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ORIGINAL INVESTIGATION

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# Pharmacokinetic-pharmacodynamic modeling of risperidone effects on electroencephalography in healthy volunteers

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**Abstract** *Rationale*: CNS-active drugs produce specific electroencephalographic changes and the concentration-effect relationship of antipsychotics may be elucidated by adopting electroencephalography (EEG) as an effect measurement tool. *Objective*: The purpose of the present study was to determine the concentration-effect relationship of risperidone by assessing the EEG effect after oral administrations of single dose risperidone in healthy young males. *Methods*: Nine healthy male volunteers received a 1 mg single oral dose of risperidone according to a placebo controlled crossover design. Plasma levels of risperidone and its active metabolite 9-hydroxyrisperidone were measured by radioimmunoassay. Quantitative EEG parameters were obtained for each of four frequency bands through spectral EEG analysis. The difference in the absolute power in the delta frequency band for the F3 lead between risperidone and placebo was used as a drug effect parameter. For pharmacokinetic-pharmacodynamic modeling, the hypothetical effect compartment kinetically linked to plasma by a first-order process was postulated. All curve fittings were done with the non-linear curve-fitting program NONLIN. *Results*: Our results showed that absolute powers in delta and theta frequency bands were higher for risperidone administration than for placebo at all EEG leads, and the maximum effects were detected at about 3 h after administration of the drug. The hysteresis loop was observed in the plot of plasma concentration of risperidone or sum of risperidone and 9-hydroxyrisperidone ($C_p$) versus EEG effect for each subject. A linear model adequately described the relationship between the effect compartment concentrations ($C_e$) and EEG effects, and the two limbs of hysteresis in the $C_p$-effect plot were collapsed in the $C_e$-effect plot for risperidone or risperidone plus 9-hydroxyrisperidone. *Conclusion*: The increases of absolute power for delta and theta frequency bands of EEG were induced by single oral administration of risperidone. The linear PK-PD model fit well with the relationship between effect compartment concentrations ($C_e$) and EEG effects of risperidone.

**Key words** Risperidone · 9-Hydroxyrisperidone · Antipsychotic · Pharmacokinetic · EEG · Pharmacokinetic-pharmacodynamic model · PK-PD

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## Introduction

Both pharmacodynamic considerations for concentration-effect relationship and pharmacokinetic information for drug dose-concentration are necessary to determine the proper drug dose and administration interval (Holford and Sheiner 1981). It is possible to analyze the relationship between the plasma drug concentration and the drug effect using only a pharmacodynamic model (Schwinghammer and Kroboth 1988), provided that the drug concentration in the effect site reaches an instant equilibrium with the plasma drug concentration and the effect of the drug appears just after it arrives at the effect site. For many drugs there is, however, a time delay between the plasma drug concentration and the drug effect and thus a pharmacokinetic-pharmacodynamic (PK-PD) model considering the delay should be considered. The time delay includes the time that it takes for a drug to move from plasma to action site and also to show its effect after binding

to its receptor (Holford and Sheiner 1981; Colburn 1998).

For drugs affecting the central nervous system (CNS), one of the most difficult issues in analyzing the drug concentration-effect relationship is measuring the drug effect on brain with an objective and qualitative variable (Mandema and Danhof 1990). CNS-active drugs produce specific electroencephalographic (EEG) changes depending on their pharmacological classes (Hermann and Irrgang 1983; Hermann and Schaerer 1986; Mandema and Danhof 1992). It is possible to obtain objective and continuous measurements of those changes using computerized quantitative EEG (QEEG) analysis. EEG is so sensitive that a very low concentration of drugs can influence EEG. QEEG analysis, therefore, has been accepted as a most valuable tool to assess the central effects of CNS active drugs on the brain (Hermann and Irrgang 1983; Herrmann and Schaerer 1986; Mandema and Danhof 1990). For humans, PK-PD modelings on drug effects measured with QEEG parameters have been performed for a number of CNS active drugs, such as ketamine (Schütler et al. 1987), etomidate (Schwilden et al. 1985; Arden et al. 1986), propofol (Schütler et al. 1986), thiopental (Hudson et al. 1983; Stanski et al. 1984; Homer and Stanski 1985), midazolam (Koopmans et al. 1988; Greenblatt et al. 1989), diazepam (Friedman et al. 1992), and phenytoin (Fink et al. 1979).

