—Notes—

Detoxication Treatment for Carbamazepine and Lithium Overdose

Hiroko UNEI,[a] Hiroaki IKEDA,*,[a] Teruo MURAKAMI,[b] Koichi TANIGAWA,[c] and Kenji KIHIRA[a]

[a]*Department of Pharmaceutical Services, Hiroshima University Hospital, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan,* [b]*Laboratory of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmaceutical Sciences, Hiroshima International University, 5–1–1 Hiro-koshingai, Kure City 737–0112, Japan and* [c]*Department of Advanced Emergency and Critical Care Center, Hiroshima University Hospital, 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan*

(Received August 9, 2007; Accepted October 22, 2007; Published online October 23, 2007)

This article reports detoxication treatments of a case of combined overdose of carbamazepine and lithium in a 38-year-old female with bipolar disorder. She was brought to the emergency unit after the family found her unresponsive and lying near empty packages for carbamazepine (corresponded to 7.7 g) and lithium carbonate (corresponded to 6.6 g) tablets. On admission, her blood pressure, heart rate and respiratory rate were 80/55 mmHg, 90 per minute and 13 per minute, respectively. Her GCS was 3 (E1, M1, V1). She received gastric lavage after intratracheal intubation, followed by administration of activated charcoal *via* gastric tube, and a large volume (800 ml/h) of lactate Ringer's solution by intravenous infusion. The serum levels of carbamazepine and lithium approximately 5 h after ingestion were 56.0 μg/ml and 3.56 mEq/l, respectively. The carbamazepine overdose was mainly treated by a 3 h charcoal hemoperfusion (CHP). The CHP treatment decreased serum carbamazepine levels by approximately 30–40% as compared with the levels simulated by Bayesian analysis using 1-point or 2-points serum level(s) (without detoxication treatment). For lithium overdose continuous infusion of Ringer's solution was effective, which increased serum sodium gradually and facilitated the elimination of lithium. In conclusion, the treatments with CHP and continuous infusion of Ringer's solution were considered to be effective for detoxification of carbamazepine and lithium overdose, respectively, when compared with those drug levels without detoxication treatment that simulated by Bayesian analysis method.

Key words——overdose poisoning; carbamazepine; lithium; detoxication treatment; charcoal hemoperfusion; Bayesian analysis

INTRODUCTION

Drug overdoses lead to a variety of poisoning symptoms over time, including impaired consciousness and hemodynamic instability. In such patients, information on time profiles of drug levels in the blood (serum) would be highly beneficial for predicting time-dependent poisoning symptoms and facilitating timely interventions that prevent adverse effects.[1,2] The present study reports a case of carbamazepine and lithium overdose in a 38-year-old female with bipolar disorder.

Carbamazepine is an anticonvulsant, mood-stabilizing drug used primarily in the treatment of epilepsy and bipolar disorders. Lithium is a mood-stabilizing drug used in the treatment of bipolar disorders. Carbamazepine is considered safe when used appropriately, but overdoses can be life threatening.[3,4–7] Lithium overdoses are divided into 3 types: acute, acute on chronic, and chronic, depending on administration modality. The severity of lithium intoxication is quite different for these distinct types of lithium poisoning.[1,8] Charcoal hemoperfusion (CHP) and injections of activated charcoal into the stomach coupled with aggressive intestinal purging are clinically effective detoxification methods for carbamazepine poisoning.[4,9–13] For lithium poisoning, careful attention must be given to the sodium and fluid balance, in addition to promoting renal clearance or hemodialysis for patients who have renal impairment.[1,8,14]

In the present study, the patient with carbamazepine and lithium overdose was treated with CHP and continuous infusion of Ringer's solution. Also, the clinical efficacy of the treatments was evaluated by measuring serum carbamazepine and lithium levels with time and by comparing the values with those drug levels without detoxication treatment that simulated by Bayesian analysis method.

