

Acta Medica Okayama

Volume 49, Issue 4

1995

Article 4

AUGUST 1995

Effects of exposure to cigarette smoke on intestinal propulsion in rats.

Katsushi Furuno* Masatoshi Okazaki[†] Kohei Eto[‡]
Hiromu Kawasaki** Yutaka Gomita^{††}

*Okayama University,

[†]Okayama University,

[‡]Okayama University,

**Okayama University, kawasaki@pheasant.pharm.okayama-u.ac.jp

^{††}Okayama University,

Effects of exposure to cigarette smoke on intestinal propulsion in rats.*

Katsushi Furuno, Masatoshi Okazaki, Kohei Eto, Hiromu Kawasaki, and Yutaka Gomita

Abstract

The effects of acute exposure to cigarette smoke and systemic administration of nicotine on intestinal propulsion were investigated in rats. The propulsive activity was measured as migration of charcoal powder in the intestine. This activity was suppressed by acute exposure (10 min) to cigarette smoke and by nicotine (0.5 mg/kg x 2, s.c.) administration. This intestinal suppression was more marked in the rats given nicotine than in those exposed to cigarette smoke, whereas the plasma concentrations of nicotine in both rats were similar. These results suggest that acute exposure to cigarette smoke and nicotine administration delay gastric emptying and/or suppress intestinal propulsion, and that some components other than nicotine contained in cigarette smoke may attenuate the suppression of intestinal propulsion induced by nicotine.

KEYWORDS: cigarette smoke, nicotine, intestinal propulsion

Effects of Exposure to Cigarette Smoke on Intestinal Propulsion in Rats

Katsushi FURUNO*, Masatoshi OKAZAKI, Kohei ETO^a, Hiromu KAWASAKI and Yutaka GOMITA

Department of Hospital Pharmacy, Okayama University Medical School and ^aOkayama University Dental School, Okayama 700, Japan

The effects of acute exposure to cigarette smoke and systemic administration of nicotine on intestinal propulsion were investigated in rats. The propulsive activity was measured as migration of charcoal powder in the intestine. This activity was suppressed by acute exposure (10 min) to cigarette smoke and by nicotine (0.5 mg/kg × 2, s. c.) administration. This intestinal suppression was more marked in the rats given nicotine than in those exposed to cigarette smoke, whereas the plasma concentrations of nicotine in both rats were similar. These results suggest that acute exposure to cigarette smoke and nicotine administration delay gastric emptying and/or suppress intestinal propulsion, and that some components other than nicotine contained in cigarette smoke may attenuate the suppression of intestinal propulsion induced by nicotine.

Key word: cigarette smoke, nicotine, intestinal propulsion

It is generally known that cigarette smoking influences gastric function in humans (1-4, 10, 11). Smoking has been shown to delay gastric emptying of solids (4) and to increase emptying of liquid components. Furthermore, the effects of smoking are modulated by some factors including age, sex and body weight. On the other hand, cigarette smoke also influences pharmacokinetics of various drugs (5-9). We have reported that the pharmacokinetics of some drugs such as cimetidine, theophylline, nicorandil and indomethacin when administered orally, are influenced by exposure to cigarette smoke in animals (6, 8). Although, the cause of these changes remains unclear, inhibition of gastric absorption and increased metabolism, elimination and distribution to tissues may be involved. Moreover, it is possible that cigarette smoke may influence intestinal propulsion in addition to

gastric emptying. Cigarette smoke contains about 4000 various components, with nicotine being one of the most pharmacologically active. Therefore, the purpose of the present study was to evaluate the effects of cigarette smoke and nicotine on intestinal propulsion in rats.

Materials and Methods

Animals. Thirty-six male Wistar rats weighing 210-235 g were used. Three to four animals were housed in each plastic cage (35 × 30 × 26 cm), and food and water were freely available, except for a fasting period of 12 h before and during the experiment, and were kept in a room maintained at 20-22°C and 60 % relative humidity on a 12-h light-dark cycle (lights on from 8:00 to 20:00). In the intestinal propulsion experiment, the animals were divided into two groups for the exposure to cigarette smoke (smoking group, n = 7; control group, n = 6) and for nicotine administration (nicotine group, n = 7; saline group, n = 6). In another experiment, the plasma concentration of nicotine was measured when cigarette smoke (n = 5) or nicotine (n = 5) was given.