As for antipsychotics, there have been studies elucidating the direct relationships between plasma drug concentrations and EEG changes through correlation or regression analyses or analysis of variance (Buck et al. 1981; Wieneke et al. 1981; Czobor and Volavka 1992; Freudenreich et al. 1997). None of these studies, however, adopted the analysis of simultaneous PK-PD model considering not only the change in plasma drug concentration and EEG effect according to time course, but also the time delay between plasma drug concentration and EEG effect.

Risperidone is a novel benzisoxazole antipsychotic which strongly antagonizes dopaminergic $D_2$ and serotonergic 5-$HT_2$ receptors (Leysen et al. 1988; Megens et al. 1994). Clinical trials have shown risperidone to be effective in the treatment of the positive symptoms (hallucinations, delusional thinking, severe excitement and unusual behavior), the negative symptoms (anergy, apathy, lack of drive, social withdrawal), and depressive mood of schizophrenia with a low incidence of extrapyramidal side effects (Borison et al. 1992; Claus et al. 1992; Choumard et al. 1993). In humans, risperidone is metabolized mainly by the liver. The major pathways include, in the order of preference, 9-hydroxylation, *N*-dealkylation, and 7-hydroxylation (Huang et al. 1993). Standard pharmacology tests performed in rats and dogs showed 9-hydroxyrisperidone to be nearly equipotent to risperidone. Other metabolites did not exhibit significant pharmacologic activities (Van Beijsterveldt et al. 1994).

The purpose of this study was to determine the PK-PD characteristics of risperidone by assessing the EEG effects according to the changes of risperidone and its active metabolite 9-hydroxyrisperidone levels after oral administrations of single dose risperidone in healthy young males.

## Materials and methods

### Subjects

Nine healthy male volunteers (all medical students) participated in the study after each signed an informed consent form. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital, Korea. The average age (±SD) of the subjects was 22.1 ± 1.8 years (age range, 19–25 years) and average body weight and height were 69.3 ± 9.0 kg and 175.0 ± 4.3 cm, respectively. All subjects had been totally drug-free for at least 1 month, alcohol and/or caffeine-free for at least 1 week before drug administrations, and had no history of medical or psychiatric disease.

### Drug administration and blood sampling

According to a single-blind, placebo-controlled crossover design, the subjects were given an oral dose of 1 mg risperidone or placebo with 150 ml water at 9 a.m. At least 2 weeks elapsed between risperidone and placebo administration. Before each administration, subjects underwent an overnight fast of at least 10 h. A lunch was served 5 h after and a dinner 10 h after administration. The subjects did not smoke and did not drink coffee on the day of the experiment.

Blood samples (10 ml each) for risperidone and 9-hydroxyrisperidone measurements were obtained before drug administration and at 15 and 30 min and 1,2,3,4,6,8,12 and 24 h after drug administration. Venous blood samples were drawn with a catheter placed in a forearm vein that was kept patent with heparinized saline solution. Plasma was separated by centrifugation and frozen at – 20°C until the time of assay.

### Plasma concentration of risperidone and 9-hydroxyrisperidone

Plasma concentrations of risperidone and 9-hydroxyrisperidone were measured by radioimmunoassay method. Two kinds of radioimmunoassay (RIA-I, RIA-II) kits provided by Janssen Pharmaceutica Co. Belgium were used for radioimmunoassays. Detailed descriptions for the assay procedures are given in the instruction manuals for the measurement included in the kits (Janssen Biotech NV 1991).