*e-mail: ike@hiroshima-u.ac.jp

A CASE PRESENTATION

Treatment A 38-year-old female weighing 55 kg with bipolar disorder had been treated with carbamazepine (tablets, Tegretol®, Novartis Pharma K.K, Tokyo, Japan) and lithium carbonate (tablets, Limas®, Taisho Pharmaceutical Co., Ltd, Tokyo, Japan) for more than two months at the outpatient clinic of Hiroshima University Hospital. During this period, the daily doses of carbamazepine and lithium carbonate were 700 mg and 600 mg, respectively. One day, the family found her lying unresponsive near empty packages of carbamazepine (corresponding to 7.7 g) and lithium carbonate (6.6 g) tablets. She was transported by ambulance to the emergency room at Hiroshima University Hospital after the ingestion. Physical examination on admission revealed: GCS E1. V1. M1., blood pressure at 80/55 mmHg, heart rate at 90 per m, and respiratory rate at 13 per m. Neither rhythm disturbance in the electrocardiograph nor convulsive seizure was observed. The patient underwent repeated gastric lavage with 7000 ml of normal saline following intra-tracheal intubation. She then received 20 g activated charcoal and 250 ml of magnesium citrate solution (13.6% liquid, Magcolol®, Horii Pharmaceutical Ind., Ltd, Osaka, Japan) *via* gastric tube. Subsequently, she received a large intravenous infusion (800 ml/h) of lactate Ringer's solution (lactate, 28 mEq/l; sodium, 130 mEq/l). During these treatments, blood was sampled to measure serum carbamazepine and lithium levels. The first sampling time of blood was assumed to be approximately 3 h after the ingestion, since the family was keeping considerable attention to her on the day. The carbamazepine overdose was more severe than that of lithium, as compared to their therapeutic levels. The carbamazepine intoxication was treated with sodium heparin-added charcoal hemoperfusion (CHP) for 3 h, which was initiated approximately 2 h after admission (5 h after ingestion). Blood was taken 7 times during these treatments to measure carbamazepine, lithium and sodium levels in serum. Blood (3 ml each) was centrifuged (Kubota KN-70, Kubota Cooperation, Tokyo, Japan) at 10000 rpm for 15 m to obtain serum samples. The serum levels of carbamazepine were measured by Fluorescence Polarization Immunoassay (FPIA) using the TDX FLX system (Abbott Japan Diagnostics Division, Tokyo, Japan), and levels of lithium and sodium were by Na/K/Li Analyzer (Ciba-Corning 654 Analyzer, Bayer Diagnostics, Tokyo, Japan). Bayesian analysis was applied to simulate the time course of both drug levels in serum[15,16] on VCM-TDM E_edition Ver. 2.04 (Shionogi & Co., Ltd.).

After intensive treatment for 3 days, the patient was transferred to a psychiatric ward. The permission of the presentation to the scientific meeting and submitting to the scientific journal of article was obtained from the patient after the completion of detoxication treatment.[17,18]

TDM Data The serum levels of carbamazepine and lithium immediately after admission were 50.5 μg/ml and 3.20 mEq/l, respectively, and at 2 h later, they were 56.0 μg/ml and 3.56 mEq/l. As described, the first sampling time of blood was assumed to be 3 h after ingestion of drugs. Using these 1-point (3 h) and 2-points (3 and 5 h after ingestion) serum data for each drug, the serum level-time profiles were obtained by the Bayesian analysis method. The simulated curves using 1-point and 2-points serum data of both carbamazepine and lithium were similar as shown in Figs. 1 and 2. No noticeable difference in estimated parameters emerged between the 1-point and 2-points Bayesian analyses (Table 1), in which the absorption rate constant alone of each drug was different from the value reported in population pharmacokinetics studies.[15]

