# INFLUENCES OF CIGARETTE SMOKE INHALATION ON PHARMACOKINETICS OF CIMETIDINE IN RATS

Kohei Eto[2], Yutaka Gomita[1,3], Katsushi Furuno[1], Kazuhisa Yao[1], Masahiro Moriyama[1] and Yasunori Araki[1]

*[1]Department of Hospital Pharmacy, Okayama University Medical School, [2]Department of Hospital Pharmacy, Okayama University Dental School, 2-5-1 Shikata-cho Okayama 700, Japan*

## SUMMARY

The influences of cigarette smoke inhalation on the pharmacokinetics of cimetidine administered orally and parenterally were investigated in rats using a smoking machine. The animals were exposed to two kinds of cigarette smoke, low- or high-nicotine•tar, inhaled for 10 min immediately after oral (50 mg/kg), intraperitoneal (25 mg/kg) or intravenous (10 mg/kg) administration of cimetidine. The plasma level after cimetidine was administered orally was lower in the absorption phase in the two cigarette smoke inhaling groups than in the non-smoking control group, and was particularly marked in the high-nicotine•tar cigarette smoke inhaling group. In contrast, no significant difference was found in cimetidine plasma level between the cigarette smoke inhaling groups and the non-smoking control group when administered intraperitoneally or intravenously. These results suggest that cigarette smoke inhalation may cause a suppression or a delay in cimetidine absorption from the gastrointestinal tract, and that the degree of influence is dependent upon the content of nicotine•tar in the cigarette smoke.

## KEY WORDS

cigarette smoke inhalation; cimetidine; rats; plasma level

[3]Author for correspondence

## INTRODUCTION

Cimetidine is an imidazole derivative and an antagonist of histamine $H_2$-receptor, which is widely used in the treatment of duodenal and gastric ulcers /1,2/. It is known that cimetidine produces a dose-dependent inhibition of gastric acid secretion /1/. Furthermore, pharmacokinetic interactions with cimetidine have been shown to occur at the levels of gastrointestinal absorption, metabolism and excretion /2/. There is a possibility that patients who are taking cimetidine for the treatment of duodenal and gastric ulcers smoke at the time of administration or have been smoking recently or in the past. With regard to the interaction with smoking, it has been reported that cimetidine decreases theophylline clearance in smokers /3/, and that the inhibition of theobromine 7-methylation by cimetidine was greater in smokers /4/. A difference in plasma levels of cimetidine between smokers and non-smokers has also been observed in elderly subjects /5/. However, there are insufficient basic studies concerning the influence of smoking on cimetidine pharmacokinetics. We have preliminarily observed that plasma levels of cimetidine, when administered orally, were markedly decreased by the inhalation of high nicotine•tar-containing cigarette smoke in rats. However, it is unclear whether the decrease in cimetidine plasma levels by smoking is attributable to the influences on drug absorption, metabolism, distribution, excretion or other factors. By including parenteral drug administration, i.e., intraperitoneal and intravenous injections, it would not be necessary to consider the absorption process from the gastrointestinal tract. In addition, intravenous administration focuses on the drug elimination process only.

In the present study, we studied the acute influences of cigarette smoke inhalation on the pharmacokinetics of cimetidine when administered orally as well as parenterally, i.e., intraperitoneally and intravenously, to rats.

### ABBREVIATIONS

| | |
|---|---|
| IS | internal standard |
| HPLC | high performance liquid chromatography |
| "L-P" | "Long-Peace®" filter cigarette |
| "M-S" | "Mild-Seven®" filter cigarette |
| AUC | the area under the plasma concentration-time curve |
| MRT | the mean residence time |

## MATERIALS AND METHODS

### Materials

*Drugs:* Cimetidine, used for oral administration in the present experiment, was supplied by Smith-Kline Fujisawa (Japan) and Tagamet® injection (a commercial product containing 100 mg cimetidine in 1 ml of water for injection; Fujisawa, Japan) was purchased for intraperitoneal and intravenous administration. Cimetidine was suspended in 0.5% sodium carboxymethylcellulose solution for oral administration and administered orally at a dose of 50 mg/kg using a gastric tube. Tagamet® injection was diluted in saline and administered intraperitoneally and intravenously at doses of 25 and 10 mg/kg, respectively. Methyl p-hydroxybenzoate was used as the internal standard (IS) for measuring the cimetidine level in the plasma by high performance liquid chromatography (HPLC).