### Drug effect measurement

For the recording of the EEG, 21 (Fpl, Fp2, Fpz, F3, F4, F7, F8, Fz C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, O2, Oz) silver chloride electrodes were placed according to the international 10-20 system. The monopolar montage, in which the arithmetic mean of both side ear electrodes ([A1+A2]/2) was adopted as the reference electrode, was used. All electrodes were fixed to the scalp with collodion, and impedance was maintained below 5 kΩ. The Cadwell Spectrum 32 was used for EEG recording (high frequency filter with cutoff frequency of 70 Hz, time constant of 0.3 s, and the sensitivity of 7.5 V/mm) and signal processing (sampling rate; 205/s). The

electro-oculogram was also measured to exclude the artifacts due to ocular or eye lid movements, using Fpz and electrode placed 1 cm below right temporal epicanthus. The EEG was recorded in a quiet room with dimmed light while the subject was awake, comfortably seated in a chair with the head leaning back and the eyes closed. The EEG was measured for 10 min before the drug administration and 15, 30 min, 1,2,3,4,6,8,12 and 24 h after the drug administration. During the day of the experiment, the subjects remained in the study unit. They were requested to remain awake till 12 h after drug administration, even during the inter-recording periods. They were allowed to read books during the inter-recording periods and constantly observed so that they did not doze off. They had a normal night's rest 12 h after drug administration and were requested to wake up 2 h before the last recording. The recorded EEG data were stored on an optical disk for analysis.

For subsequent EEG signal processing, 20 artifact-free epochs of 2.5 s duration were selected from each recording. The epoch selection was done visually, and EEG segments containing artifacts (muscle activity, ocular artifacts, and movement potentials) or manifesting a decrease in vigilance were rejected. The two basic criteria for recognizing drowsiness were (1) the dissolution and fragmentation of occipital alpha rhythm with a shift to the anterior regions, and (2) an enhanced frequency variation with polyrhythmic disintegration of resting EEG into slower and faster components (Bente 1979; Streitberg et al. 1987). The selected individual EEG epochs were subjected to signal processing which consists of fast Fourier transformation and spectral analysis. Absolute power, interhemispheric power asymmetry and interhemispheric coherence in the delta (0.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5), and beta (12.5–30) were obtained by spectral analysis. Absolute power means the actual electrical activity of a particular frequency band in each EEG lead. Interhemispheric power asymmetry means the percent ratio of electrical activity of each frequency band between left and right hemisphere (Fp1/Fp2, F3/F4, F7/F8, C3/C4, T3/T4, T5/T6, P3/P4, O1/O2). Interhemispheric coherence is the electrical phase difference between both hemispheres.

Wilcoxon sign rank test was performed to compare the EEG changes in each frequency band and each time point after risperidone administration with those after placebo administration.

## Data analysis

### *Pharmacokinetic analysis*

Curve fitting was done with the non-linear curve-fitting program NONLIN (Metzler et al. 1974). The plasma concentration-time data of risperidone or sum of active moieties (risperidone plus 9-hydroxyrisperidone) from the nine individuals were fitted with a one-compartment open model (Gibaldi and Perrier 1975), using the equation:

$$C_p(t) = \frac{F \bullet D \bullet ka}{V_d \bullet (k_a - k_e)} \left(e^{-k_e(t-t_{lag})} - e^{-k_a(t-t_{lag})}\right)$$

in which $C_p(t)$ is the risperidone or active moiety plasma concentration at time t, t is time after dosage (h), F is bioavailability after oral administration, D is the dose of administrated drug (mg), $V_d$ is the volume of distribution (L), $k_a$ is the absorption rate constant ($h^{-1}$), $k_e$ is the elimination rate constant ($h^{-1}$), and $t_{lag}$ is the lag time [i.e., the time between drug administration and the start of drug absorption (h)]. Because bioavailability (F) is not known after oral intake for each subject, the ratio between $V_d$ and F (designated as $V_d/F$) is used.

### *Pharmacodynamic parameter*

To describe the effect of risperidone on the EEG, the difference ($\Delta$) in absolute power in delta frequency band between risperidone and placebo administration was used. There were no differences in the course of the EEG effects between the leads on the right-hand and left-hand sides. Therefore, for the analysis presented in this article, the F3 lead was chosen arbitrarily.