The serum carbamazepine level (56.0 μg/ml) at 5 h after ingestion was approximately 4-fold higher than the maximal therapeutic level (15 μg/ml). Thus, the overdose of carbamazepine was considered to be more severe than that of lithium. The serum carbamazepine level after 3-h CHP treatment was lower than the simulated level by the Bayesian analysis method (without detoxification treatment) (Fig. 1). CHP treatment could decrease the area under the concentration-time curve of serum carbamazepine from 0 to 44 h (AUC_{0-44}) after ingestion, which was calculated by a trapezoidal rule, by approximately 30% of the simulated serum levels by the Bayesian analysis method (without detoxification treatment) (Table 2). Without the CHP treatment, it may take 32 h for serum carbamazepine level to fall to the upper therapeutic level in the patient. However, the CHP treatment could reduce the time to 21 h after ingestion (Fig. 1, Table 2).

Lithium level in the patient (3.56 mEq/l) was approximately 3-fold higher than the maximal therapeu-

Table 1. Pharmacokinetic Parameters of Carbamazepine and Lithium in Overdose in a 38-year-old Female that Calculated by the Bayesian Method

Parameter	Carbamazepine			Lithium		
	Population	1-point	2-points	Population	1-point	2-points
Elimination rate constant (h^{-1})	0.0292	0.0292	0.0295	0.0266	0.0265	0.0273
Half life (h)	23.8	23.7	23.5	26.1	26.2	25.4
Absorption rate constant (h^{-1})	1.230	0.354	0.389	1.500	0.083	0.070
Distribution vol. (l/kg)	1.61	1.70	1.84	0.79	0.79	0.80
Clearance (l/kg/h)	0.047	0.050	0.054	0.021	0.021	0.022

Doses of carbamazepine and lithium carbonate were assumed to be 7700 mg and 6600 mg, respectively. For pharmacokinetic analysis, the lag time before absorption was set at 0. Population means the average value obtained by population pharmacokinetics data. 1-point: Basian analysis was made using 1-point serum level of each drug (3 h after ingestion). 2-points: Basian analysis was made using 2-points serum levels of each drug (3 and 5 h after ingestion).

Table 2. Effect of Detoxification Treatments on Pharmacokinetic Parameters of Carbamazepine and Lithium in Overdose in a 38-year-old Female Patient

Parameter	Carbamazepine		Lithium	
	Simulated	Observed	Simulated	Observed
Peak serum level (μg/ml or mEq/l)	61.6	56.0	3.65	3.56
Time to reach Peak level (h)	6.0	4.8	4.5	4.8
AUC_{0-44} (μg·h/ml or mEq·h/l)	1817	806	102	64
Time to therapeutic level (h)	57.5	21.2	46.0	21.1

Doses of carbamazepine and lithium carbonate were assumed to be 7700 mg and 6600 mg, respectively. Parameters were simulated by Baysian method using 2-points serum levels at 3 and 5 h after ingestion.

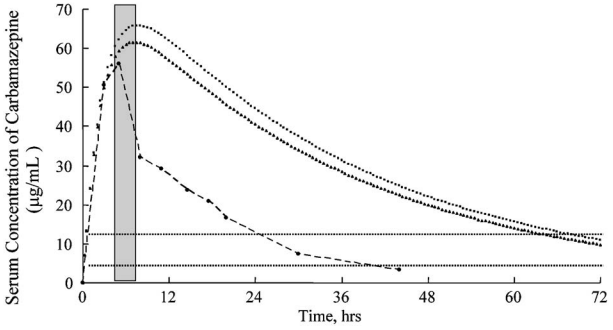

Fig. 1. Time Course for Serum Carbamazepine Following Ingestion of 7.7 g Carbamazepine in a 38-year-old Female

A 3-h charcoal hemoperfusion (CHP) was carried out 5 h after ingestion. Closed circles with broken line represent the observed serum carbamazepine concentrations before, during and after detoxication treatments. Two dotted lines represent the time courses for serum carbamazepine simulated by the Bayesian method using 1-point (■) and 2-points (●) serum levels prior to CHP treatment (without detoxication treatment). ----- : Therapeutic range of carbamazepine is 4–12 μg/ml in serum. ▭: Charcoal Hemoperfusion (3 h)

