

Relation between Drug-Induced Taste Disorder and Chelating Behavior with Zinc Ion; Statistical Approach to the Drug-Induced Taste Disorder, Part II

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There are many reports that the drug-induced taste disorder is ascribable to the chelate reaction of a drug with zinc ion and the following zinc deficiency. As a quantitative measure of the chelating ability of drugs with zinc ions, the chelating ability was estimated from the electrode potential change of the $Zn^{2+}/Zn(Hg)$ system during the addition of a drug. The electrode potential was measured in a water–*N,N*-dimethylformamide mixed solution and in an aqueous solution depending on the solubility of the drugs. The observed electrode potential change showed a positive correlation to the frequency of the drug-induced taste disorder that was supplied from the manufacturer of the original drug. The regression analysis was carried out assuming that the frequency of the taste disorder and the electrode potential change was linear. The *F*-values, *p*-values, and *R*²-values were 4.29, 0.13, 0.589, and 4.15, 0.13, 0.580, respectively. The positive correlation between the drug-induced taste disorder and the electrode potential change appeared evident if the uncertainty in the frequency of the taste disorder was taken into consideration. Thus the assumption of the zinc ion chelating mechanism on the drug-induced disorder was also evident except for cisplatin. The frequency of the drug-induced taste disorder of bezafibrate was estimated to be 0.4–0.5 from the regression analysis.

Key words drug-induced taste disorder; zinc ion; chelate; electrode potential

The taste disorder is an important problem in order to improve the quality of life for many patients, especially the aged. There are numerous causes of the taste disorder such as aging, radiation, lack of oral hygiene, vitamin B deficiency, zinc deficiency, and numerous drugs.¹⁾ An epidemiologic survey²⁾ on the cause of dysgeusia in 2278 patients over the decade from 1981 to 1990 suggested that the most frequent cause was the drug-induced taste disorder. The drug-induced taste disorder can be reduced and the quality of life will also be improved if an adequate method to anticipate the frequency of the taste disorder was developed.

Few systematic studies to anticipate the frequency of the drug-induced taste disorder have been conducted. The frequently proposed theory is the chelating ability of drugs with zinc ions. Many cases have been reported that suggested the efficacy of oral zinc treatments.^{3,4)} Reflecting such an efficacy of the zinc ion, Tarui found that urinary zinc increased when the chelating agents were administered, while only a slight change in the concentration in urinary iron and copper was observed.^{5,6)} Prasad *et al.* mentioned the zinc metabolism in patients and found that zinc ions are closely associated with certain metalloenzymes such as metal-requiring enzymes, hormones, and vitamins.⁷⁾ Thereafter, various diseases have been ascribed to the zinc deficiency through the enzymatic mechanism including DNA synthesis and cell division.⁸⁾ Henkin and coworkers proposed that zinc ions were localized in the taste bud membrane and the lack of zinc ions disturbed the role of gustin in the growth of the taste bud.^{9,10)} They also examined the oral zinc treatment in relation to the carbonic anhydrase VI deficiency, a zinc-dependent enzyme.¹¹⁾

The chelate reaction of drugs with zinc ion has drawn attention as the cause of the drug-induced taste disorder. On the other hand, it is also true that many reports have doubted

the role of the zinc ion on the taste disorder.^{12,13)} Therefore the relation between the chelating ability of drugs with zinc ions and the taste disorder should be quantitatively examined. Sekimoto and Tomita measured the stability constant of furosemide and captopril with zinc ions in dioxane using polarography to experimentally elucidate the chelate reaction with zinc ions.¹⁴⁾ They could not succeed in establishing a general relation between the stability constant and the frequency of the drug-induced taste disorder because the number of drugs that could be measured using polarography was quite limited.