### *PK-PD modeling*

To describe the time course of the effect, a hypothetical effect compartment was included in the pharmacokinetic-pharmacodynamic (PK-PD) model (Holford and Sheiner 1981), thus accounting for the possibility of a delay between plasma concentration and EEG effect. Drug moves from plasma to this hypothetical effect compartment according to the first-order process:

$$C_e(t) = \frac{D \bullet k_a \bullet k_{eo}}{V_d/F} \left( \frac{e^{-k_{et}}}{(k_a - k_e)(k_{eo} - k_e)} + \frac{e^{-k_{at}}}{(k_e - k_a)(k_{eo} - k_a)} + \frac{e^{-k_{eot}}}{(k_e - k_{eo})(k_a - k_{eo})} \right)$$

In this equation, $C_e(t)$ is the drug concentration in the effect compartment at time t (ng/ml) and $k_{eo}$ is the rate constant for elimination of drug from the effect compartment ($h^{-1}$). The smaller the time delay between plasma drug concentration change and drug effect, the higher value of $k_{eo}$ is obtained. The parameter indicating the time delay, $t_{1/2\text{-}keo}$ is defined as $0.693/k_{eo}$. The other parameters are the pharmacokinetic parameters described above. The following linear model was used to describe the relationship between the effect compartment risperidone or risperidone plus 9-hydroxyrisperidone concentration and the drug effect:

$$E(t) = A \bullet C_e(t) + B$$

In this equation, E(t) is the value of the drug effect (effect on EEG) at time t, and A is the slope and B is the intercept of the linear model. All curve fitting was done with the non-linear curve fitting program NONLIN, and A,B, and $k_{eo}$ values of each subject were obtained.

# Results

## Pharmacokinetic profile

The plasma risperidone or active moiety (risperidone plus 9-hydroxyrisperidone) concentration-time data fit well with the one-compartment open model in all nine individual subjects. The pharmacokinetic parameters of risperidone and active moiety based on the compartmental analysis are listed in Table 1.

## QEEG change after risperidone administration

The absolute power of delta and theta frequency bands was significantly increased for all topographic brain areas after risperidone administration compared to placebo administration ($P < 0.01$; Wilcoxon sign rank test). Figures 1 and 2 represent the differences of absolute power at each time point between risperidone and placebo administration according to time course in delta and theta frequency bands, respectively (for F3 lead).

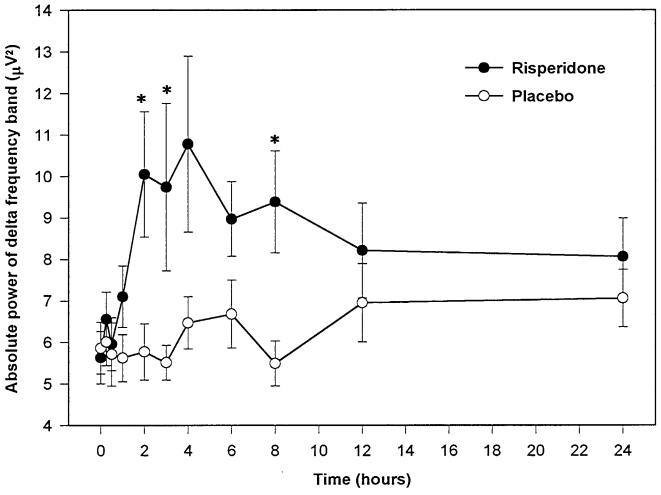


**Fig. 1** Comparison of absolute powers of delta frequency band in the F3 lead at each time point between risperidone (●) and placebo (○) administration ($n = 9$). *Vertical bars* show mean ± SE. $^{*}P < 0.05$, significantly increased compared with placebo administration (Wilcoxon sign rank test)

