Effects of Moxifloxacin on Serum Glucose Concentrations in Rats

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Moxifloxacin, a fluoroquinolone antimicrobial agent, has been reported to cause serum glucose abnormalities such as hyper- and hypoglycemia. The purpose of the present study was to investigate the effect of moxifloxacin on serum glucose concentrations in rats. Rats were intravenously injected with moxifloxacin and samples of their arterial blood were collected periodically. Serum glucose concentrations increased with moxifloxacin at 100 mg/kg, and temporal elevations were observed in serum epinephrine and histamine concentrations. On the other hand, intravenous injection of moxifloxacin at 75 mg/kg did not affect serum glucose, epinephrine, or histamine concentrations. Serum immunoreactive insulin concentrations remained unchanged by moxifloxacin both at 75 and 100 mg/kg. In conclusion, moxifloxacin can induce histamine release, leading to an increase in serum epinephrine concentrations and hyperglycemia.

Key words moxifloxacin; hyperglycemia; histamine; epinephrine; rat

Moxifloxacin, a novel fluoroquinolone antimicrobial agent, has a broad spectrum of activity against Gram-positive, Gram-negative, and anaerobic pathogens, and has been widely used for the treatment of various infectious diseases both in outpatients and inpatients. However, it has been reported to cause abnormalities in blood glucose concentrations such as hypoglycemia and hyperglycemia.

Abnormalities in serum glucose concentrations are well-documented adverse effects of fluoroquinolones. Previously, enoxacin, lomefloxacin, norfloxacin, ofloxacin, levofloxacin, ciprofloxacin, and gatifloxacin have been reported to cause hypoglycemia, and ofloxacin and gatifloxacin have been reported to cause hyperglycemia. It has been thought that gatifloxacin-induced glucose abnormalities are more frequent than those by other fluoroquinolones. In Japan, an Emergency Safety Information statement about gatifloxacin-induced hypoglycemia and hyperglycemia was issued in 2003, and gatifloxacin was recently withdrawn from the market. It is inferred that the occurrence of dysglycemia in most of fluoroquinolones other than gatifloxacin is infrequent. However, as these adverse effects sometimes require hospitalization and are life-threatening, we need to pay attention to the occurrence of dysglycemia in using most of fluoroquinolones.

Since some fluoroquinolones are known to stimulate the secretion of insulin by blocking the ATP-sensitive potassium channels of pancreatic β-cells, it is thought that fluoroquinolone-induced hypoglycemia is caused by an increase in insulin secretion. As for hyperglycemia, it has been reported that, in animal studies, oral administration of gatifloxacin at 270 or 810 mg/kg/d for 1 month caused the vacuolation of pancreatic β-cells. In addition, it has been reported that gatifloxacin can decrease islet insulin content by using isolated pancreatic islets, suggesting that repeated doses of gatifloxacin can reduce serum insulin concentrations by a disorder in pancreatic β-cells. Previously, we reported that a single intravenous injection of gatifloxacin and levofloxacin, which induce an increase or decrease in serum glucose concentrations that was dose dependent, and that increased release of histamine led to an increase in epinephrine secretion and hyperglycemia.

In the present study, we investigated the effect of moxifloxacin on serum glucose concentrations in rats in order to clarify the mechanisms of moxifloxacin-induced abnormalities in serum glucose concentrations.

MATERIALS AND METHODS

Animals Male Wistar rats (Japan SLC, Hamamatsu, Japan) weighing 220–290 g were used. Rats were housed in a controlled environment and fasted overnight before the experiment. They had indwelling cannulas implanted in the left carotid artery and jugular vein under light ether anesthesia. Animal experiments were performed in accordance with The Guidelines for Animal Experiments of Tokyo Medical and Dental University.

Materials Moxifloxacin hydrochloride was obtained from Bayer HealthCare AG (Leverkusen, Germany). Gatifloxacin hydrate as an internal standard was obtained from Kyorin Pharmaceutical Co., Ltd. (Tokyo, Japan). All other chemicals were of analytical grade.

Effect of Moxifloxacin on Serum Glucose, Epinephrine, Histamine, and Immunoreactive Insulin Concentrations in Rats Rats received an intravenous injection of moxifloxacin at a dose of 75 or 100 mg/kg through the cannula. Blood samples were obtained periodically to determine serum glucose, epinephrine, histamine, and immunoreactive insulin concentrations. An equivalent volume of normal saline was injected into control rats.

