A Kinetic Study of Chlorpromazine on the Hyperglycemic Response in Rats. I. Effect of Chlorpromazine on Plasma Catecholamines

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The effect of chlorpromazine (0.5 and 4 mg/kg) on plasma catecholamines (adrenaline and noradrenaline) concentrations was investigated in rats. After an i.v. bolus administration of chlorpromazine, plasma adrenaline and noradrenaline concentrations showed a dose dependent increase. In order to clarify the pharmacokinetics of catecholamines in plasma, i.v. infusion of adrenaline or noradrenaline was also carried out. Plasma catecholamines after i.v. infusion showed typical characteristics of a one compartment model with a zero order production rate of endogenous catecholamines. From the data observed, a mathematical model was constructed to elucidate the relationship between the pharmacokinetics (brain concentrations) and the pharmacologic effect (plasma catecholamines concentrations) of chlorpromazine in rats. The results indicated that the time courses of plasma adrenaline and noradrenaline concentrations after an i.v. administration of chlorpromazine were described reasonably well by a simple pharmacokinetic-pharmacodynamic model.

Keywords — chlorpromazine; hyperglycemia; pharmacokinetics; pharmacodynamics; adrenaline; noradrenaline

Introduction

Many reports have indicated that chlorpromazine (CPZ) induces hyperglycemia in several species.1) Since the hyperglycemic effect is inhibited by adrenalectomy, adrenal demedulatation and by pretreatment with ganglionic blocking agents, it has been generally agreed that the hyperglycemia due to CPZ is closely related to the release of catecholamines from the adrenal medulla.2) Fujimori et al.3) demonstrated that CPZ stimulated the central nervous system to release adrenaline (ADR) from the adrenal medullas of rats. It was also reported that CPZ increased the urinary excretion of catecholamines in vivo.4) Although there are many reports on the mechanisms of the hyperglycemic, hypothermic and neuroleptic effects of CPZ, there have been only a few attempts to investigate the relationship between pharmacokinetics and pharmacodynamics of CPZ in vivo.

In the present study, the time courses of plasma concentrations of catecholamines after intravenous administration of CPZ were determined to study the pharmacologic effect of CPZ. The purpose of this study was to clarify the concentration–effect relationship of CPZ in the rat, using a mathematical model.

Materials and Methods

Chemicals — Chlorpromazine hydrochloride (CPZ, JP grade, Nakarai Chemical Co., Kyoto, Japan), l-adrenaline (ADR, Bosmin® Inj., JP grade, Daiichi Seiyaku Co., Tokyo, Japan) and l-noradrenaline (NOR, reagent grade, Nakarai Chemical Co., Kyoto) were purchased commercially and were used without further purification. All other chemicals were of reagent grade and were also obtained commercially.

Animal Experiments — Male albino rats (Wistar strain, Shizuoka Laboratory Animal Center, Hamamatsu, Japan) weighing 250 to 350 g were used. Under light ether anesthesia, each rat was cannulated with a polyethylene tubing (PE50, Clay Adams, Parsippany, NJ) which was attached with a Silastic medical grade

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tubing (0.51 mm in i.d. and 0.94 mm in o.d.,
Dow Corning Co., Midland, MI) into the left
femoral vein (for catecholamines infusion) and
the right jugular vein (for drug administration
and blood sampling). Catheters were tunneled
under the skin to exit at the nape of the neck.
All animals were allowed at least an overnight
period for recovery, with water and food availa-
ble. CPZ was dissolved in 1 ml of physiological
saline (JP XI, Otsuka Pharmaceutical Co.,
Tokyo, Japan) and was administered into the
jugular vein in dose levels of 0.5 and 4 mg/kg.
Blood samples (0.45 ml each) were withdrawn
from the jugular vein at 10, 20, 30, 45, 60, 90,
120, 180, 240 and 360 min after the administra-
tion. The blood samples were mixed with 10 μl
of pH 7.0 buffer solution containing ethylene-
glycol bis(β-aminoethylether) N, N', N", N"-
tetraacetic acid (EGTA; 90 mg/ml) and gluta-
thonine (60 mg/ml), immediately. After cen-
trifugation (at 10000 rpm for 2 min), 200 μl of
plasma were obtained and stored at −20 °C
until analysis. ADR or NOR was dissolved in
physiological saline and was infused via the
femoral vein at a rate of 40 μg/kg/h (flow rate:
0.032 ml/min) for 30 min using an infusion
pump (KN type, Natsume Seisakusho Co.,
Tokyo, Japan). Blood samples (0.45 ml) were
withdrawn from the jugular vein and were treat-
ed in the same manner as described above. All
animal experiments were carried out in the con-
sicous and unrestrained condition at the room
temperature of 23 ± 1 °C with the relative
humidity of 50%. Every experiment was started
at 11 a.m. to minimize the diurnal variation in
rats.