The authors have planned in a previous study¹⁵⁾ to examine the relation between the drug-induced taste disorder and the chelating ability of drugs with zinc ions using the statistical procedure. The electrode potential of the zinc amalgam electrode, $Zn^{2+}/Zn(Hg)$, was used to quantitatively measure the chelating ability of drugs with zinc ions. The calculation procedure was also developed to numerically anticipate the frequency of the taste disorder for the drugs that have not been mentioned in the interview forms. In this study, the case of the drug-induced disorder was examined for drugs that were mentioned in the listing of ethical drugs 2006 published by JAPIC.¹⁶⁾ The frequency of the drug-induced taste disorder was supplied from each DI center of the corresponding manufacturer of the original drug. The experimental apparatus was improved in this study using an electroplated zinc amalgam electrode. The electrode potential of the $Cu^{2+}/Cu(Hg)$ system was also examined in order to compare the chelating ability between Zn^{2+} and Cu^{2+} .

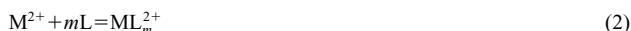
Experimental

Theory In general, the measure of the chelating ability is expressed by the equilibrium constant *K*. One of the methods to evaluate the stability constant is measuring the electrode potential based on the Nernst equation. The electrode potential of the metal amalgam electrode, $Zn^{2+}/Zn(Hg)$ and

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Cu²⁺/Cu(Hg), was used in this study.

The electrode reaction, complex formation, stability constant, and the electrode potential of the metal electrode are described by the following equations where M denotes zinc or copper, and L denotes a certain neutral ligand.



$$K = \frac{[ML_m^{2+}]}{[M^{2+}][L]^m} \quad (3)$$

$$E_{(ML_m^{2+}/M)} = E_{(ML_m^{2+}/M)}^\circ + \frac{RT}{2F} \ln[ML_m^{2+}] - \frac{mRT}{2F} \ln[L] \quad (4)$$

$$E_{(ML_m^{2+}/M)}^\circ = E_{(M^{2+}/M)}^\circ - \frac{RT}{2F} \ln K \quad (5)$$

where m is the number of ligands, K is the stability constant, $E_{(ML_m^{2+}/M)}$ is the observed electrode potential, $E_{(ML_m^{2+}/M)}^\circ$ is the standard electrode potential of the M²⁺/M system or M²⁺/M(Hg), R is the gas constant, T is the thermodynamic temperature, F is Faraday constant, and [] indicates the molar concentration.

Theoretically, K is calculated from these equations under specific experimental conditions. However, the measurement based on the Nernst equation to calculate K is difficult because most of the drugs have a very low solubility in an aqueous solution, and the experimental conditions that satisfy above equations are hard to establish. Accordingly, the chelating ability of drugs was evaluated from the electrode potential change ΔE when a known amount of a drug was added to the M²⁺/M(Hg) system as proposed in a previous study.¹⁵⁾

Apparatus and Electrode The experimental apparatus used to measure the electrode potential of M²⁺/M(Hg) is illustrated in Fig. 2 of the previous study.¹⁵⁾ The zinc or copper amalgam electrode was prepared by electroplating. A platinum sphere with a 0.5 mm radius was dipped in a 0.1 mol/l aqueous Hg₂²⁺ solution (prepared by mixing Hg(NO₃)₂ and mercury metal). A cathodic current of 10.0 mA was passed for 5 min to electroplate the mercury. The mercury-plated electrode was then dipped in a 0.1 mol/l aqueous solution of Zn(NO₃)₂ or Cu(NO₃)₂. Cathodic currents of a 0.5 mA and a 0.1 mA were passed for 4 min to prepare the Zn²⁺/Zn(Hg) and Cu²⁺/Cu(Hg) electrodes, respectively. Using the electroplated Zn²⁺/Zn(Hg) electrode in a 3.0 × 10⁻⁴ mol/l Zn²⁺ solution, the reproducibility was -0.9790 ± 0.0070 (S.D.) V vs. the Ag/AgCl reference electrode ($n=15$). The reproducibility of

the Cu²⁺/Cu(Hg) electrode was +0.0558 ± 0.0075 (S.D.) V vs. Ag/AgCl ($n=15$).