*Cigarettes:* To expose animals to cigarette smoke, "Long-Peace®" filter cigarettes ("L-P") and "Mild-Seven®" filter cigarettes ("M-S") supplied by Japan Tobacco Inc., Japan, were used. The weight of an "L-P" cigarette was 1.023 g. The nicotine and tar contents in the smoke from an "L-P" cigarette were 2.2 and 23 mg per cigarette, respectively, when smoked until two-thirds consumed using a smoking machine (the inhalation conditions were as follows: inhalation volume - 35 ml, duration - 2 sec and interval - 1 min). For "M-S", the weight was 0.938 g and the nicotine and tar contents were 1 and 14 mg per cigarette, respectively.

### Methods

*Animals:* Male Wistar rats weighing 170-355 g were used as the subjects. They were divided into 3 groups for experiments of oral, intraperitoneal and intravenous administration, and each group was further divided into 3 or 4 groups of "L-P" and/or "M-S" cigarette smoke inhaling rats, non-smoking restrained control rats and non-smoking unrestrained rats. Four or five animals were housed together in a 26 x 36 x 25 cm plastic-walled cage, and food and water were given *ad libitum* except during a fasting period of 12 h before and during the experiment. The animals were maintained on a 12 h light-dark cycle (light on from 8:00 to 20:00) at a room temperature of 22-24°C and a relative humidity of approximately 60%.

*Apparatus for cigarette smoking:* A smoking machine (Borgwaldt, Hamburg II Type) was used to expose animals to cigarette smoke. The apparatus consisted of a smoking head to which up to 30 cigarettes can be attached, the smoking channel, the smoking chamber slide piece, the inhalation chamber and 10 animal holders to expose animals to smoke. The cigarettes attached to the smoking head were individually lit with a lighter and the smoking head was turned. The smoke from the lit cigarettes was pumped through the smoking channel into the inhalation chamber. The smoke was mixed with air at a ratio of 1 (smoke) : 7 (air) and sent into the inhalation chamber. Each animal in the holder was exposed to the smoke in the inhalation chamber. In the present experiment, 15 cigarettes were lit initially and the remaining 15 cigarettes were lit immediately after the first 15 cigarettes had burned out. Animals were exposed to the smoke for 10 min. The inhalation frequency was 15/min. Three to 6 animals were exposed simultaneously.

*Blood collection and extraction procedures:* The peripheral part of the tail vein was slightly incised under light local anesthesia of ethyl aminobenzoate ointment. Blood samples for measuring the cimetidine plasma level were collected repeatedly in a capillary (60 $\mu$l, Miles Sankyo Co.) from the tail vein of each animal. Plasma separation was performed by centrifugation at 11,500 rpm for 3 min using a hematocrit centrifuge (Compur M 1100, Miles-Sankyo Co.). 20 $\mu$l samples of the plasma were used for the determination of drug plasma concentrations.

Cimetidine and the IS were extracted using a Bond-Elut® C18 cartridge (Analytichem Int.). 20 $\mu$l of plasma containing cimetidine and IS were passed through the Bond Elut® C18 cartridge which had previously been washed twice with 1 ml methanol and twice with 1 ml distilled water. After the cartridge was washed with 1 ml of 0.05 M $(NH_4)_2HPO_4$, cimetidine and the IS were then eluted with 250 $\mu$l methanol. 40 $\mu$l of the eluate was used for HPLC.