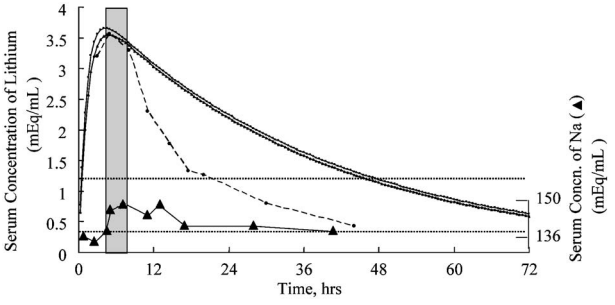

Fig. 2. Time Courses for Serum Lithium (solid circles) and Sodium Ions (triangles) Following Ingestion of 6.6 g Lithium Carbonate in a 38-year-old Female

A 3-h charcoal hemoperfusion (CHP) was carried out 5 h after ingestion. Closed circles with broken line and closed triangles with solid line represent the observed serum lithium and sodium concentrations, respectively, before, during and after detoxication treatments. Two dotted lines represent the time courses for serum lithium simulated by the Bayesian method using 1-point (■) and 2-points (●) serum levels prior to CHP treatment (without detoxication treatment). ----- : Therapeutic range of lithium is 0.4–1.2 mEq/ml in serum. ▭: Charcoal Hemoperfusion (3 h)

tic level (1.25 mEq/l). During constant infusion of lactate Ringer's solution, the elimination of lithium from plasma appeared to be facilitated, in association with the increase in serum Na concentrations (Fig. 2). The AUC_{0-44} of serum lithium was lower by 38% than that simulated by the Bayesian analysis method (without detoxification treatment) (Table 2). Without the treatment, it may take 48 h for serum lithium level to fall to the upper therapeutic level in the patient. The intravenous infusion of lactate Ringer's solution could reduce the time to 21 h after ingestion (Fig. 2, Table 2).

DISCUSSION

Accidental or intentional poisoning by drug overdose occurs at a high rate. Among antiepileptic drugs, carbamazepine is reportedly the second most common overdose drug in U.S., following valproic acid.[19–22] Four distinct stages of carbamazepine poisoning have been reported. Based on serum carbamazepine levels the stages are: potentially catastrophic relapse at $<11\ \mu g/ml$; drowsiness, ataxia at 11–15 $\mu g/ml$; combativeness, hallucinations at 15–25 $\mu g/ml$; and coma, seizures at $>25\ \mu g/ml$[3,4–7,23–25]. In the present case, the serum level of carbamazepine at the second mesurement (possibly 5 h after ingestion) was 56.0 $\mu g/ml$ (Fig. 1). Similarly, the severity of lithium poisoning reportedly correlates with serum lithium levels, although lithium poisoning differs with drug history as described above. Symptoms of severe toxicity, which can be life-threatening, include marked delirium, coma and seizures at >2.5 mmol/l in serum, though morbidity and mortality are rare.[1,8,26] In the present case, the serum lithium level possibly 5 h after ingestion was 3.56 mEq/l.

Carbamazepine is mostly eliminated by hepatic metabolism, with only 1% to 3% renal excretion, and lithium is eliminated mostly to the urine by glomerular filtration and secretion.

