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COMPATIBILITY AND STABILITY TESTS OF RISPERIDONE WITH SOFT-DRINKS BY ISOTHERMAL TITRATION MICROCALORIMETRY

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Isothermal titration microcalorimetry has been applied to investigate the compatibility testing of risperidone oral solution with soft-drinks and the interaction with tea tannin such as (–)-epigallocatechin, (–)-epicatechin, theaflavin and their gallates. In aqueous solution, risperidone was exothermically bound to tea tannin with binding affinity (10^3–10^4 M^{-1}), small enthalpy and entropy changes reflecting van der Waal's interaction to form an insoluble complex at 1:1 molar ratio. The heat effect of risperidone titrated into soft-drinks containing tannin was exothermic and proportional to the quantity of the complex. While, no significant heat effect was found for risperidone titrated into a pet-bottled water and an infusion of parched barley without tea tannin. These results were agreed with stability testing of risperidone in some soft-drinks by HPLC method.

Keywords: *compatibility, epicatechin, epigallocatechin, isothermal titration microcalorimetry, risperidone, theaflavin*

Introduction

It is important to take medication with a cup of water. The administration of a medicine with beverage may accentuate or diminish the activity of the medicine as a result of physical or chemical compatibility. Risperidone is a new drug for schizophrenia with benzisoxazole skeleton (Fig. 1). Compared with butyrophenone drugs such as haloperidol, risperidone has an equivalent antagonism of dopamine D_2 and beneficial effects on sedation, anti-hallucination action and anti-delusion action [1]. In this area, medication noncompliance has been often induced some problem. Patients, who are unable to swallow solid foods, who dislike to have many tablets, and who take a chronic course of the disease, can't accept to take tablets and granule. RISPADAL™ Liquid (oral solution of 1 mg mL^{-1} risperidone) has been developed to improve treatment compliance in such patients, and the following information as a method of administration is described in the package insert: if necessary RISPADAL™ Liquid may be diluted with mineral water, orange juice or black coffee (to reduce the bitter taste). The liquid should not be mixed with tea. However, it remains unclear how incompatibility occurs when risperidone is mixed with tea. In this study, the compatibility of risperidone with soft-drinks and the interaction mechanism with typical tea tannin were investigated using isothermal titration calorimetry (ITC) and the usefulness of ITC for the compatibility and stability testing of drugs was evaluated.

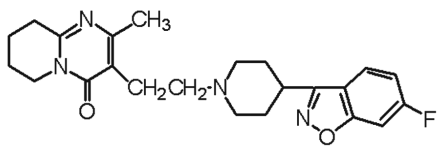

Fig. 1 Chemical structure of risperidone

Experimental

Materials

Risperidone and RISPADAL™ Liquid (risperidone; 1 mg mL^{-1}) were received as gift sample from Janssen Pharmaceutica, Inc. (Titusville, NJ). In RISPADAL™ Liquid, the inactive ingredients are tartaric acid, benzoic acid, sodium hydroxide and purified water (pH 2.0 ~ 4.0). (–)-Epigallocatechin (EGC), (–)-epigallocatechin gallate (EGCg), (–)-epicatechin (EC), (–)-epicatechin gallate (ECg), and theaflavin 3'-O-gallate (TFg) were purchased from Nagara Science (Gifu, Japan) and used without further purification. Risperidone and the tea tannin were dissolved in tartaric acid-sodium tartrate buffer solution at pH 3.0. As typical soft-drinks, commercially pet-bottled water, green tea, black tea, oolong tea, and infusion of parched barley were used. All other chemicals were analytical grade.

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Table 1 Stability of risperidone in soft-drinks

Soft drinks	(Tannin mg/dL)	Risperidone remaining (mass/v%)		
		Initial	Just after mixing	24 h after mixing
Green tea	(60.0)	100.0	77.7	71.5
Black tea	(37.0)	100.0	38.3	17.3
Oolong tea	(32.0)	100.0	22.8	18.2
Infusion of parched barley	(0.0)	100.0	100.1	99.8
Water	(0.0)	100.0	100.6	100.2

RISPADAL™ Liquid (risperidone: 1 mg mL^{-1}) and each soft drink were mixed at a ratio of 3 : 97 (*v*/*v*). The pH values of RISPADAL™, soft drinks and the mixture were about 3, 7, and 4, respectively. The risperidone remained in the mixture was measured by HPLC method

Stability testing of RISPADAL™ Liquid in soft-drinks

Rispadal™ Liquid and each soft-drink were mixed at a ratio of 3:97 (*v*/*v*) and allowed stand at room temperature for 24 h. Risperidone remaining in the mixed solution was analyzed at intervals by HPLC (Shimadzu LC10A; Shimadzu Co. Ltd, Kyoto, Japan) utilizing a UV detector at 275 nm. The analytical column used was Mightysil RP-18GP (100×4.6 mm i.d.). The mobile phase was composed of ammonium acetate solution and acetonitrile (78:22). The flow rate was 15 mL min^{-1} and sample injection volume was 10 μL. Amount of tannin in soft-drinks was measured by colorimetry at 540 nm [2].