Reagents and Drug Samples Deionized water was prepared using ion exchange resins and a filtering system (Puric Model-R, Japan Organo Co., Ltd., Japan). KNO₃ and Hg(NO₃)₂ were reagent grade. The mercury was purified in our laboratory using aerated dilute nitric acid.

Drug Samples The drug induced taste disorder has been mentioned in more than 60 drugs in the listing of ethical drugs 2006 published by JAPIC.¹⁶⁾ Commercially available drugs were initially selected from them. The chloride salts were then excluded to avoid the formation of Hg₂Cl₂. From the remaining drugs, 6 drugs were selected as samples that were soluble in dimethylformamide (DMF). Six other drugs that are soluble in water were also selected. These drugs are listed in Table 1. The electrode potential of bezafibrate was measured although the case of the taste disorder was not mentioned in the listing. The possibility of the taste disorder due to bezafibrate was mentioned in a previous study.¹⁵⁾ As a statistical treatment, it is very important to notice that no arbitrary selection of drugs was assigned in this study.

Electrode Potential Measurement Each drug was dissolved in *N,N*-dimethylformamide (DMF) or in ultrapure water to prepare the 0.05 mol/l stock solution. The test solution was prepared by mixing 30.0 ml of 0.1 mol/l aqueous KNO₃ and 4.0 ml of DMF. The pre-addition of 4.0 ml DMF was done to avoid the effect of adsorption of the DMF. As for the aqueous system, the test solution was composed of 34.0 ml of a 0.1 mol/l aqueous KNO₃ solution.

After adding the Zn²⁺ or Cu²⁺ stock solution to prepare the 3.0 × 10⁻⁴ mol/l solution of M²⁺, the dissolved oxygen was removed by bubbling purified nitrogen gas. The starting potential of M²⁺/M(Hg) was first recorded. The stock solution of drug was then added to the test solution to adjust the concentration of 9.0 × 10⁻⁴ mol/l that was three times greater than the metal ion concentration, and the change in the electrode potential ΔE of M²⁺/M(Hg) was recorded.

Regression Analysis JMP ver. 6 (SAS Institute Inc., U.S.A.) was used for the regression analysis.¹⁷⁾

Results and Discussion

Overview of the Drug Examined The six drugs that were soluble in DMF and five drugs that were soluble in water are listed in Table 1. The frequency of the drug-induced taste disorder and corresponding parent population are listed in the same table. The frequency and the population were supplied from each DI center of the corresponding

Table 1. Potential Change ΔE of Zn²⁺/Zn and Cu²⁺/Cu Systems and Statistical Data Supplied from Manufacturers

(a) Measured in water-DMF mixed solution

Drugs	ΔE (Zn ²⁺ /Zn)	S.D.	ΔE (Cu ²⁺ /Cu)	S.D.	Frequency %	Population n
	mV		mV			
Diclofenac sodium	3.0	3.7			0.0002	3965
Sulfasalazine	27.0	7.2			0.3	Not inquired
Levodopa	47.8	18.0	21.7	4	0.33	7333
Acetazolamide	70.0	8.1			0.6	989
Alacepril	44.3	13.2	25.7	4.5	0.79	632
Cisplatin	-3.1	0.8			2.9	103
Bezafibrate	39.3	3.8	7.7	8.1	Not inquired	

(b) Measured in aqueous solution

Drugs	ΔE (Zn ²⁺ /Zn)	S.D.	ΔE (Cu ²⁺ /Cu)	S.D.	Frequency %	Population n
	mV		mV			
Diclofenac sodium	-8.7	3.7			0.0002	3965
Nicotine	-6.3	7.1			0.11	3538
Levodopa	73.5	11.1			0.33	7333
Acetazolamide	32.3	2.5			0.6	989
Penicillamine	81.7	3.5	44.0	8.2	1.41	8110
Bezafibrate	43.7	12.0			Not inquired	