*Determination of cimetidine plasma levels by HPLC:* The cimetidine plasma levels were determined by HPLC (Waters Assoc., Pump, Type 510 with UV detector, Type 481), and the area of the peaks was calculated using a Data Module (Waters Assoc., Type 730). A stainless steel column packed with octadecyl silica ($\mu$Bondapak® C18, with a 10 $\mu$m particle size, Waters Assoc.) was used and the column was maintained at room temperature. The sample was injected using an automatic sample processor (Waters Assoc., Type

WISP 710B). The mobile phase was 35% methanol : 0.05 M $(NH_4)_2HPO_4$, pH 8.4 (35:65), and the flow rate was 1.5 ml/min. Cimetidine and IS were detected at 228 nm.

*Experimental procedures:* The animals in the cigarette smoke inhaling and the non-smoking restrained control groups were held one each in an animal holder of the smoking machine. The animals in the cigarette smoke inhaling group were exposed for 10 min to smoke in the inhalation chamber after drug administration, and the non-smoking restrained control rats were not exposed. The animals in the non-smoking unrestrained group were not held in the animal holder and not exposed to the cigarette smoke. All animals were bled and 60 $\mu$l blood samples were collected repeatedly from the tail vein of each animal and cimetidine plasma levels were measured using HPLC.

The pharmacokinetic parameters, the area under the plasma concentration-time curve (AUC) and the mean residence time (MRT) for each animal were estimated by model-independent moment analysis using a personal computer program /6,7/.

*Statistics:* Results were evaluated statistically using Student's two-tailed t-test.

## RESULTS

The retention times of cimetidine and the IS in the HPLC chromatogram were 4.7 and 7.1 min, respectively. There was no marked interfering peak on the chromatogram of blank plasma and peaks were well separated.

The influences of cigarette smoke inhalation on plasma level of cimetidine when administered orally, intraperitoneally or intravenously are shown in Figures 1, 2 and 3, respectively.

The plasma level of cimetidine administered orally at a dose of 50 mg/kg was lower in the drug absorption phase in the "L-P" and the "M-S" cigarette smoke inhaling groups (especially in the "L-P" cigarette smoke inhaling group) than in the non-smoking restrained control and the non-smoking unrestrained groups (Fig. 1). There was no difference between the non-smoking restrained control group and the non-smoking unrestrained group. Cimetidine plasma levels in the non-smoking restrained control group increased after drug administration, and reached approximately 5 $\mu$g/ml after 1 h

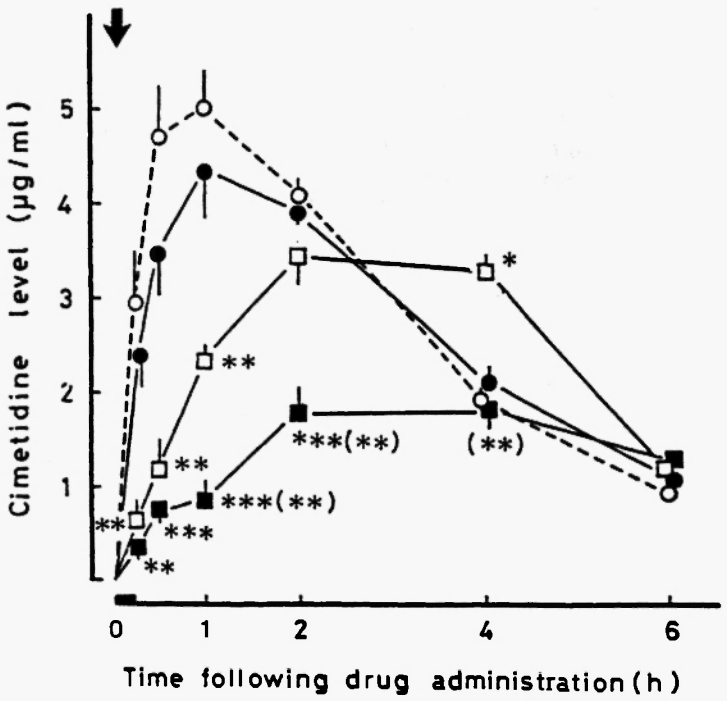


**Fig. 1:** Influence of cigarette smoke inhalation on plasma levels of cimetidine administered orally (50 mg/kg) to rats. Each point indicates the mean with S.E.M. (vertical bars). o—o, non-smoking unrestrained group (n=8); ●—●, non-smoking restrained control group (n=9); □—□, "Mild-Seven●" cigarette smoke inhaling group (n=5); ■—■, "Long-Peace●" cigarette smoke inhaling group (n=5). The solid block line and arrow indicate the period of cigarette smoke inhalation and the drug dosing time, respectively. Significant differences in comparison to the non-smoking restrained control group at * $p < 0.05$, ** $p<0.01$ and *** $p<0.001$, and to the "Mild-Seven●" cigarette smoke inhaling group at (**) $p<0.01$.

