Co-administration of Magnesium Oxide Reduces the Serum Concentration of Hydrophobic Basic Drugs in Patients Treated with Antipsychotic Drugs

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INTRODUCTION

Polypharmacy and overdosing of antipsychotic drugs in patients with schizophrenia are serious problems,1,2 because they increase medical expenses and delay rehabilitation.3 As antipsychotic drugs suppress nerve excitation by blocking dopamine receptors in the brain, but they exhibit anticholinergic action as a side effect.4 Anticholinergic action suppresses intestinal motility and causes constipation.5 Laxatives are frequently administered concomitantly to patients. Magnesium oxide (MgO) is widely used as an inexpensive laxative. However, MgO, as a side effect, may be suppressed due to an increase in the stomach pH following MgO administration. Therefore, MgO might be suppressed due to an increase in the stomach pH following MgO administration. Therefore, MgO co-administration is better to avoid while taking antipsychotic drugs and anticholinergic drugs.

MgO reacts with the gastric acid to neutralize and raise the pH in the stomach.7 Therefore, MgO is used as an antacid. As antipsychotic drugs inhibit not only intestinal motility via anticholinergic action but also gastric acid secretion, it is predicted that the pH in the stomach of patients with schizophrenia may be higher than that in healthy subjects.

Because several antipsychotic drugs are lipophilic-basic-compounds with high lipid solubility and the solubility of their molecular form is very low, their solubility is remarkably decreased because of pH elevation in the stomach. Based on these results, it is predicted that drug absorption from the intestine and the drug concentration in the serum will decrease. It is highly important to clarify the effect of MgO administration on the serum drug concentration for effective, safe, and appropriate medication therapy. However, the relationship between MgO administration and the serum concentration of antipsychotic drugs in patients with schizophrenia has not been reported. Therefore, in the present study, we investigated the effect of MgO administration on the concentration of antipsychotic drugs in the blood of patients with schizophrenia. The serum concentrations of biperiden, zotepine, and risperidone were assayed using an LC/MS system. The correlation between the daily dose of MgO and the relative-drug-concentration (rCp) in each patient was examined. As the MgO dose was increased, the risperidone concentration decreased. The correlation coefficient decreased for risperidone, zotepine, and biperiden, in the same order. To clarify the difference in the suppression potency of MgO on the three drugs, the relationship between the physical properties and the correlation coefficients of each drug was carefully examined. A strong correlation was observed between the pKa and the correlation coefficient. Patients with schizophrenia are often prescribed antipsychotic drugs, which have anticholinergic action and tend to suppress gastric acid secretion. We concluded that basic drug absorption might be suppressed due to an increase in the stomach pH following MgO administration. Therefore, MgO co-administration is better to avoid while taking antipsychotic drugs and anticholinergic drugs.

Key words schizophrenia; acidity constant; anti-cholinergic action; gastric secretion; drug solubility

Participants The participants were all patients with schizophrenia admitted to the Heartful Kawasaki Hospital between June and October 2016, who had been administered the same medications repeatedly for more than a week. Written consent was obtained from all participants voluntarily prior to participation in this study. The study protocol was approved by the Ethics Review Board of Meiji Pharmaceutical University (Approval No.: 2806). To protect patient privacy, personal...
Conversion to Chlorpromazine  Conversion of antipsychotic drugs to chlorpromazine (CP) was calculated using the conversion formula.9)

Blood Collection and Measurements  Venous blood (10mL) was collected in the morning, after an overnight fast, before the administration of antipsychotic drugs with and without the co-administration of MgO.9 A portion of the sample was transferred to the Clinical Laboratory of Heartful Kawasaki Hospital for routine biochemical tests, and the remaining portion was transferred into another tube. The sample tube was transferred to the Laboratory of the Department of Drug Metabolism and Disposition, Meiji Pharmaceutical University for determining the drug concentration. Briefly, the blood samples were centrifuged at 1000×g for 5min to isolate the serum, which was then frozen and stored until further analysis. For serum drug concentration analysis, a five-fold volume of methanol was added to the serum isolated from patients, mixed, rested for 30–40 min, centrifuged at 5000×g for 1 min for deproteinization, and the supernatant was filtered using a membrane of 0.1-µm pore size.

The concentrations of biperiden, zotepine, and risperidone were assayed using an LC/MS system (Shimadzu LC-MS 2020, Japan). The assay conditions were as follows: column, C18-ODS (2×50 mm, Tosoh Corporation, Japan); mobile phase, gradient solution consisting of 20mM ammonium formate and acetonitrile (2–70%); flow rate, 0.2mL/min; mode of analysis, SIM measurement.