In the present case, the carbamazepine and lithium overdose was mainly treated by gastric lavage, administration of activated charcoal, intravenous volume loading, and CHP. Administration of activated charcoal followed by the gastric lavage treatment are thought to have effectively removed the drugs remaining in the stomach, since the absorption rate constants for both carbamazepine and lithium estimated by Bayesian analysis were fairly lower than reported values.[15,16] Bayesian analysis is performed by using fractional individual patient data (1–4 samples) under steady state and population pharmacokinetic parameters and is applied to settle adequate dosage schedules of drugs from individual pharmacokinetic parameters. This technique has proven useful for TDM for drugs with narrow therapeutic ranges, including the aminoglycosides, digoxin, anticonvulsants, lithium and theophylline, particularly where drug concentrations are measured during relatively complicated dosage regimens.[27] In the present study, the Bayesian analysis method was utilized to simulate the time profiles of carbamazepine and lithium overdosed by using 1-point and 2-points serum drug data and reported population pharmacokinetic parameters. As a result, the simulation was made only by changing absorption rate constants from reported population pharmacokinetic parameters (Table 1). The carbamazepine was treated with CHP, since the efficacy of CHP for carbamazepine poisoning has been well documented.[6,9–13] As shown in Fig. 1, CHP increased carbamazepine elimination dramatically. In parallel, the lithium overdose was treated with intravenous sodium and volume loading, since the reabsorption of lithium ions at the renal proximal tubule could be suppressed by a higher concentration of sodium ions and a greater volume of renal-tubule fluid, resulting in increased renal excretion of lithium ions.[8] The continuous infusion of Ringer's solution increased serum sodium gradually, and serum lithium levels clearly decreased as a result (Fig. 2). Hemodialysis is also reportedly a useful detoxification method for lithium, especially in patients with serum lithium levels higher than 3.5 mEq/l or renal impairment[1,8,28].

For patients who ingest multiple substances simultaneously, it is important to set treatment priorities as soon as possible. The severity of poisoning will vary, so the detoxification method will differ in each case. In this study, CHP was effective in decreasing serum carbamazepine, but not lithium. Therefore monitoring and predicting drug level-time profiles were important tools in deciding treatment priorities.

The Bayesian dosing program is clinically valid when two feedback levels are known.[29,30] In the present study, we compared 1-point serum data at 3 h and 2-points at 3 and 5 h after ingestion. In clinical situations, the 1-point Bayesian analysis may be more useful because there may not be time to take two blood samples before initiating treatment. Previously, the Bayesian method was applied to a theophylline overdose (2400 mg, sustained-release tablet) in a young female.[31] The initial observed serum theophyllin level at 2 h was within the therapeutic level (10–20 $\mu g/\mu l$). However, Bayesian analysis indicated that the maximal toxic level (32 $\mu g/ml$) would be reached at 12 h after ingestion. It was also estimated more than 28 h would elapse before the serum theophyllin level decreased to the upper therapeutic level. Although only the 1-point serum theophyllin level (2 h after ingestion) was used for the Bayesian analysis, the predicted values were quite close to the observed

values thereafter.

In the present study, Bayesian analysis method was applied to a case of carbamazepine and lithium overdose in deciding the treatment strategy most likely to prevent convulsions and arrhythmia under artificial ventilation[30] and in evaluating clinical efficacy of detoxication treatments. As shown in Figs. 1 and 2, 1-point serum levels of carbamazepine and lithium were nearly as predictive of serum level profiles as the 2-points data. To simulate the time course of serum drug concentrations from 1-point or 2-points serum drug levels pharmacokinetically, it will be very important to know the time of injestion correctly. In the present case, the family did know her suicide tendency and observed her carefully on a daily basis. Thus, her ingestion time of carbamazepine and lithium was speculated with a fairly short margin of error. In general, however, it will be not easy to speculate the ingestion time correctly. In such case, multiple simulation curves of Baysian analysis should be prepared by applying the different ingestion times. Then, by determining the second and/or the third points of substance levels during the first-aid treatment, an appropriate simulation curve by Baysian analysis may be selected.

CONCLUSION

A case of combined overdose of carbamazepine and lithium was treated successfully with a 3 h charcoal hemoperfusion and continuous intravenous infusion of a large volume (800 ml/h) of lactate Ringer's solution. These treatments were considered to be effective in facilitating the elimination of both drugs from serum, as evaluated by Baysian analysis method pharmacokinetically.