then gradually decreased to approximately 1 μg/ml after 6 h. There were significant differences after 0.25, 0.5, 1 and 2 h ($p<0.01$ at 0.25 h and $p<0.001$ at 0.5, 1 and 2 h) between the "L-P" cigarette smoke inhaling group and the non-smoking restrained control group, and after 0.25, 0.5 and 1 h between the "M-S" cigarette

smoke inhaling group and the non-smoking restrained control group ($p<0.01$). In contrast, plasma level after 4 h in the "M-S" cigarette smoke inhaling group was higher than in the non-smoking restrained control group ($p<0.05$). Compared with the "M-S" cigarette smoke inhaling group, cimetidine plasma levels in the "L-P" cigarette smoke inhaling group were also lower after 1, 2 and 4 h ($p<0.01$). For the pharmacokinetic parameters, the AUC value in the "L-P" cigarette smoke inhaling group was lower and the MRT values in the "L-P" and the "M-S" cigarette smoke inhaling groups were higher than in the non-smoking restrained control group, as shown in Table 1. There were significant differences in the MRT values between these groups ($p<0.001$). The AUC value in the "L-P" cigarette smoke inhaling group was significantly lower than in the non-smoking restrained control group ($p<0.01$), but not in the "M-S" cigarette smoke inhaling group. The AUC value in the "M-S" cigarette inhaling group was higher than that in the "L-P" cigarette smoke inhaling group ($p<0.01$).

The plasma level of cimetidine in the non-smoking restrained control group when administered intraperitoneally at a dose of 25 mg/kg decreased gradually from 0.25 h after administration and had almost disappeared after 2 h, and that in the "L-P" cigarette smoke inhaling group also decreased gradually as in the non-smoking restrained control group (Fig. 2). There were no differences between the non-smoking restrained control and the non-smoking unrestrained rats. For pharmacokinetic parameters, there were no differences in the AUC and the MRT values between the three groups.

The plasma levels of cimetidine in the "L-P" cigarette smoke inhaling, the non-smoking restrained control and the non-smoking unrestrained groups when administered intravenously at a dose of 10 mg/kg, also decreased from 0.17 h after administration (Fig. 3). There was no significant difference in the drug plasma level, nor in the AUC and MRT values, between these three groups.

## DISCUSSION

It is important to know whether cigarette smoking influences drug therapy, and particular attention should be given to drug plasma levels of drugs having narrow therapeutic ranges. There are numerous clinical studies related to the influence of cigarette smoke on the pharmacokinetics of such drugs as theophylline, lidocaine, phenothiazines, benzodiazepines, tricyclic anti-

TABLE 1

The area under plasma concentration-time curve (AUC) and the mean residence time (MRT) of cimetidine in the cigarette smoke inhaling rats, the non-smoking restrained control rats and the non-smoking unrestrained rats

| Parameters / Groups | n | AUC ($\mu$g•h/ml) | MRT (h) |
|---|---|---|---|
| *oral administration* | | | |
| Non-smoking unrestrained | 8 | 17.23±0.80 | 2.22±0.11 |
| Non-smoking restrained control | 9 | 16.44±0.83 | 2.42±0.11 |
| "M-S" C. smoke inhaling | 5 | 15.70±0.78 | 3.05±0.05*** |
| "L-P" C. smoke inhaling | 5 | 8.93±1.12** (**) | 3.33±0.11*** |
| *i.p. administration* | | | |
| Non-smoking unrestrained | 6 | 5.43±0.09 | 0.65±0.01 |
| Non-smoking restrained control | 5 | 5.61±0.81 | 0.65±0.01 |
| "L-P" C. smoke inhaling | 6 | 4.75±0.15 | 0.65±0.01 |
| *i.v. administration* | | | |
| Non-smoking unrestrained | 3 | 11.68±1.44 | 0.95±0.04 |
| Non-smoking restrained control | 3 | 12.94±0.99 | 0.90±0.05 |
| "L-P" C. smoke inhaling | 3 | 13.67±0.78 | 0.96±0.01 |

