J. Pharm. Pharmacol. 1991, 43: 811-812
Communicated April 16, 1991

Influence of standard and nicotine-reduced cigarette smoke on plasma concentrations of isosorbide dinitrate and its metabolites in rats

YUTAKA GOMITA, KATSUSHI FURUNO, YASUNORI ARAKI, *Department of Hospital Pharmacy, Okayama University Medical School, Okayama 700, Japan*

Abstract—Rats dosed orally with isosorbide dinitrate (1 mg kg^{-1}) were exposed to smoke from standard and nicotine-reduced cigarettes for 8 min using a smoking machine. Plasma concentrations of isosorbide dinitrate and 5-isosorbide mononitrate, one of its major metabolites were approximately equal in the exposed groups, but were lower than in the non-smoking control group. The 2-isosorbide mononitrate concentration was also lower in the group exposed to smoke from standard cigarettes. Since the pharmacokinetics were influenced by smoke from both types of cigarette smoke, the effect may be attributed in large part to non-nicotine components of the smoke.

The actions of many drugs are influenced by emotional stress, environmental circumstances and body conditions (Barrett & Dimascio 1966; Nakano et al 1980; Gomita et al 1983; Hansten 1985). In general, some drug effects may be altered by changes in the sensitivity of the site of its action and the pharmacokinetics of the drug itself. Clinical studies have shown that the pharmacokinetics of some drugs are influenced by smoking. For example, theophylline is eliminated more rapidly in smokers (Jenne et al 1975; Jusko 1978) and the frequency of drowsiness caused by phenothiazines or benzodiazepines is lower in smokers (Boston Collaborative Drug Surveillance Program 1973; Swett 1974; Hansten 1985).

Nitrate compounds such as the vasodilators isosorbide dinitrate (ISDN) and nicorandil are widely used to treat angina. We have previously studied the acute influence of smoking on the pharmacokinetics of nicorandil, using nicotine-containing standard cigarettes and nicotine-reduced cigarettes, and found that plasma nicorandil concentrations after oral administration are mainly influenced by components of cigarette smoke other than nicotine (Gomita et al 1990).

In the present experiment we sought to determine whether or not cigarette smoking influences the pharmacokinetics of ISDN, and whether this influence depends on nicotine or on other components of cigarette smoke. Nicotine-containing standard cigarettes and nicotine-reduced cigarettes were used.

Materials and methods

Animals. Thirty male Wistar rats, 182–208 g, were divided into three groups; the nicotine-reduced cigarette smoke exposure (NR) group, the standard cigarette smoke exposure (ST) group and the non-smoking control group. Each of these groups was further divided into 2 sub-groups, in which a blood sample was collected at either 15 or 30 min after drug administration. Animals were housed three or four per cage in 26 × 36 × 25 cm plastic-walled cages, and had free access to food and water except during the smoking experiment. The animals were maintained on a 12 h light-dark cycle (lights on from 0800 to 2000 h) at 22–24°C and approximately 60% relative humidity.

Drugs. ISDN (pure powder, donated by Eisai Co.) was suspended in a solution of 0·5% carboxymethylcellulose sodium, and was orally administered (1 mg kg^{-1}) through a gastric tube in a volume of 1 mL kg^{-1}. Isomanide dinitrate was used as an internal standard in the gas chromatography (GC) method described below.

Correspondence: Y. Gomita, Department of Hospital Pharmacy, Okayama University Medical School, Okayama 700, Japan.

Cigarettes. Cigarettes used in the present experiment were nicotine-containing standard cigarettes ("Seven Star" without filter; mean wt 0·834 g/cigarette; nicotine content, 1·881%) and nicotine-reduced cigarettes ("Seven Star" as above with nicotine content, 0·255%) which were supplied by the Smoking Research Foundation.

Apparatus for cigarette-smoke exposure. The smoking machine (Borgwaldt, Hamburg II) consists of a smoking head, to which up to 30 cigarettes can be attached, a smoking channel, a smoke exposure chamber and 10 animal holders for exposing the animals to the smoke. The cigarettes attached to the smoking head were individually lit and the smoking head rotated. The smoke from the cigarettes was pumped to the smoking channel, mixed with air at a ratio of 1:7 and sent to the smoke exposure chamber. In the present experiment, 15 cigarettes were initially lit and the remaining 15 cigarettes were lit after the first 15 cigarettes had burned out. Animals were exposed to the smoke for 8 min. The inhalation duration of the machine was 2 s and the frequency was 15 min^{-1}. Five animals were exposed simultaneously.