Analytical Method of Catecholamines
Plasma catecholamines were determined by a
radioenzymatic method (CAT-A-KIT, Upjohn
Co., Kalamazoo, MI).

Estimation of model parameters was carried
out as described previously.5a)

Results and Discussion

Effect of CPZ on Plasma Catecholamines

Time courses of plasma ADR and NOR
levels before and after i.v. administration of

Fig. 1. Time Course of Plasma ADR Levels after an
Intravenous Administration of CPZ
Upper panel; 0.5 mg/kg, lower panel; 4 mg/kg. The plotted
points represent the observed data and the solid lines
represent the calculated values using Eq. 5 in the text. CPZ
was administered at time zero and the ADR values at time
zero represent the control levels. Each experimental point
is shown as the mean ± S.E. (n = 3).

Fig. 2. Time Course of Plasma NOR Levels after an
Intravenous Administration of CPZ
Upper panel; 0.5 mg/kg, lower panel; 4 mg/kg. The plotted
points represent the observed data and the solid lines
represent the calculated values using Eq. 6 in the text. CPZ
was administered at time zero and the NOR values at time
zero represent the control levels. Each experimental point
is shown as the mean ± S.E. (n = 3).
CPZ (0.5 and 4 mg/kg) are shown in Figs. 1 and 2, respectively. The control levels of plasma ADR and NOR were 0.056 and 0.168 ng/ml, respectively, and these values are consistent with the report of Micalizzi et al. After CPZ administration, the plasma ADR and NOR concentrations were increased in a dose dependent manner. At 4 mg/kg dose, the maximum plasma ADR concentration was about 0.23 ng/ml at 20 min after dosing and gradually returned to the control level thereafter. While, the maximum level in plasma NOR concentration was about 1.4 ng/ml at 10 min after CPZ injection which also returned gradually to the control level.

Several investigators have suggested that the hyperglycemic effect of CPZ is closely related to the sympathetic nerve stimulation and ADR release from the adrenal medulla. The present results indicates consistency with the literature.

**Infusion of Catecholamines**

The time courses of plasma ADR and NOR levels before, during and after constant rate i.v. infusion of catecholamines (40 µg/kg/h for 0.5 h) are shown in Fig. 3 (ADR) and Fig. 4 (NOR). Both catecholamines levels reached peak concentrations just after the start of infusion, suggesting that ADR and NOR had extremely short half lives in plasma.

**Description of the Model**

In order to clarify the relationship between CPZ disposition and plasma catecholamine concentration, a kinetic model was constructed with the following assumptions, (1) the dispositions of both catecholamines, ADR and NOR, can be described by one-compartment open model; (2) the endogenous catecholamines are produced by zero order rate kinetics and are eliminated from plasma by first order kinetics; (3) the site of action of CPZ is in the brain and (4) the production rates of ADR and NOR increase in proportion to the brain (biophase) concentration of CPZ directly. A schematic diagram of the model is shown in Fig. 5. After an intravenous infusion of either ADR or NOR, the change in plasma catecholamines were described by the following equations.

\[
\frac{dC_{ADR}}{dt} = k_{ADR0} + \frac{I_{ADR}}{V_{d,ADR}} - k_{ADRe} C_{ADR} \quad (1)
\]

![Fig. 3. Time Course of Plasma ADR Levels before, during and after the Constant Infusion of ADR in Rats](image1)

The plotted points represent the observed data and the solid line represents the calculated values using Eq. 1 in the text. Each experimental point is shown as the mean ±S.E. (n = 3).