Cigarette smoking. The brand of cigarette used for exposing the animals to smoke was "Long-Peace[®]", weighing 1.023 g/cigarette, and the nicotine used for systemic administration experiment was free base solution, which was kindly supplied by Japan Tobacco, Co. (Tokyo, Japan). To expose cigarette smoke to animals, a smoking machine (Hamburg II, Borgwaldt, Germany) was used. The apparatus mainly consists of the smoking head to which up to 30 cigarettes can be attached, the smoking channel, the smoking chamber and the inhalation chamber for animal's smoking. The cigarette smoke was pumped into the chamber through the smoking channel. The smoke in the inhalation chamber was mixed with air at a ratio of 1 (smoke): 7 (air). The animal restrained in the holder was exposed to the smoke

* To whom correspondence should be addressed.

in the inhalation chamber. Seven animals were exposed simultaneously to the smoke for 10 min under the condition at a puff duration of 2 sec and a frequency of 15 puff/min. Six animals were used as non-smoked control group.

Measurement of intestinal propulsion.

All animals were orally administered at a volume of 0.2 ml/100 g body weight with a 0.5 % suspension of charcoal powder as a marker for measuring propulsion. In the cigarette smoke exposure experiment, immediately after the charcoal administration, the cigarette smoked group was exposed for 10 min using the smoking machine. The animals in the non-smoked control group were restrained in the holder but were not exposed to the smoke. In the nicotine administration experiments, immediately after the charcoal powder administration, nicotine 0.5 mg/kg or saline (1 ml/kg) was subcutaneously administered twice every 15 min. Thirty minutes after the administration of charcoal powder in both experiments, each rat was decapitated under diethylether anesthesia and laparotomized. The length of the intestine in which charcoal was contained (the distance from pylorus) was macroscopically measured. Intestinal propulsion was calculated as a percentage of distance the charcoal powder travelled/total length of small intestine (from pylorus to ileo-cecal junction).

Determination of plasma nicotine concentration. Blood samples of approximately 5 ml were collected from the descending abdominal aorta using a heparinized syringe after the laparotomy under the diethylether anesthesia. The plasma was separated by centrifugation (3,000 rpm for 15 min). The plasma nicotine concentration following exposure to cigarette smoke and administration of nicotine were determined using a high performance liquid chromatograph (HPLC; Waters-Millipore, MA, USA) equipped with electrochemical detector (Model 5100A Crouchem, ESA Inc. MA, USA). A stainless-steel column was packed with octadecyl silica (LiChro-CART RP-18e, 125 × 4 mm I. D., Cica-MERCK Co., Tokyo, Japan). The mobile phase was 5 % organic solvent (acetonitrile: methanol, 1: 3 by volume) in 2 mM phosphate buffer (pH 3.0) containing 0.25 mM sodium octyl sulfate. The HPLC assay procedure was carried out by a modification of the Chen-Yie *et al.* (12). The extraction solvent of nicotine from plasma was changed from acetonitrile to diethylether in the process of sample pretreatment. In the preliminary experiment, the exposure (for 10 min) to the cigarette smoke and the systemic administration of nicotine (0.5 mg/kg ×

2) showed similar behavioral changes such as slight ataxia and almost the same nicotine concentrations in the plasma immediately after the exposure and at 8-10 min after the nicotine administration. Therefore, each blood sample was collected immediately after the cigarette smoke exposure for 10 min and at 10 min after the nicotine administration.

Statistical analysis was performed by means of the two-tailed Student's unpaired *t*-test.

Results

Effect of cigarette smoking. Fig. 1A shows the effect of cigarette smoke exposure on the propulsion of the small intestine in rats. The distance the charcoal powder travelled was 60.9 % of total length of small intestine in the non-smoked control group and 48.8 % in the cigarette smoke-exposed group, and the difference was significant ($P < 0.01$).

Effect of nicotine administration. The influence of systemic nicotine administration on the propulsion of the small intestine is shown in Fig. 1B. Systemic administration of nicotine 0.5 mg/kg suppressed the propulsive activity of small intestine. The distance the charcoal powder travelled was 67.9 % of the total length of the small intestine in the saline control group and 12.9 % in the nicotine group, and the difference was significant ($P < 0.01$).

Effects of cigarette smoking and nicotine administration on plasma nicotine concentration. Fig. 2 shows the plasma concentration of nicotine immediately after the exposure to cigarette smoke and at 10 min after the last injection of nicotine. The nicotine plasma concentration after the exposure to cigarette smoke and the nicotine administration was 137 ± 31 ($n = 5$) ng/ml and 106 ± 14 ($n = 5$) ng/ml (mean \pm SE), respectively. There was no significant difference between the groups.