Blood sampling. Approximately 5 mL blood samples were collected from the descending abdominal artery under diethylether anaesthesia 15 or 30 min after drug administration. Plasma was separated by centrifugation (3000 rev min^{-1} for 10 min) and 2 mL of plasma was used for gas chromatographic determination of the concentration of ISDN and its metabolites, 5-isosorbide mononitrate (5-ISMN) and 2-isosorbide mononitrate (2-ISMN).

GC analysis. Concentrations of ISDN and its metabolites were determined by a modification of the method of Santoni et al (1984), using a gas chromatograph equipped with a ^{68}Ni (10 mCi) electron capture detector (GC-ECD JGC-20KE, Nihondenshi Co.). Columns (2 mm inside diam. and 2 m length) packed with Gaschrom Q 100–120 mesh coated with 3% OV-1 and 3% OV-3 were used to measure ISDN and its metabolites, respectively. The columns were pre-heated for one day. The column and injection temperature were maintained at 155°C with argon as the carrier gas. The carrier gas was mixed with argon–methane (90:10) under 3 kg cm^{-2} pressure.

The plasma was extracted twice with 4 mL n-hexane after the addition of 4 mg of internal standard to 1 mL of plasma containing ISDN. Following evaporation, the extracts were reconstituted with 100 μL of ethylacetate, and 5 μL was injected into the gas chromatograph. 5-ISMN and 2-ISMN were measured after adding the internal standard to the residue obtained after the above extraction; the residue was extracted 3 times with 4 mL of diethylether. The extracts were evaporated and then reconstituted with 100 μL of ethylacetate, and 5 μL was injected into the gas chromatograph.

Table 1. Plasma concentrations of isosorbide dinitrate (ISDN) and its metabolites, 5-isosorbide mononitrate (5-ISMN) and 2-isosorbide mononitrate (2-ISMN) in rats exposed to cigarette smoke.

Experiment (n = 5)	ISDN (ng mL^{-1})	5-ISMN (ng mL^{-1})	2-ISMN (ng mL^{-1})	Ratios 5-ISMN / ISDN	Ratios 2-ISMN / ISDN
15 min					
Control	55·6 ± 12·5	257·6 ± 28·8	64·0 ± 7·0	5·2 ± 0·8	1·3 ± 0·1
Standard	24·3 ± 2·3*	137·8 ± 16·0**	22·1 ± 3·2**	5·8 ± 0·7	0·9 ± 0·1
Nicotine-reduced	26·7 ± 7·0*	133·8 ± 16·9**	35·5 ± 12·2*	5·6 ± 0·6	1·2 ± 0·1
30 min					
Control	30·0 ± 4·2	304·6 ± 35·9	57·3 ± 8·8	5·1 ± 0·8	1·3 ± 0·1
Standard	26·5 ± 4·2	280·0 ± 36·6	45·0 ± 6·08	5·8 ± 0·7	0·9 ± 0·1
Nicotine-reduced	27·0 ± 4·0	305·4 ± 42·8	53·2 ± 8·5	5·6 ± 0·6	1·3 ± 0·1

ISDN at a dose of 1 mg kg^{-1} was administered orally. Each value represents the mean ± s.e.m. Asterisks indicate significant difference from the control (* $P < 0.05$ and ** $P < 0.01$, Duncan's test).

The limits of detection at a signal-to-noise ratio of 2 were 0·3 ng mL^{-1} for ISDN, 1·0 ng mL^{-1} for 5-ISMN and 0·5 ng mL^{-1} for 2-ISMN, and the rates of recovery averaged 68·0 (63·8–74·1) % for ISDN, 82·6 (81·6–83·6)% for 5-ISMN and 80·1 (75·6–83·1) % for 2-ISMN (n = 4 each). The coefficients of variation of simultaneous within-day assays were 4·1–7·4% for ISDN, 5·8–10·5% for 5-ISMN and 6·3–9·2% for 2-ISMN (3 times a day, n = 3), and those of between-day assays were 2·4–7·5% for ISDN, 4·4–7·7% for 5-ISMN and 3·5–10·8% for 2-ISMN (5 days, n = 3), indicating good reproducibility.