For the pharmacokinetic analysis of moxifloxacin, rats received an intravenous injection of moxifloxacin at a dose of 10, 75, or 100 mg/kg, and blood samples were obtained until 4 h to determine serum moxifloxacin concentrations. Pharmacokinetic parameters were analyzed with a two compartment model.

Analytical Methods Serum glucose concentrations were determined by the glucose oxidase method using a Glucose CII-test Wako (Wako Pure Chemical Industries, Ltd., Osaka, Japan). Serum immunoreactive insulin concentrations were determined by enzyme immunoassay using a Glazyme Insulin-EIA TEST (Wako Pure Chemical Industries, Ltd.). Serum epinephrine and histamine concentrations were determined by the immunometric method using a Screening Assay Kit EIA (Wako Pure Chemical Industries, Ltd.).

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determined by high performance liquid chromatography as previously described, and 400 and 100 μL of serum were used for epinephrine and histamine assays, respectively.

Serum concentrations of moxifloxacin were determined by high performance liquid chromatography with UV detection, and the method for the determination of serum gatifloxacin was used.23

Statistical Methods All data represent the mean±S.E. Statistical evaluations were performed using Tukey–Kramer’s multiple comparison test. Differences were considered significant at p<0.05.

RESULTS

Changes in serum glucose concentrations after intravenous injection of moxifloxacin were shown in Fig. 1A. Serum glucose concentrations significantly increased 5, 15, and 30 min after the injection of moxifloxacin at 100 mg/kg, and the maximal concentration was 140±4 mg/dL at 15 min after the injection. On the other hand, serum glucose concentrations remained unchanged by the injection of moxifloxacin at 75 mg/kg.

Changes in serum histamine and epinephrine concentrations after intravenous injection of moxifloxacin were shown in Figs. 1B and C, respectively. Intravenous injection of moxifloxacin at 100 mg/kg caused temporal increases in serum histamine and epinephrine concentrations. The maximal concentration of serum histamine after the injection of moxifloxacin at 100 mg/kg was 80±13 ng/mL at 5 min, and the maximal concentration of serum epinephrine was 0.68±0.05 ng/mL at 15 min. Serum histamine and epinephrine concentrations were not affected by the injection of moxifloxacin at 75 mg/kg.

Serum immunoreactive insulin concentrations after intravenous injection of moxifloxacin were shown in Fig. 1D. They remained unchanged by the injection of moxifloxacin at 75 or 100 mg/kg.

Time profiles of the serum concentration of moxifloxacin after intravenous injection were shown in Fig. 2. Pharmacokinetic parameters were summarized in Table 1. Total body clearance and the volume of distribution in the central compartment after the injection of moxifloxacin at 100 mg/kg was significantly lower than that after the injection of moxifloxacin at 10 mg/kg.

Fig. 1. Serum Concentrations of Glucose (A), Histamine (B), Epinephrine (C), and Immunoreactive Insulin (D) after Intravenous Injection of Saline (○, n=6), Moxifloxacin at 75 mg/kg (▲, n=7), or Moxifloxacin at 100 mg/kg (■, n=6) in Rats

Each point represents the mean±S.E. *p<0.05 significantly different from the control group (Tukey–Kramer’s test).
DISCUSSION

Fluoroquinolone antimicrobial agents are generally safe and well tolerated but some of them can cause severe dysglycemia, although this is rare. Hypoglycemia was reported with many fluoroquinolones, while hyperglycemia was reported with a few such as gatifloxacin, ofloxacin, a racemic compound of levofloxacin, and moxifloxacin. In a pooled-analysis of phase II/III clinical trials and postmarketing studies, it has been reported that the administration of moxifloxacin has no clinically relevant effect on blood glucose homeostasis because the incidence was comparable in the moxifloxacin and comparator group. However, other fluoroquinolones such as levofoxacin were contained in the comparator antimicrobials of this report, suggesting that the risk of dysglycemia induced by moxifloxacin could not be evaluated accurately. In the present study, we investigated the effect of moxifloxacin on serum glucose concentrations in rats. After intravenous injection of moxifloxacin at 100 mg/kg, serum glucose concentrations temporally increased (Fig. 1A). Serum histamine and epinephrine concentrations also increased by the injection of moxifloxacin at 100 mg/kg (Figs. 1B, C). We previously showed that a single intravenous injection of gatifloxacin at 100 mg/kg or levofloxacin at 300 mg/kg can induce histamine release, leading to increased epinephrine secretion and hyperglycemia. The present result was consistent with those of gatifloxacin and levofloxacin and suggests that moxifloxacin-induced histamine release can induce enhancements in epinephrine secretion, resulting in an increase in serum glucose concentrations.