![Fig. 4. Time Course of Plasma NOR Levels before, during and after the Constant Infusion of NOR in Rats](image2)

The plotted points represent the observed data and the solid line represents the calculated values using Eq. 2 in the text. Each experimental point is shown as the mean ±S.E. (n = 3).
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Fig. 5. Diagrammatic Representation of the Effect of CPZ on the Plasma Catecholamines in the Rat

\[ \frac{dC_{NOR}}{dt} = k_{NOR0} + \frac{I_{NOR}}{V_{d,NOR}} - k_{NORE} C_{NOR} \]  (2)

where \( C_{ADR} \) and \( C_{NOR} \) are the plasma concentrations of ADR and NOR, \( k_{ADR0} \) and \( k_{NOR0} \) are the production rates of endogenous ADR and NOR, \( I_{ADR} \) and \( I_{NOR} \) are the infusion rates of ADR and NOR, \( V_{d,ADR} \) and \( V_{d,NOR} \) are the distribution volume of ADR and NOR, and \( k_{ADR} \) and \( k_{NORE} \) are the first-order rate constants for the elimination of ADR and NOR, respectively. Before the infusion, Eqs. 1 and 2 are reduced to Eqs. 3 and 4, respectively.

\[ 0 = k_{ADR0} - k_{ADR} C_{ADR0} \]  (3)

\[ 0 = k_{NOR0} - k_{NORE} C_{NOR0} \]  (4)

where \( C_{ADR0} \) and \( C_{NOR0} \) are the plasma concentrations of ADR and NOR, respectively at the control state (before medication). The endogenous catecholamine production rates, \( k_{ADR0} \) and \( k_{NOR0} \), were calculated by these equations and are listed in Table I.

The plasma catecholamine concentrations after CPZ administration were described by the following equations.

\[ \frac{dC_{ADR}}{dt} = k_{ADR0} + \alpha C_{BR} - k_{ADR} C_{ADR} \]  (5)

\[ \frac{dC_{NOR}}{dt} = k_{NOR0} + \nu C_{BR} - k_{NORE} C_{NOR} \]  (6)

where \( C_{BR} \) is the brain concentration of CPZ, and \( \alpha \) and \( \nu \) are the proportional constants for the pharmacologic response of CPZ on the production rates of endogenous ADR and NOR, respectively.

**Data Fitting and Estimation of the Model Parameters**

The solid lines shown in Figs. 3 and 4 represent the calculated values of the time courses of ADR and NOR, according to Eqs. 1 and 2, respectively. Although the model employed here was relatively simple, the calculated values adequately described the observed data. The estimated parameters are shown in Table I. Among the parameters, the products of \( k_{ADR0} \) and \( V_{ADR} \) or \( k_{NOR0} \) and \( V_{NOR} \) represent the endogenous production rate of the catecholamine in plasma at the control state. The present result is fundamentally consistent with the result of Robinson et al. \(^{7a}\) in dogs, on a body weight basis.

In order to clarify the elimination kinetics of catecholamines in plasma, we used relatively high infusion rates of exogenous catecholamines. Since there is a homeostatic system for the blood pressure by the adrenal, plasma catecholamine levels during and after a small amount of catecholamine infusion might be influenced considerably by the change of endogenous catecholamine productions in the body. Thus, relatively high dosages of catecholamines...
were indispensable for obtaining the disposition constants of catecholamines. In the present study, the elimination kinetics of ADR and NOR from plasma were assumed to be simple first order kinetics without any control systems. It is well known that the metabolic pathways of catecholamines are O-methylation, deamination and cojugation. Since there has been no report indicating that these metabolic pathways are controlled by the blood pressure homeostatic system in the body, a simple first order model was used in this study. As shown in Table I, the elimination half lives for ADR and NOR were about 1 min, and this result is consistent with the report of Axelrod et al. \(^{7b}\)