Isothermal titration microcalorimetry

Microcalorimetric measurements were performed with a Thermal Activity Monitor 2277 system (Thermo-Metric AB, Järfälla, Sweden) at 25°C. A sample cell was initially filled with a 3.0 mL of soft-drink or tea tannin solution as a titrand for measuring the compatibility heat or the binding heat of risperidone, respectively. The solution of risperidone as a titrant was injected as 16 portions of 15 μL into the sample cell and the mixed solution was stirred with a turbine at 70 rpm. Control experiment in the compatibility testing was done by titrating pH 3.0 buffer solution into each soft-drink instead of the risperidone solution.

The binding heat (ΔQ) was proportional to the amount of the complex formed between risperidone and tea tannin. For a one-step reaction, the equilibrium aspect of the interaction was correlated through the mass law, and ΔQ was expressed as a function of the total concentrations of risperidone (L_t) and tea tannin (S_t) in the solution (V mL) as follows:

$$\Delta Q=\frac{\Delta HV}{2}\left(1/K+nS_t+L_t-\sqrt{(1/K+nS_t+L_t)^2-4nS_tL_t}\right)$$

where K and n are the binding constant and the binding stoichiometry, respectively. The parameters were estimated using the nonlinear regression analysis [3].

Results and discussion

Stability of risperidone in soft-drinks

The results of stability testing of Rispadal™ Liquid in some commercial soft-drinks are summarized in Table I. In the soft-drinks containing tea tannin, risperidone remaining in the solution decreased immediately after mixing and the mixed solutions became cloudy. The ratio of decrease was independent of amounts of tannin in soft-drinks and no decomposed compound of risperidone was detected during a testing period. These cases are shown in physical incompatibility, which is usually the result of drug insolubility or physical complexation.

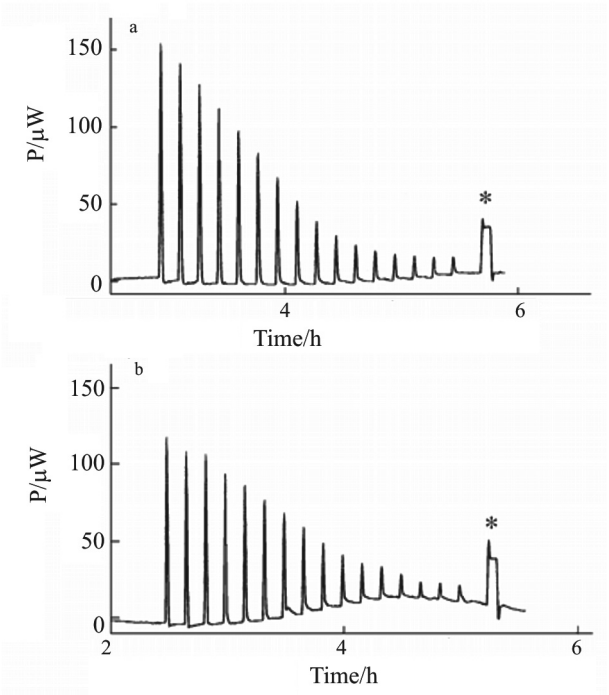

Fig. 2 Heat flow of a – risperidone and b – pH 3.0 buffer solution titrated into a green tea. * Standard heat flow (30 μW)

Heat effect for compatibility testing of risperidone with soft-drinks

Figures 2 shows the thermograms of risperidone solution (1 mg mL^{-1}: 2.44 mM) and pH 3.0 buffer solution titrated into a green tea. Same results for the risperidone titration into a black tea and oolong tea were obtained. On the other hand, no significant heat effect was found to risperidone titrated into a pet-bottled water and an infusion of parched barley. The reaction heat between risperidone and some soft-drinks, which was corrected by the corresponding heat of control titration, was plotted *vs*. the total concentration of risperidone (Fig. 3). The heat effect exothermically increased with increasing the concentrations of tea tannin contained in green tea. Although a similar tendency was shown in the reaction heat for the compatibility of risperidone with black tea and oolong tea, the heat effect was slightly higher than that caused in risperidone-green tea compatibility. Since the reaction heat was corresponding to the complex formed in the solution, risperidone could more easily form complex with tea tannin in black tea and oolong tea than in green tea. These results were agreed with the stability testing of Rispadal™ Liquid with commercially soft-drinks (Table I).