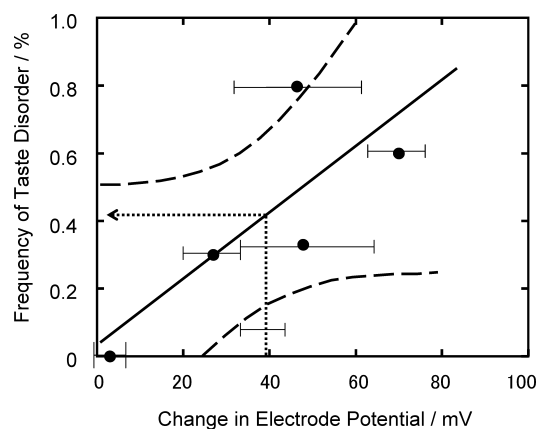


Fig. 1. Correlation Diagram between Frequency of Taste Disorder and Change in Electrode Potential of Zn^{2+}/Zn System Observed in Water-DMF Solution

Dotted line: bezafibrate. Broken line: confidence interval (α -level: 0.1).

manufacturer of the original drug. Several other drugs that were soluble in DMF were also examined. They were found to be insoluble in the water-DMF mixed solution, *e.g.*, danazole, miconazole nitrate, and mitotane.

Change in the Electrode Potential The reproducibility of the electrode potential of $Zn^{2+}/Zn(Hg)$ and $Cu^{2+}/Cu(Hg)$ was about 0.007 V in the 0.1 mol/l KNO_3 solution containing 3.0×10^{-4} mol/l Zn^{2+} or Cu^{2+} . The change in the electrode potential ΔE upon the addition of the 9.0×10^{-4} mol/l drug is listed in Table 1 together with the standard deviation S.D. To account for the experimental data, a linear relation was assumed for the regression analysis using JMP between the frequency of the drug-induced drug taste disorder and the change in the electrode potential. The result of cisplatin was excluded because (1) the chelating ability cannot be expected from its chemical formula, and (2) the effect of the physiological action is very strong and a different mechanism for the taste disorder was postulated. The results of the regression analysis are shown in Figs. 1 and 2 by excluding cisplatin. In Fig. 2, the electrode potential changes due to diclofenac sodium and nicotine was thought to be zero because the negative change is impossible in the present chelating mechanism. The negative change may be ascribed to adsorption of the drugs. The linear relation, *F*-value, *p*-value, and R^2 based on the analysis by JMP were as follows:

$$\begin{aligned} Zn^{2+}(\text{Water-DMF}): y &= 0.0093x + 0.047 \\ F: 4.29, p: 0.13, R^2: 0.589 \end{aligned} \quad (6)$$

$$\begin{aligned} Zn^{2+}(\text{Water}): y &= 0.011x + 0.078 \\ F: 4.15, p: 0.13, R^2: 0.580 \end{aligned} \quad (7)$$

where *y* is the frequency of the taste disorder and *x* is the change in the electrode potential with ΔE in mV. The positive relation between the frequency of the taste disorder and the change in the electrode potential was observed in the measurement either in the water-DMF or in aqueous solution. It seems difficult to draw a direct conclusion whether the present correlation is statistically significant. The difficulty arises not in the reliability of the electrode potential, but in the frequency of the taste disorder although a sufficient population was examined by the manufacturers. The most fundamental problem is that no quantification has been made on the de-

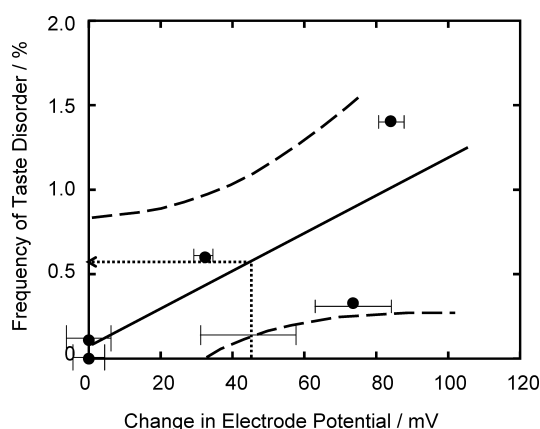


Fig. 2. Correlation Diagram between Frequency of Taste Disorder and Change in Electrode Potential of Zn^{2+}/Zn System Observed in Aqueous Solution

Dotted line: bezafibrate. Broken line: confidence interval (α -level: 0.1).

gree of the taste disorder. In addition, the drug-induced taste disorder tends to be disregarded among the various side effects. Considering such inadequacies, the confidential interval was plotted in the figure assuming that the α -level=0.1 rather than the typical 0.05. Such positive relation using α -level=0.1 suggests the significance for further investigation between the drug-induced taste disorder and the complex formation with Zn^{2+} .