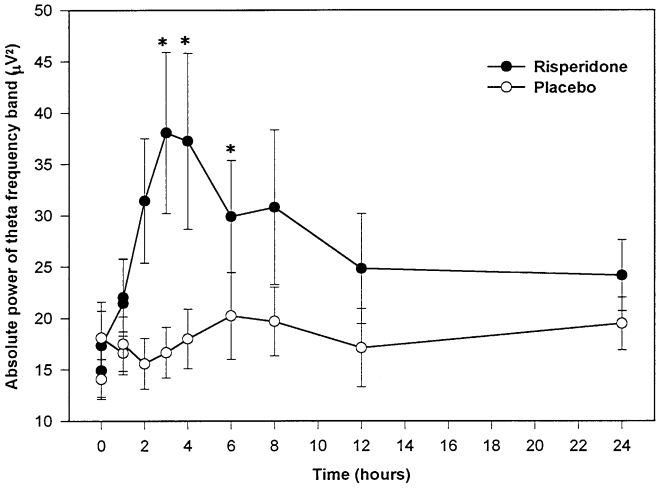


**Fig. 2** Comparison of absolute powers of theta frequency band in the F3 lead at each time point between risperidone (●) and placebo (○) administration ($n = 9$). *Vertical bars* show mean ± SE. $^{*}P < 0.05$, significantly increased compared with placebo administration (Wilcoxon sign rank test)

In alpha and beta frequency bands, there was no difference of absolute power for all topographic areas. For all frequency bands, the significant differences in interhemispheric asymmetry or interhemispheric coherence were not observed for the eight comparative topographic areas (Fp1/Fp2, F3/F4, F7/F8, C3/C4, T3/T4, T5/T6, P3/P4, and O1/O2) between risperidone and placebo administrations.

## PK-PD modeling

For all nine individual subjects, the counterclockwise hysteresis loops were observed in the risperidone or sum of active moieties plasma concentration-EEG effect, indicating the presence of the time delay between plasma concentration change and drug effect. The parameters of the linear model explaining the relationship between risperidone or risperidone plus 9-hydroxyrisperidone concentrations and EEG effects are listed in Table 1. The $t_{1/2\text{-keo}}$ is significantly smaller

**Table 1** Parameters of pharmacokintetic and pharmacokinetic-pharmacodynamic models of risperidone and risperidone plus 9-hydroxyrisperidone ($t_{max}$ time of peak concentration, $C_{max}$ peak plasma concentration, *CL* clearance)

| Parameters | Risperidone (Mean ± SD) | Risperidone plus 9-hydroxyrisperidone (Mean ± SD) |
|---|---|---|
| Pharmacokinetic | | |
| $k_a$(1/h) | 5.07 ± 3.65 | 6.02 ± 5.22 |
| $t_{max}$(h) | 1.54 ± 0.88 | 1.8 ± 1.3 |
| $C_{max}$(ng/ml) | 5.6 ± 2.5 | 19.9 ± 6.1 |
| $V_d$/F(l) | 177.2 ± 81.9 | 47.7 ± 18.6 |
| $k_e$(1/h) | 0.18 ± 0.09 | 0.10 ± 0.03 |
| $t_{1/2}$(h) | 4.65 ± 1.93 | 7.7 ± 2.9 |
| CL/F(l/h) | 32.5 ± 22.7 | 4.68 ± 0.50 |
| Pharmacokinetic-pharmacodynamic | | |
| $t_{1/2\text{-keo}}$(h) | 0.74 ± 0.43 | 0.44 ± 0.30 |
| A | 1.22 ± 0.59 | 0.35 ± 0.19 |
| B | 0.06 ± 0.63 | 0.08 ± 0.73 |