Statistical analysis. Results were evaluated using one-factor analysis of variance (ANOVA) followed by Duncan's test.

Results and discussion

In the present experiment, we studied the influence of smoking on ISDN pharmacokinetics using nicotine-reduced and standard cigarettes (Table 1). The plasma ISDN concentrations in the NR and the ST groups after the drug was orally administered were lower than in the control group. This is the same pattern of results as found previously for nicorandil (Gomita et al 1990). Thus, the alterations of ISDN concentrations can be attributed in large part to components of cigarette smoke other than nicotine.

The concentration of plasma ISDN metabolites 5-ISMN in both the NR group and the ST group were both lower 15 min after drug administration compared with non-smoking controls, but the plasma 2-ISMN concentration at 15 min in the ST group was lower than in the NR group. The ratios of 5-ISMN to ISDN and 2-ISMN to ISDN at 15 and 30 min were virtually the same among the three groups. This may mean that exposure to standard or nicotine-reduced cigarette smoke does not influence the metabolism of ISDN to 5-ISMN and to 2-ISMN. Accordingly, the lowered ISDN plasma concentrations induced by smoke exposure may be attributed to changes in other processes, including drug absorption, tissue distribution or excretion. It has also been reported that acute cigarette smoking accelerates the rate at which the liquid component of a meal leaves the stomach (Grimes & Goddard 1978) and inhibits the basal level of gastroduodenal motility (Ertel et al 1985). The influence of cigarette smoking on drug absorption from the gastrointestinal tract may therefore be one cause of the lowered plasma concentrations of ISDN.

This work was supported by a grant from the Smoking Research Foundation. The authors are indebted to Miss S. Fijiwara for her technical assistance.

References

Barrett, J. E., Dimascio, A. (1966) A comparative effect on anxiety of the "minor tranquilizers" in "high" and "low" anxious volunteers. Dis. Nerv. Syst. 27: 483–486

Boston Collaborative Drugs Surveillance Program (1973) Clinical depression of the central nervous systems due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. N. Engl. J. Med. 188: 277–280

Ertel, G., Herman, B., Murthy, S. N. S., Dinoso, V. P. (1985) The effect of smoking (s) on gastroduodenal motility (GDM), pH changes in the proximal duodenum (PD), and gastrointestinal hormones. Gastroenterology 88: 1375

Gomita, Y., Eto, K., Furuno, K., Araki, Y. (1990) Effects of standard cigarette- and nicotine-less cigarette-smoke-inhalings on nicorandil plasma levels in rats. Pharmacology 40: 312–317

Gomita, Y., Kataoka, Y., Ichimaru, Y., Ueki, S. (1983) Methamphetamine mortality to emotional stimuli administered in the form of affective communication. Life Sci. 32: 941–947

Grimes, D. S., Goddard, J. (1978) Effect of cigarette smoking on gastric emptying. Br. Med. J. 2: 460–461

Hansten, P. D. (1985) Phenothiazine interactions (Chapter 13) and Miscellaneous Interactions (Chapter 16). In: Hansten, P. D. (ed.) Drug Interactions—Clinical Significance of Drug–drug Interactions. 5th edn Lea & Febiger, Philadelphia, pp 346–355 and 378–437

Jenne, J., Nagasawa, H., McHugh, R., MacDonald, F., Wyse, E. (1975) Decreased theophylline half-life in cigarette smokers. Life Sci. 17: 195–198

Jusko, W. J. (1978) Role of tobacco smoking in pharmacokinetics. J. Pharmacokinet. Biopharm. 6: 7–39

Nakano, S., Ogawa, N., Kawazu, Y. (1980) Influence of neuroticism on oral absorption of diazepam. Clin. Pharmacol. Ther. 27: 370–374

Santoni, Y., Rolland, P. H., Cano, J.-P. (1984) Determination of isosorbide dinitrate and its mononitrate metabolites in human plasma using Extrelut purification and capillary column gas-liquid chromatography. J. Chromatogr. 306: 165–172

Swett, C. (1974) Drowsiness due to chlorpromazine in relation to cigarette smoking. Arch. Gen. Psychiatry 31: 211–213