The serum Mg concentration was measured using the xylidyl blue method.10)

Relative Drug Concentration  Because the drug concentration in serum is affected by a patient’s body weight and dose amount, the actual measured drug concentration was corrected by the dose per kilogram body weight. The relative-drug-concentration [rCp((µg/L)/(mg/kg))] was calculated using the following formula: rCp = Cp/(D/Wt), where, Cp, Wt, and D represent the actual measured drug concentration (µg/L), body weight (kg), and daily drug dose (mg), respectively.

Effect of MgO Co-administration  Patients were classified into MgO co-administered group and non-administered group for each drug, and statistical analysis was performed to determine whether there was a difference in the rCp between these two groups for each drug.

Relationship between the Serum Mg Concentration and rCp  To clarify the effect of serum Mg concentration on the rCp, the relationship between the serum Mg concentration and rCp in patients was studied for each drug.

Table 1. Patients’ Profile

| MgO       | Biperiden | Zotepine | Risperidone |
|-----------|-----------|----------|-------------|
|           | without   | with     | without     | with     | without   | with     |
| Male/Female | 4/5       | 13/26    | 9/4         | 15/19    | 4/4       | 6/15     |
| Age (y.o.)  | 60±18     | 60±12    | 61±11       | 59±11    | 59±14     | 60±14    |
| range      | 37–80     | 30–84    | 34–80       | 39–76    | 34–81     | 40–82    |
| Body weight (kg) | 57.4±18.3 | 55.1±11.0 | 59.4±10.9  | 55.1±10.2 | 60.0±14.3 | 54.2±11.4 |
| Chlorpromazine equivalent dose (mg) | 1104±1109 | 1611±1103 | 890±601   | 1617±1305 | 1554±1302 | 1774±1484 |
| range      | 174–4173  | 300–4236 | 94–1990   | 150–5906 | 174–4173  | 300–4236 |
| Patients with abnormal hepatic function* | 0         | 0        | 0          | 0        | 0          | 0        |

Mean ± standard deviation. *Normal range of hepatic function, AST: 7–38IU/L; ALT: 4–44IU/L.
Fig. 1. Effect of MgO Co-administration on the rCp of Biperiden (A), Zotepine (B), and Risperidone (C)

Fig. 2. Correlation of the Serum Mg Concentration with the rCp of Biperiden (A), Zotepine (B), and Risperidone (C)

The horizontal and vertical lines indicate the serum Mg concentration and the rCp of each drug. The straight line and curve in each graph indicate the regression line and the 95% confidence limit. The correlation coefficients of biperiden, zotepine, and risperidone were 0.23, 0.06, and −0.06, respectively.

Fig. 3. Correlation between the Daily Dose of MgO and the rCp of Biperiden (A), Zotepine (B), and Risperidone (C)

The horizontal and vertical lines indicate the daily dose of MgO and rCp of each drug. The straight line and curve in each graph indicate the regression line and the 95% confidence limit. The correlation coefficients of biperiden, zotepine, and risperidone were −0.02, −0.21, and −0.40, respectively.
pressed by MgO co-administration. However, if the factor affecting the pharmacokinetics of a drug is the Mg concentration, either MgO dose or Mg concentration in the serum is considered to affect the pharmacokinetics of a drug. If the factor affecting the pharmacokinetics of a drug is MgO dose, MgO acts on the absorption process of the drug from the intestinal tract. However, if the factor affecting the pharmacokinetics of the drug is the Mg concentration of the serum, MgO acts on the dynamics of the drug in the body (namely, distribution, metabolism, and excretion). As a strong correlation was observed between the MgO dose and rCp in this study, we considered that MgO mainly affected the absorption process of the drug. By the way, the serum drug concentration was not detected in some patients. As they were hospitalized and taking medications repeatedly, it is considered that the drug concentrations could not be detected due to differences in the dosage and/or the pharmacokinetic properties among the patients.

It is known that the drug concentration at steady state depends on the total body clearance. It is also widely known that the hepatic clearance and liver weight decrease with aging. The three drugs used in this study are metabolized by the liver. As the hepatic clearance is considered proportional to the liver weight, the rCp was corrected by liver weight or liver weight ratio. However, there was no improvement in the correlation between the corrected rCp and MgO dose and Mg concentration. The following can be considered as factors that contributed to these results. The percent of lipid in the body increases with aging and therefore the distribution volume of the lipophilic drug increases with age. In addition, the hepatic clearance decreases with age. It is speculated that the increase in the volume of distribution and the decrease in hepatic clearance of the drugs negate each other; hence, the influence of liver weight or liver weight ratio on the rCp was not observed.

Several factors may contribute to the mechanism by which the pK_a of a drug is related to the intestinal drug absorption inhibition potency of co-administered MgO. The following three factors are considered to be associated with it: 1) the three drugs used in this study are hydrophobic basic drugs, 2) their pK_a is 6 or more, and 3) each patient continued to take antipsychotic drugs.