The solid lines shown in Figs. 1 and 2 are the calculated values of plasma ADR and NOR levels after i.v. administration of CPZ, according to Eqs. 1 through 6. The values for \(C_{BR}\) in Eqs. 5 and 6 were calculated by a blood flow limited model, according to the previous paper, and all of the pharmacokinetic parameters for CPZ disposition were adopted from the previous report. \(^{5a}\) The calculated values for \(C_{ADR}\) and \(C_{NOR}\) agree pretty well with the observed data. Pharmacodynamic parameters used in the calculation are also listed in Table I.

In order to describe the relationship between pharmacologic intensity and the concentration of the drug quantitatively, many types of models such as the linear model, the log-linear model, the \(E_{max}\) model and the sigmoid \(E_{max}\) model (Hill’s equation) have been suggested. \(^{8}\) In previous papers, we reported that the effect of CPZ on the body temperature was correlated with the brain level of CPZ, using a conventional Hill’s equation and a body temperature-regulation model. \(^{5}\) Accordingly, we calculated the effect of CPZ on the plasma catecholamines using a Hill’s equation, as shown in the following equations.

\[
\frac{dC_{ADR}}{dt} = k_{ADR0} + \frac{E_{max,ADR} C_{BR} r_{1}}{EC(50)_{ADR} r_{1} + C_{BR} r_{1}} - k_{ADR} C_{ADR}
\]

\[
\frac{dC_{NOR}}{dt} = k_{NOR0} + \frac{E_{max,NOR} C_{BR} r_{2}}{EC(50)_{NOR} r_{2} + C_{BR} r_{2}} - k_{NOR} C_{NOR}
\]

where \(E_{max,ADR}\) and \(E_{max,NOR}\) are the maximum effects of CPZ, EC(50) \(_{ADR}\) and EC(50) \(_{NOR}\) are the CPZ concentrations which produce 50% of \(E_{max}\) values, and \(r_{1}\) and \(r_{2}\) are the Hill’s constants of ADR and NOR, respectively. The calculated curves of ADR and NOR after i.v. administration of CPZ also agreed with the corresponding observed data using the following pharmacodynamic parameters; \(r_{1} = 0.821\), EC(50) \(_{ADR}\) = 4.98 mg/ml, \(E_{max,ADR}\) = 0.899 mg/ml/h, \(r_{2} = 0.849\), EC(50) \(_{NOR}\) = 2.54 mg/ml and \(E_{max,NOR}\) = 3.73 mg/ml/h. However, some of the parameters such as EC(50) \(_{ADR}\) and EC(50) \(_{NOR}\) were extremely large compared with the pharmacologic significance. Data analysis using the Akaike’s information criterion (AIC) \(^{9}\) was also carried out. In the linear model (Eqs. 5 and 6), AIC values of the ADR and NOR studies were \(-77.8\) and \(-17.6\), respectively. Whereas, in the sigmoid \(E_{max}\) model (Eqs. 7 and 8), AIC values of the ADR and NOR studies were \(-74.1\) and \(-10.7\), respectively. These results suggest that the linear model, rather than the sigmoid \(E_{max}\) model, is more suitable for the description of the effect of CPZ on the secretion of catecholamines in rats. Therefore we adopted a linear function in this study. The effect of CPZ on the plasma catecholamine levels were reasonably described by the linear model. The assumptions described above therefore, might be appropriate.

Pharmacodynamics in respect to plasma catecholamines and pharmacokinetics of CPZ have been investigated. The time course of the pharmacologic effect of CPZ was well explained by a simple pharmacokinetic-pharmacodynamic model. It has been generally agreed that the hyperglycemic effect of CPZ is closely related to the levels of endogenous catecholamines in the body. The relationship between CPZ disposition and the hyperglycemic effect in rats will be elucidated in the subsequent paper.
References


