolved in saline (25% w/v). Following tracheal cannulation they were respired with air by means of a ventilator (Harvard). The right external jugular vein was cannulated for heparinization and the left carotid artery was cannulated for the removal of blood samples. Heparin (100 units) was given i.v. to prevent coagulation of the blood samples taken from the carotid artery. After surgery, each animal received a single oral dose of piroxicam (10 mg kg^{-1}) by gastric intubation in a volume of 10 mL kg^{-1}. Blood samples were collected at 15, 30, 60 and 90 min after piroxicam administration and transferred to centrifuge tubes. The plasma, obtained by centrifugation, was stored at 4 C until assayed.

Piroxicam determinations. Unchanged piroxicam in plasma was determined according to the method of Wiseman et al (1976) as follows: 1 mL plasma, acidified with 0·25 mL M HCl was mixed with 5 mL ethylene dichloride using a vortex mixer for 2 min. The layers were separated by centrifugation and a portion of the organic layer (4 mL) was extracted with $NaHCO_3$: Na_2CO_3 (0·1 M, pH 9·0) buffer (5mL). The optical density of the aqueous phase was determined at 250 and 350 nm. The calibration curve, obtained from the addition of known amounts of piroxicam to blank plasma and extracted as described above, was linear between 5·0 and 30·0 $\mu g\ mL^{-1}$.

Results

The plasma piroxicam concentrations of the control and pretreated rats are shown in Fig. 1. Phenobarbitone, 3,4-benzpyrene and ethanol pretreatments decreased plasma piroxicam concentrations significantly at all times compared with controls. The results of smoke experiments are given in Fig. 2. Immediately after the smoke exposure there was no significant decrease in the piroxicam plasma concentration profile; 24 h after exposure however, there was a significant decrease.

Discussion

Tobacco smoke contains over 3000 chemicals, of which relatively few have been investigated for their pharmacological and toxicological effects. Smoking has the potential for causing a high incidence of altered drug disposition and effects in man and animals, the most common effect being an increase in biotransformation rate as a result of induction of drug-metabolizing enzymes.

Piroxicam is rapidly absorbed after oral administration, and has a half-life of 45–50 h in man (Wiseman & Hobbs 1982). In

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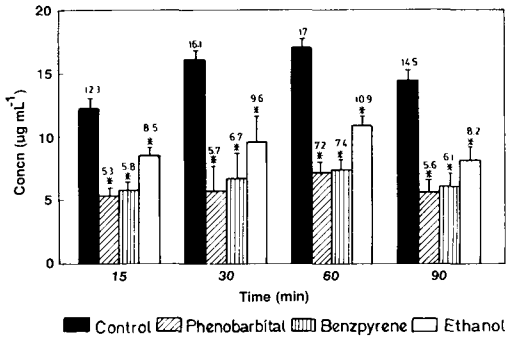

FIG. 1. Plasma piroxicam concentrations in control and pretreated rats. Each bar represents the mean value obtained from 7 individual rats (n = 7). *$P < 0.05$ compared with controls.

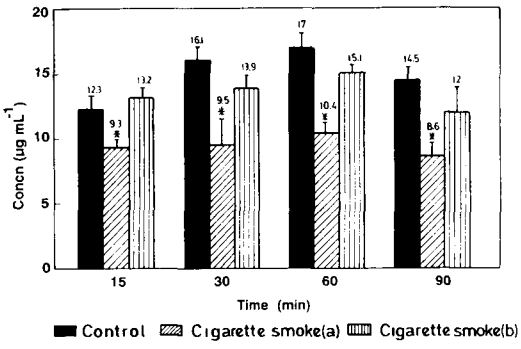

FIG. 2. Plasma piroxicam concentrations at different time intervals in control, 24 h after and immediately after cigarette smoke exposed rats. Each bar represents the mean value obtained from 7 individual rats (n = 7). *$P < 0.05$ compared with controls.

the control group of our experiments, its plasma concentration profile showed an increase with time, giving a peak at 60 min consistent with the findings of Schiantarelli et al (1981).

The major metabolite of piroxicam results from hydroxylation of the pyridyl ring and this metabolite together with its glucuronide conjugate accounts for the excretion of up to 50% of the daily dose (Twomey & Hobbs 1978). Other metabolites have also been identified in animals but they do not have major importance in man (Wiseman & Hobbs 1982). The metabolites of piroxicam have little or no anti-inflammatory activity in animal models (Wiseman & Boyle 1980). Our results demonstrate that in rats pretreated with enzyme inducers or 24 h after cigarette smoke exposure piroxicam plasma concentrations were significantly diminished.

The decrease was greatest in the phenobarbitone group, being approximately 57–65% of the control values.

3,4-Benzpyrene, which produces an increase in the modified form of cytochrome P450, namely P448, produced decreases in piroxicam plasma concentrations of between 53–58% of the control values, possibly because the activity of aryl hydrocarbon hydroxylase in many tissues is increased markedly by polynuclear aromatic hydrocarbons (PAHs) (Welch et al 1972; Pantuck et al 1974).

Ethanol pretreatment decreased plasma concentrations by approximately 31–43% compared with the controls. The decrease observed in this group may be related to increased drug availability for the activated enzyme system (Stein et al 1963) and is compatible with the findings that ethanol is a relatively weak inducer and that an activation of the drug metabolizing enzyme system can be observed 24 h after a single dose of ethanol (Powis 1975; Strubelt et al 1978).

The results obtained from the smoke exposure experiments confirm the literature indicating the stimulatory effect of smoking on biotransformation pathways of various drugs (Miller 1977; Graziano & Dorough 1984). Piroxicam plasma concentrations in rats, 24 h after exposure to cigarette smoke, were 24–41% lower than control values. This may be the result of increased metabolism of the drug either in the gastrointestinal tract or during the 'first-pass' through the liver, due to the effects of poly aromatic hydrocarbons in the smoke.

Immediately after the cigarette smoke exposure, piroxicam plasma concentration was not significantly influenced which is consistent with a time-dependent enzyme induction effect. Our results suggest that cigarette smoke exposure decreases piroxicam plasma concentrations and the underlying mechanism may be the induction of liver enzyme activity.

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