Discussion

Concerning the effects of acute exposure to cigarette smoke on pharmacokinetics of various clinical drugs, we have previously reported that the plasma concentrations of drugs such as nicorandil, cimetidine, theophylline and indomethacin are decreased by exposure to cigarette smoke in animals (6, 8). However, it is not clear which processes such as gastric emptying, small intestinal pro-

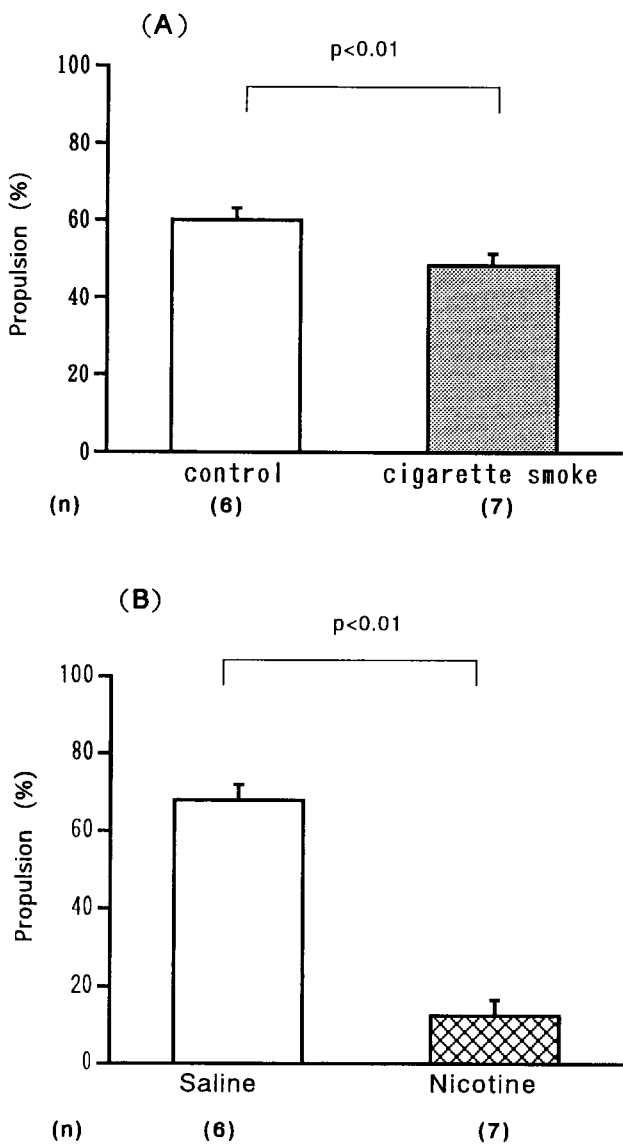


Fig. 1 Effects of exposure to cigarette smoke (A) and systemic nicotine administration (B) on propulsion of the small intestine in rats. Immediately after oral administration of charcoal powder, the rats were exposed to cigarette smoke for 10 min using a smoking machine, or were given nicotine 0.5 mg/kg \times 2 (every 15 min). Thirty minutes after the treatment, each rat was decapitated under the ether anesthesia and laparotomized, and the distance the charcoal powder travelled in the intestine was macroscopically measured. The ordinate indicates the percentage of distance the charcoal powder travelled/total length of small intestine. Each column and bar indicates the mean \pm SE of 6 rats (control group and saline group) or of 7 rats (cigarette smoke group and nicotine group). Statistical difference between both groups: $P < 0.01$, by student's unpaired *t*-test.

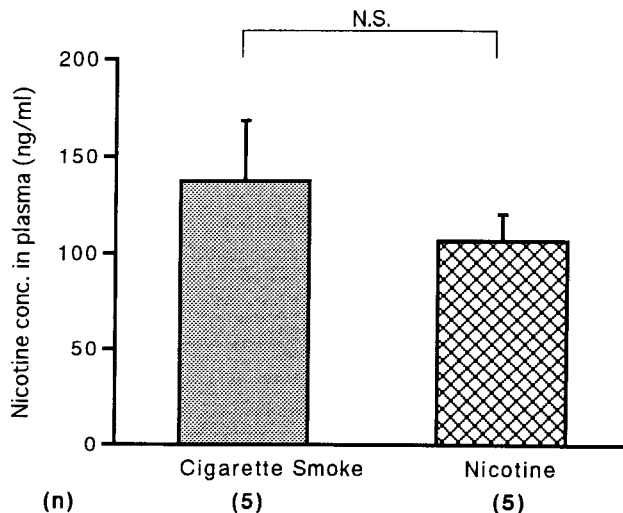


Fig. 2 Nicotine plasma concentrations after exposure to cigarette smoke for 10 min and systemic nicotine administration (0.5 mg/kg twice) in rats. Blood samples were obtained from the descending abdominal aorta using a heparinized syringe immediately after smoking and at 10 min after the nicotine administration. Five animals were used in each group. Each column and bar indicates the mean \pm SE. N.S.: not significant