Generally, the ratio between the molecular-form and the ion-form of a drug is determined by Henderson–Hasselbalch equation. The ion-form drugs are generally considered to be water-soluble. If the solubility of the molecular form is 1, basic drug solubility increases exponentially when the pH of the solution is lower than the pK_a. In the case of the drug used in this study, the theoretical solubility changes based on the pH profile as shown in Fig. 4. Usually, the pH in the stomach of a healthy person is 1 to 3. Even if MgO is administered to a healthy person, risperidone is known to be metabolized by MgO co-administration.

**DISCUSSION**

In this study, we examined the effect of MgO co-administration on the serum drug concentration in patients with schizophrenia. We found that the serum concentrations of basic drugs decrease in proportion to the MgO dose. Moreover, a strong correlation was observed between the correlation coefficient (MgO dose vs. rCp) and the pK_a of the drugs studied. The serum drug concentration is determined by the dynamics of drug in the four processes, namely, absorption, distribution, metabolism, and excretion. When MgO affects drug concentration, either MgO dose or Mg concentration in the serum is considered to affect the pharmacokinetics of a drug. If the factor affecting the pharmacokinetics of a drug is MgO dose, MgO acts on the absorption process of the drug from the intestinal tract. However, if the factor affecting the pharmacokinetics of the drug is the Mg concentration of the serum, MgO acts on the dynamics of the drug in the body (namely, distribution, metabolism, and excretion). As a strong correlation was observed between the MgO dose and rCp in this study, we considered that MgO mainly affected the absorption process of the drug. By the way, the serum drug concentration was not detected in some patients. As they were hospitalized and taking medications repeatedly, it is considered that the drug concentrations could not be detected due to differences in the dosage and/or the pharmacokinetic properties among the patients.

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**Table 2. Comparative List of the Physical Properties and Correlation Coefficients of Three Drugs**

| Physical Property                  | Biperiden | Zotepine | Risperidone |
|-----------------------------------|-----------|----------|-------------|
| Correlation coefficient (rCp vs. MgO dose) | −0.02     | −0.21    | −0.4        |
| Correlation coefficient (rCp vs. Mg conc) | 0.23      | 0.06     | −0.06       |
| Molecular weight                  | 311.46    | 331.86   | 410.48      |
| pK_a                              | <6.2      | 7        | 8.24        |
| Solubility (mg/L)                 | 25.1      | 0.8      | 2.8         |
| Partition coefficient (Log)       | 4.25      | 4.51     | 2.5         |
| Melting point (°C)                | 114       | 91–94    | 170         |
| Bioavailability (%)               | 87        | 87       | 70          |
| Protein binding ratio (%)         | 60        | 97       | 88          |
| Main elimination route            | Hepatic metabolism | Hepatic metabolism | Hepatic metabolism |
| Volume of distribution (L/kg)     | 50–60     | 109      | 1–2         |
| Half life (h)                     | 18–24     | 18–19    | 4–24        |
in the liver and converted to paliperidone. As the amount of metabolites varies depending on the genetic type of the metabolic enzyme, in this study we limited only to measure the parent compound. In the stomach, the pH is lower than 6. The three drugs may completely dissolve at a pH lower than this. However, in the case of the patients in this study, gastric acid secretion was significantly suppressed by the antipsychotic drugs administered, and the pH in the stomach was increased to 6–7. When the pH was increased further to 8–9 by MgO co-administration, the solubility of risperidone decreases to approximately one hundredth as compared with that at pH 6–7. However, the solubility of zotepine and biperiden decreased by about one-tenth and half, respectively. This phenomena corresponded well with the results of the present study. It is considered that the pH in the stomach is increased by the antipsychotic drugs administered, and that the pH in the stomach is further increased by MgO co-administration. Thus, the drug absorption in the intestine is suppressed by MgO co-administration. Moreover, polypharmacy and overdosing of antipsychotics are induced in patients with schizophrenia. To avoid this vicious cycle, the co-administration of MgO to patients with schizophrenia should be suppressed or other laxatives should be prescribed.

We believe that it is important to clarify the pharmacokinetic parameters of each drug. However, the participants were hospitalized patients with schizophrenia, and changing the administration route or dosage of drugs may adversely affect the patients’ therapeutic outcome. Furthermore, monitoring the stomach pH in the patients is important to clarify whether our consideration is valid or not. However, in order to monitor the stomach pH of a patient, it is necessary to attach a special device to the patient. These treatments are expected to cause mental and physical stresses to the patients. From the perspective of effective and safe medication therapy and ethics, we believe that it is extremely difficult to perform these studies on patients with schizophrenia.

Conflict of Interest The authors declare no conflict of interest.

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