AUC values were calculated 0 to 6 h after oral administration, 0 to 4 h after intraperitoneal administration, and 0 to 3 h after intravenous administration. Each value represents the mean ± S.E.M. n, number of animals used; "L-P" C., "Long-Peace®" cigarette; "M-S" C., "Mild-Seven®" cigarette. Significant difference in comparison to the non-smoking restrained control group at ** $p < 0.01$ and *** $p<0.001$. Asterisks in parentheses were compared with the "M-S" cigarette smoke inhaling group at ** $p<0.01$.

depressants, and pentazocine /8-12/. Theophylline is eliminated more rapidly in smokers than in non-smokers, and smoking shortens its half-life, increases clearance, and reduces levels in the blood more rapidly /9-11/. Drowsiness induced by phenothiazines or benzodiazepines is less likely to occur in smokers. The bioavailability of oral lidocaine is reduced in smokers, and plasma

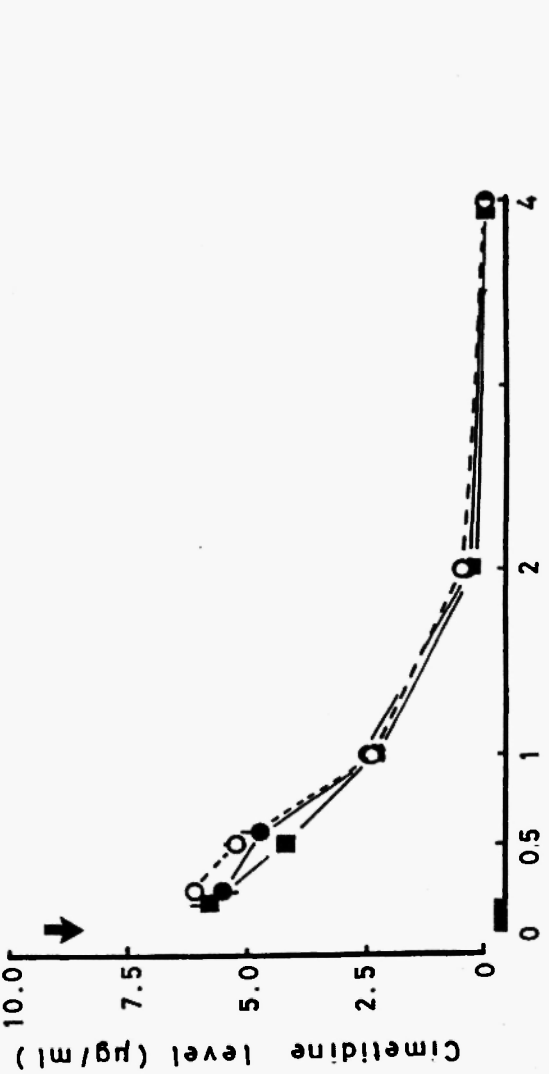


**Fig. 2:** Influence of cigarette smoke inhalation on plasma levels of cimetidine administered intraperitoneally (2.5 mg/kg) to rats. Each point indicates the mean with S.E.M. (vertical bars). o—o, non-smoking unrestrained group (n=6); ●—●, non-smoking restrained control group (n=5); ■---■, "Long-Peace®" cigarette smoke inhaling group (n=6). The solid block line and arrow indicate the period of cigarette smoke inhalation and the drug dosing time, respectively.