Comparison of Zn^{2+} and Cu^{2+} There are many physiologically active substances containing Zn^{2+} and Cu^{2+} that act as an active center for physiological action. Furthermore, the competitive physiological action between Zn^{2+} and Cu^{2+} has been widely investigated, such as in enzymatic activities. Tarui has reported that urinary zinc increased when the chelating agents were administered, while only a slight change in the concentration of the urinary copper was observed.^{5,6)}

Considering the many physiological compounds containing Zn^{2+} and Cu^{2+} , the chelating ability of Cu^{2+} with drugs was examined for comparison. These results are shown in Table 1. The number of the observed experimental data was four including bezafibrate. Other drugs represented large positive potential changes presumably because of the oxidation reaction by Cu^{2+} . Although the number of observed data was few, the potential changes in the $Cu^{2+}/Cu(Hg)$ system was lower than that of the corresponding $Zn^{2+}/Zn(Hg)$ system in all the drugs examined without exception. It is well known that the stability constants of Cu^{2+} with various ligands are generally greater than those of Zn^{2+} as seen in the data book.¹⁸⁾ The present result is consistent with Tarui's findings.^{5,6)} These facts suggest that the drugs with stronger chelating ability for Zn^{2+} than with Cu^{2+} have a possibility to induce the taste disorder.

Anticipation of the Frequency of the Taste Disorder If the regression equation, Eqs. 6 or 7 actually elucidated the relation between the chelating ability and the drug-induced taste disorder, the frequency of the taste-disorder caused by the drug administration could be estimated. The case of the drug-induced taste disorder due to bezafibrate is not mentioned in the listing of ethical drugs 2006 published by JAPIC.¹⁶⁾ On the other hand, the possibility of a drug induced taste disorder of bezafibrate was reported in a previous

study.¹⁵⁾ The frequency of the drug-induced taste disorder of bezafibrate was estimated from the electrode potential change in the $Zn^{2+}/Zn(Hg)$ system using regression Eqs. 6 and 7. The result is shown in Figs. 1 and 2 by the dotted lines. It was 0.41 and 0.56 in Figs. 1 and 2, respectively. The dependency of the frequency will be determined in a future clinical investigation.

Conclusion

The chelating ability of drugs with Zn^{2+} or Cu^{2+} can be estimated from the chemical formula of the drugs, and the possibility of the drug-induced taste disorder can also be anticipated from the chemical formula. However, a true evaluation will be elucidated from the quantitative analysis such as the stability constant of the metal ion complex. The electrode potential change of the $Zn^{2+}/Zn(Hg)$ was examined during the addition of the drug, and a positive relation between the potential change and the frequency of the drug-induced taste disorder was observed in this study. The assumption that the drug-induced taste disorder is ascribed to the zinc chelating ability seems plausible. If this is true, the drug-induced taste disorder can be anticipated from the electrode potential change, and such information would be required in the package inserts or interview form.

It should also be emphasized that not all the drug-induced taste disorders are ascribed to the zinc chelating ability. For example, cisplatin was expected to have a different mechanism for the taste disorder if the present results were taken into consideration. So far, the drug-induced taste disorders have been disregarded in clinical cases and the systematic examination of the drug-induced taste disorder has been ignored. Accordingly, it is also emphasized that the degree of the drug-induced taste should be quantified using the five-

level rating system. To do so, the correlation between the clinical frequency of the drug-induced taste disorder and the electrode potential change will become more reliable. For example, it is suggested that the drugs different from the regression Eqs. 6 or 7 have a possibility to have different mechanism for the drug-induced taste disorder.

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