Heat effect of risperidone binding to monomeric tea tannin

The calorimetric titrations of risperidone with monomeric tea tannin were examined at pH 3.0 and 25°C.

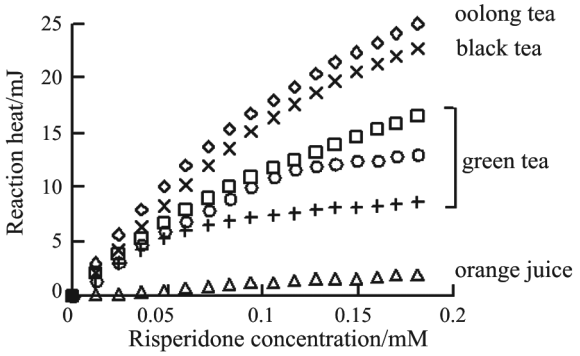

Fig. 3 Reaction heat of risperidone with some soft-drinks

The estimated values of the binding and thermodynamic parameters are summarized in Table 2. Risperidone was exothermically bound to monomeric tea tannin with binding affinity (10^3–10^4 M^{-1}) at 1:1 stoichiometry in aqueous solution. The binding affinity increased in the order of TFg>EGCg>ECg>EGC>EC, and the binding was characterized by small enthalpy change (ΔH= –13~ –5 kJ mol^{-1}) and entropy change (ΔS=16~58 J mol^{-1} K^{-1}), reflecting van der Waal's interaction rather than hydrophobic interaction and hydrogen bond formation.

Complex formation between risperidone and tea tannin

The final solutions after the calorimetric titrations of tea tannin with risperidone got cloudy, and produced white precipitates when left to stand as it is overnight. On measuring FAB-mass spectrum of each product, a high intensity peak of the 1:1 complex was observed. It was indicated that risperidone bound with monomeric tea tannin and formed an insoluble complex at the molar ratio of 1:1 in aqueous solution.

Among tea tannin used in this study, EGCg is the main constituent of green tea polyphenols and may account for 50–80% of the total catechin in green tea. The other major catechins are ECg, EGC, and EC. TFg is the specific red pigment exudated from black tea and oolong tea and produced by enzymic oxidation and condensation reaction between EC (or ECg) and EGC (or EGCg). Furthermore, the prolonged autoxidation or enzymic oxidation of catechin let to the formation of polymers resulting from repeated condensation reactions. From the results that the binding affinity of TFg with risperidone was ten times higher than those of other monomeric catechins (Table 2), it is suggested that risperidone would easily bind to catechin polymers to form complexes. Moreover considering that the values of K and $-\Delta H$ for EGCg and ECg were larger than those for EGC and EC, respectively, the galloyl group of tea tannin would also play an important role in the binding with risperidone. Thus, the formation of the insoluble complexes causes the incompatibility of Rispadal™ Liquid with tea beverages to reduce the absorption of risperidone. The mechanisms for risperidone-tea tan-

Table 2 Binding and thermodynamic parameters for risperidone binding to tea tannins at pH 3.0 and 25°C

	n	$K/10^3$ M^{-1}	$-\Delta H$/kJ mol^{-1}	$-\Delta G$/kJ mol^{-1}	ΔS/J $mol^{-1}K^{-1}$
EGCg	1.2±0.1	1.54±0.18	13.4±1.7	18.0±0.3	15.7
EGC	1.1±0.1	1.00±0.21	10.3±2.1	17.1±0.4	23.0
ECg	1.0±0.2	1.15±0.15	6.92±1.1	17.3±0.2	35.9
EC	1.0±0.2	0.73±0.24	4.57±1.4	16.3±0.3	39.5
TFg	1.0±0.1	9.15±0.62	5.18±0.1	22.6±0.4	58.4

nin interaction in aqueous solution and the structures of their complexes could be clarified by further studies such as NMR spectrometry and molecular dynamic simulation.

Conclusions

It was demonstrated that risperidone formed the insoluble complex with tannin in tea leaves such as green tea catechin and theaflavin to reduce the risperidone content. In particular, risperidone formed complexes with monomeric tannins at a molar ratio of 1:1 by a relatively weak binding force. The isothermal titration microcalorimetry could be utilized as a rapid method for evaluating the compatibility testing and the physico-chemical interaction for drugs.

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