pulsion, absorption, peripheral blood flow, distribution, metabolism and excretion are related to the decreased plasma concentrations of these drugs. Yoshida *et al.* (6) reported that the pharmacokinetic parameters of indomethacin orally administered in rats, such as the time to reach the maximum blood concentration (T_{max}) and the area under the time-concentration curve from 0 to 4 h (AUC_{0-4}), significantly decreased after cigarette smoke and nicotine administration, but AUC_{0-24} (the AUC from 0 to 24 h) of this drug did not decrease. Furthermore, cigarette smoke did not influence the pharmacokinetics of indomethacin after intravenous administration. These results indicate that cigarette smoke affects drug absorption in the gastrointestinal tract. Thus, the suppression of intestinal propulsion by cigarette smoke or nicotine seems to be one of the factors that influence the pharmacokinetics of drugs. However, it is also possible that drug absorption may be affected by decreased gastric mucosal blood flow due to the nicotine-induced increase in the release of catecholamines (13).

In the present experiment, there was a marked

difference in the propulsive activity between exposure to cigarette smoke and nicotine administration; nicotine induced more marked suppressive effect than that of exposure to cigarette-smoke. However, the nicotine plasma concentrations after exposure to cigarette smoke were almost the same as that after nicotine administration. Cigarette smoke is well known to contain some alkaloids, tar and about 4,000 various substances other than nicotine, but the pharmacological effects of most of these substances are still unknown. It is possible that some components other than nicotine in the cigarette smoke attenuates the inhibitory effect of nicotine on the motility of the small intestine.

In conclusion, the present results suggested that cigarette smoke and nicotine causes the inhibition of intestinal propulsive activity, which may affect the pharmacokinetics of various drugs.

Acknowledgments. This study was supported in part by the Grant-in-Aid for Scientific Research (no.056718198) from the Ministry of Education, Science and Culture of Japan.

References

1. Grimes DS and Goddard J: Effect of cigarette smoking on gastric emptying. *Br Med J* (1978) **12**, 460-461.
2. Notivol R, Carrio I, Cano L, Estorch M and Vilardell F: Gastric emptying of solid and liquid meals in healthy young subjects. *Scand J Gastroenterol* (1984) **19**, 1107-1113.
3. Hanson M and Lilja B: Gastric emptying in smokers. *Scand J Gastroenterol* (1987) **22**, 1102-1104.
4. Miller G, Palmer KR, Smith B, Ferrington C and Merrick M V: Smoking delays gastric emptying of solids. *Gut* (1989) **30**, 50-53.
5. Jenne J, Nagasawa H, McHugh R, MacDonld F and Wyse E: Decreased theophylline half-life in cigarette smokers. *Life Sci* (1975) **17**, 195-198.
6. Yoshida T, Gomita Y and Oishi R: Effect of cigarette smoke on pharmacokinetics of oral, intrarectal, or intravenous indomethacin in rats. *Naunyn-Schmiedeberg's Arch Pharmacol* (1991) **344**, 500-504.
7. Norman TR, Burrows GD, Maguire KP, Rubinstein G, Scoggins BA and Davies B: Cigarette smoking and plasma nortriptyline levels. *Clin Pharmacol Ther* (1977) **21**, 453-456.
8. Gomita Y, Eto K, Furuno K, Okazaki M and Araki Y: Influence of cigarette smoke on pharmacokinetics of nicorandil, theophylline and cimetidine in rats. *Jpn J Pharmacol* (1989) **49** (Suppl.) 342P.
9. Gomita Y, Eto K, Furuno K, Mimaki Y and Araki Y: Influence of long-term cigarette smoke on pharmacokinetics of nicorandil and theophylline in rats. *Jpn J Pharmacol* (1990) **52** (Suppl) 332P.
10. Silvette H, Hoff EC, Larson P and Haag HB: The action of nicotine on central nervous system function. *Pharmacol Rev*, (1962) **14**, 137-173.
11. Clark PBS: Nicotine and smoking: A perspective from animal studies. *Psychopharmacology* (1987) **92**, 135-143.
12. Chen-Yie C, Dian JN and Crooks PA: High-performance liquid chromatography with electrochemical detection for the determination of nicotine in plasma. *J Pharm Sci* (1988) **77**, 277-279.
13. Valenzuela JE, Defilippi C and Csendes A: Manometric studies on the human pyloric sphincter: Effect of cigarette smoking, metoclopramide and atropine. *Gastroenterology* (1976) **70**, 481-483.

Received February 23, 1995; accepted May 30, 1995.