In the previous study with gatifloxacin, the concentration of serum glucose increased by approximately 250 mg/dL 15 min after intravenous injection of gatifloxacin at 100 mg/kg, and the concentration of serum histamine increased by 600 mg/mL. In the present study, the concentration of serum glucose increased by approximately 140 mg/dL at 15 min after intravenous injection of moxifloxacin at 100 mg/kg, and the concentration of serum histamine increased by 80 mg/mL. These findings suggest that the capability of histamine release by moxifloxacin may be weaker than that by gatifloxacin. On the other hand, intravenous injection of levofloxacin at 200 and 300 mg/kg caused an increase in serum histamine concentrations in a dose-dependent manner, while 100 mg/kg did not affect serum epinephrine concentrations. Although the effect of levofloxacin at 100 mg/kg on serum histamine concentrations was not examined, moxifloxacin may induce histamine release at lower doses than levofloxacin.

Several studies to investigate the mechanism of fluoroquinolone-induced histamine release have been reported previously. Furuhata et al. showed that ciprofloxacin can induce the release of histamine from rat peripheral mast cells in a dose-dependent manner. Mori et al. reported that intravenous injection of levofloxacin and ciprofloxacin produced dose-related elevations in plasma histamine level in anaesthetized dogs and rats, and that, in vitro study, levofloxacin and ciprofloxacin induced non-cytotoxic secretion of histamine from canine or rat skin mast cells in a concentration-dependent manner. In addition, Mori et al. demonstrated that the mechanism of levofloxacin-induced histamine release may be closely linked to activation of pertussis toxin-sensitive G proteins. These findings suggest that moxifloxacin can also cause histamine release from mast cells.

Serum concentrations of immunoreactive insulin remained unchanged by intravenous injection of moxifloxacin at 75 or 100 mg/kg (Fig. 1D), and hypoglycemia was not observed under the present conditions (Fig. 1A). Our previous study with gatifloxacin and levofloxacin showed that an increase in insulin secretion occurred at lower drug concentrations than the increase in histamine release and epinephrine secretion; therefore, hypoglycemia was observed at low drug concentrations. The present result suggests that moxifloxacin, different from gatifloxacin and levofloxacin, caused an increase in histamine release and epinephrine secretion without affecting insulin secretion.

The present study was performed in fasted rats; hence, the fasting condition may affect the response of serum glucose concentrations. Bertrand et al. reported that intravenous injection of cibenzoline caused an increase in insulin and hypoglycemia at 1 mg/kg in fed rats, but at 3 mg/kg in fasted rats. Ghaly et al. reported that fluoroquinolones in a clinically relevant concentration range are not initiators, but rather enhancers of glucose-induced insulin secretion. Considering these findings, further investigation into the non-fasted condition is required to clarify moxifloxacin-induced hypoglycemia.

Total body clearance of moxifloxacin after the injection at
100 mg/kg was lower than that at 10 mg/kg (Table 1). Following intravenous injection, moxifloxacin is rapidly metabolized to acyl glucuronide and N-sulfate in the liver, unlike gatifloxacin and levofloxacin, which are mainly excreted by the kidneys. It has been reported that the rate of renal excretion of moxifloxacin in unchanged compound is 8.4% of the dose after intravenous injection in rats. These findings suggest that the conjugation of moxifloxacin in the liver may be saturated at a high dose of moxifloxacin, resulting in a decrease in total body clearance. Renal failure has been recognized as one of the risk factors for gatifloxacin-induced dysglycemia because serum concentrations of gatifloxacin were relatively high due to the delayed renal excretion of gatifloxacin. In moxifloxacin, severe hepatic impairment may be a risk factor for moxifloxacin-induced dysglycemia.

Diabetes mellitus is also recognized as a risk factor for gatifloxacin-induced hyper- and hypoglycemia because these adverse effects mainly occurred in patients with diabetes mellitus. Previously, we reported that gatifloxacin-induced histamine release and epinephrine secretion were not different between normal and diabetic rats, and that the shortage of insulin secretion can induce hyperglycemia at a lower drug concentration in diabetic rats. On the other hand, intravenous administration of moxifloxacin at 100 mg/kg induced histamine release and epinephrine secretion without affecting serum immunoreactive insulin concentrations. This result suggests that the effect of diabetes mellitus on drug-induced hyperglycemia may be different between gatifloxacin and moxifloxacin. Further investigation will be needed to clarify the effect of diabetes mellitus on moxifloxacin-induced dysglycemia.

In conclusion, moxifloxacin can induce histamine release, leading to an increase in serum epinephrine concentrations and hyperglycemia.

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