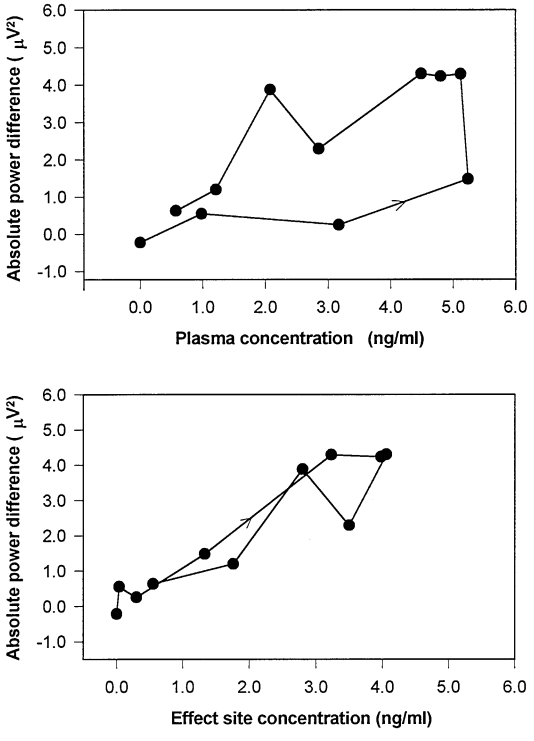


**Fig. 3** The mean plasma concentration of risperidone versus the mean EEG effect hysteresis plot (*upper*), and the mean effect compartment concentration of risperidone versus the mean EEG effect curve showing the collapse of the two limbs of hysteresis plot (*lower*) after single oral administration of 1 mg risperidone. The *arrow* indicates the direction of time course

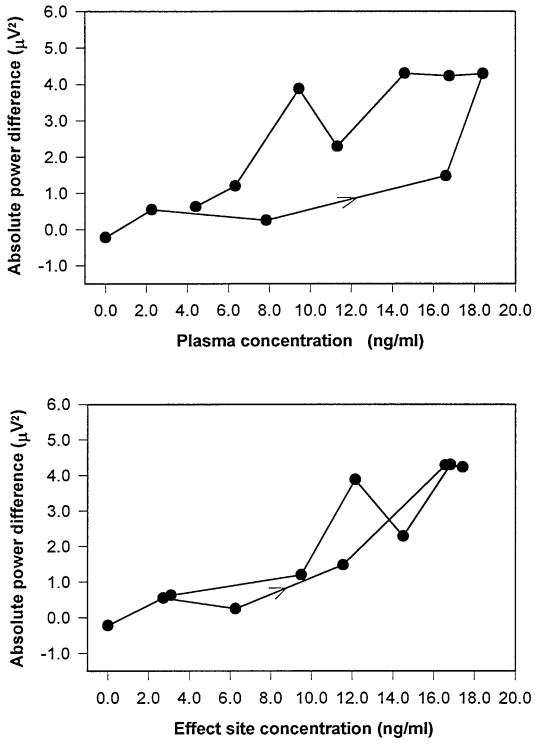


**Fig. 4** The mean plasma concentration of risperidone plus 9-hydroxyrisperidone versus the mean EEG effect hysteresis plot (*upper*), and the mean effect compartment concentration of risperidone plus 9-hydroxyrisperidone versus the mean effect curve showing the collapse of the two limbs of hysteresis plot (*lower*) after single oral administration of 1 mg risperidone. The *arrow* indicates the direction of time course

in the risperidone-plus-9-hydroxyrisperidone model than in the risperidone-only model ($P < 0.01$; Wilcoxon sign rank test). The EEG effects predicted by the linear model were significantly correlated with the observed EEG effects (model considering only risperidone: $P < 0.05$, $r = 0.838$; model considering both risperidone and 9-hydroxyrisperidone: $P < 0.05$, $r = 0.735$). The mean plasma concentration-mean EEG effect data of risperidone formed a hysteresis plot and the two limbs of the hysteresis plot were collapsed in the mean effect compartment concentration-mean EEG effect plot (Fig. 3). For the plot including risperidone plus 9-hydroxyrisperidone concentration instead of risperidone concentration, the same results were observed (Fig. 4).