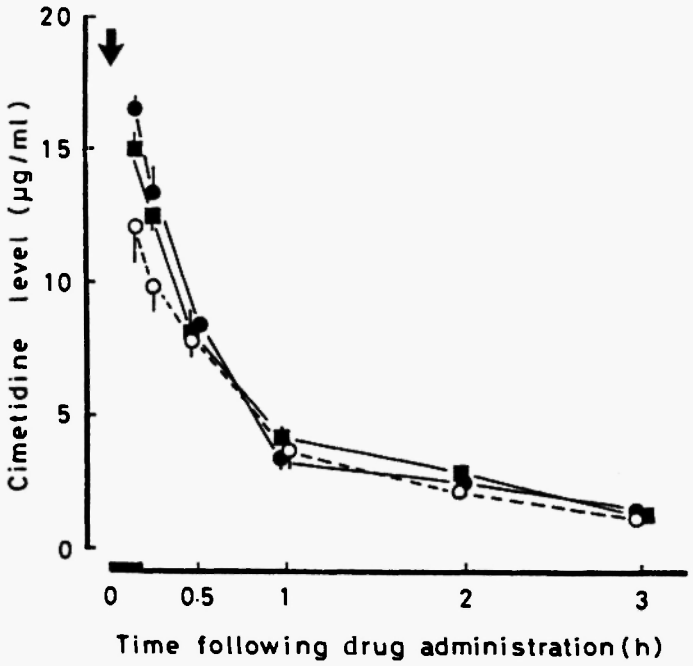


**Fig. 3:** Influence of cigarette smoke inhalation on plasma levels of cimetidine administered intravenously (10 mg/kg) to rats. Each point indicates the mean with S.E.M. (vertical bars). o—o, non-smoking unrestrained group (n=3); ●—●, non-smoking restrained control group (n=3); ■—■, "Long-Peace®" cigarette smoke inhaling group (n=3). The solid block line and arrow indicate the period of cigarette smoke inhalation and the drug dosing time, respectively.

levels of amitriptyline, desipramine, imipramine, and nortriptyline in smokers are lower than in non-smokers. In addition, smokers required larger doses of pentazocine than non-smokers when pentazocine was used as a supplement for nitrous oxide anesthesia /9/. However, it is not yet clear whether cigarette smoking influences the pharmacokinetics of many other drugs used in therapy.

Cimetidine is widely used as a therapeutic agent for the treatment of duodenal and gastric ulcers, and its therapeutic effect

is related to plasma level /2/. In the present study, the elevation of cimetidine plasma level after oral administration was suppressed by inhalation of two kinds of cigarette smoke, notably by the "L-P" cigarette smoke with a high nicotine•tar content. The MRT values in the "L-P" and the "M-S" cigarette smoke inhaling groups were higher than in the non-smoking restrained control group, and the AUC value in the "L-P" cigarette smoke inhaling group was lower. However, there was no difference in the AUC value between the "M-S" cigarette smoke inhaling and the non-smoking restrained control groups.

The cimetidine plasma levels when administered parenterally, intraperitoneally or intravenously, were not influenced by the inhalation of cigarette smoke. These results indicate that inhalation of cigarette smoke influences the plasma level of cimetidine when administered orally, but not parenterally. That is, the drug absorption process from the gastrointestinal tract may be influenced by cigarette smoking.

Cimetidine is a polar hydrophilic compound. Its absorption from the gastrointestinal tract is good when administered orally /1/, and its partition coefficient in octanol is 0.1 at pH 5, 1.5 at pH 7 and 2.7 at pH 9.5. It is said that cigarette smoking inhibits the secretion of pancreatic fluid and bicarbonate from the pancreas, resulting in a decrease in the pH in the gastrointestinal tract /13-15/. When considering the partition coefficient of cimetidine, its lipid solubility seems also to be lowered by the decrease in medium pH. Accordingly, when the pH in the gastrointestinal tract is decreased by cigarette smoking, the decrease in cimetidine absorption from the gastrointestinal tract may be anticipated. It is also said that smoking causes a decrease in gastrointestinal mucosal blood flow as well as in motility /16-18/. These changes may also cause a decrease and/or delay of cimetidine absorption from the gastrointestinal tract. Further studies such as influences of long-term cigarette smoke inhalation on drug therapy are needed.

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