## Discussion

Absolute powers for both delta and theta frequency bands were increased significantly in all whole areas of the brain in the case of risperidone administration compared to placebo. However, there were no significant changes in interhemispheric asymmetry and interhemispheric coherence for all frequency bands after risperidone administration. In previous studies for various antipsychotic agents, EEG activity (power) increases of low frequency bands, such as delta and theta, following antipsychotic medication have been consistently reported (Fink 1969, 1978; Itil et al. 1974; Herrmann 1982; Coppola and Herrmann 1987; Malow et al. 1994), which are similar to our findings. Czobor and Volavka (1993), however, reported no absolute power changes for all four frequency bands, whereas the changes in interhemispheric power asymmetry appeared for theta and beta frequency bands, after risperidone administration. This apparent disagreement with our results might reflect the differences in study design and subjects. The subjects in their study were schizophrenic patients aged from 18 to 65 years and 2–16 mg risperidone was administered for about 5 weeks on average. The changes in interhemispheric power asymmetry induced by risperidone might be associated with lateralized hemispheric dysfunction (Lohr and Caligiuri 1997) or reversal of cerebral asymmetry (Tiihonen et al. 1998) in schizophrenia.

The time delays between plasma drug concentration and EEG activity were observed for all subjects. Because of these time delays, the plotting between the plasma concentrations and the EEG effects of risperidone (or risperidone plus 9-hydroxyrisperidone) at all the sampling time points showed a counterclockwise hysteresis loop for each subject. Postulating that the drug moves to the effect compartment as the first order process from plasma, the time delays from the plasma concentrations to the EEG effects of risperidone could be explained. Also, the hysteresis loops observed in the plasma drug concentration-drug effect plots collapsed in the effect compartment concentration-effect of risperidone (or risperidone plus 9-hydroxyrisperidone) plots. These findings are similar to the results from the PK-PD simultaneous model analyses for benzodiazepines such as midazolam (Greenblatt et al. 1988; Koopmans et al. 1988) and diazepam (Friedman et al. 1992). The time to reach plasma-effect compartment equilibrium ($t_{1/2\text{-keo}}$) might be one of the most important factors explaining the interindividual or interdrug difference in the onset of drug action. It might be possible to identify such differences by calculating $t_{1/2\text{-keo}}$.

The appearance of active metabolite and the increase of the metabolite-to-parent drug ratio according to time course might also contribute, at least partially, to the formation of a counterclockwise hysteresis loop (Holford and Sheiner 1981). 9-Hydroxyrisperidone was known to have an equipotent pharmacologic effect to risperidone in animal studies (Van Beijsterveldt et al. 1994). The finding that there was no difference in the prolactin response to risperidone between poor metabolizers and extensive metabolizers of the cytochrome P450 IID6 activity in relation to the formation of 9-hydroxyrisperidone indicates that this metabolite might have the same pharmacologic effect as risperidone in humans also (Huang et al. 1993). As seen in Table 1,

the $t_{1/2\text{-keo}}$ in the model considering only risperidone as an active moiety was significantly larger than that in the model including both risperidone and 9-hydroxyrisperidone. This result supports that the gradual increment of the 9-hydroxyrisperidone-to-risperidone (metabolite-to-parent drug) ratio as well as the risperidone movement from plasma to effect compartment contributes to the occurrence of the time delay between plasma risperidone concentration and EEG change.

We attempted a linear-model fit between drug concentration and drug effect for EEG. Because the dose of risperidone (1 mg) in our study was too small to produce plasma levels of active moiety to achieve the near maximum effect of drug, the $E_{max}$ model or sigmoid $E_{max}$ model could not be fitted properly to our data. The possibility that the $E_{max}$ or sigmoid $E_{max}$ model may be more suitable to explain the concentration-effect relationship of risperidone with a high dose of risperidone therefore cannot be excluded. It is, however, very difficult to make a subject, especially a normal healthy volunteer, kept alert, which is one of the essential conditions for the appropriate assessment of QEEG parameters, after administrating high dose of risperidone.

In conclusion, absolute powers of delta and theta frequency bands were significantly higher in all topographic areas after single oral administration of 1 mg risperidone, compared to placebo. There were no significant differences in interhemispheric coherence and asymmetry between risperidone and placebo administration. Linear PK-PD model fit well with the relationship between effect comparement concentrations ($C_e$) and EEG effects and the two limbs of hysteresis in the plasma concentration ($C_p$)-effect plot collapsed in the effect compartment concentration ($C_e$)-effect plot for risperidone or risperidone plus 9-hydroxyrisperidone.

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