REFERENCES

1) Dawson A. H., Whyte I. M., *Br. J. Clin. Pharmacol.*, **48**, 278–283 (1999).
2) Dawson A. H., Whyte I. M., *Br. J. Clin. Pharmacol.*, **52**, 97S–102S (2001).
3) Graudins A., Peden G., Dowsett R. P., *Emerg. Med.*, **14**, 89–94 (2002).
4) Crome P., *Med. Toxicol.*, **1**, 261–285 (1986).
5) Fisher R. S., Cysyk B., *J. Toxicol. Clin. Toxicol.*, **26**, 477–486 (1988).
6) Cameron R. J., Hungerford P., Dawson A. H., *J. Toxicol. Clin. Toxicol.*, **40**, 507–512 (2002).
7) Spiller H. A., Carlisle R. D., *J. Toxicol. Clin. Toxicol.*, **40**, 81–90 (2002).
8) Timmer R. T., Sands J. M., *J. Am. Soc. Nephrol.*, **10**, 666–674 (1999).
9) Chan K. M., Aguanno J. J., Jansen R., Dietzler D. N., *Clin Chem.*, **27**, 1300–1302 (1981).
10) De Groot G., Van Heijst A. N., Maes R. A., *J. Toxicol. Clin. Toxicol.*, **22**, 349–362 (1984).
11) Sethna M., Solomon G., Cedarbaum J., Kutt H., *Epilepsia*, **30**, 71–73 (1989).
12) Montoya-Cabrera M. A., Sauceda-Garcia J. M., Escalante-Galindo P., Flores-Alvarez E., Ruiz-Gomez A., *Arch. Med. Res.*, **27**, 485–489 (1996).
13) Deshpande G., Meert K. L., Valentini R. P., *Pediatr. Nephrol.*, **13**, 775–777 (1999).
14) Linder M. W., Keck P. E. Jr., *Clin. Chem.*, **44**, 1073–1084 (1998).
15) Higuchi S., Fukuoka R., Aoyama T., Horioka M., *J. Pharmacobiodyn*, **11**, 158–174 (1988).
16) Hori R., Okumura K., Kitazawa S., Koshiro A., Saitoh Y., Higuchi S., Mizugaki M., Yamaji A., Rikihisa T., Tanigawara Y., *Yakuzaigaku*, **49**, 304–312 (1989).
17) Koppel C., Schirop T., Ibe K., Tenczer J., Ehrenburg J., Gayer J., *Intensive Care Med*, **13**, 358–360 (1987).
18) Kerbusch T., Mathot R. A., Otten H. M., Meesters E. W., van Kan H. J., Schellens J. H., Beijnen J. H., *Pharmacol. Toxicol.*, **90**, 243–245 (2002).
19) Litovitz T. L., Klein-Schwartz W., White S., Cobaugh D. J., Youniss J., Drab A., Benson B. E., *Am. J. Emerg. Med.*, **18**, 517–574 (2000).
20) Litovitz T. L., Klein-Schwartz W., White S., Cobaugh D. J., Youniss J., Omslaer J. C., Drab A., Benson B. E., *Am. J. Emerg. Med.*, **19**, 337–395 (2001).
21) Litovitz T. L., Klein-Schwartz W., Rodgers G. C. Jr., Cobaugh D. J., Youniss J., Omslaer J. C., May M. E., Woolf A. D., Benson B. E., *Am. J. Emerg. Med.*, **20**, 391–452 (2002).
22) Askenazi D. J., Goldstein S. L., Chang I. F., Elenberg E., Feig D. I., *Pediatrics.*, **113**, 406–409 (2004).
23) Weaver D. F., Camfield P., Fraser A., *Neurology.*, **38**, 755–759 (1988).

24) Bridge T. A., Norton R. L., Robertson W. O., *Pediatr. Emerg. Care*, **10**, 260–263 (1994).
25) Stremski E. S., Brady W. B., Prasad K., Hennes H. A., *Ann. Emerg. Med.*, **25**, 624–630 (1995).
26) Bailey B., McGuigan M., *Ther. Drug Monit.*, **22**, 650–655 (2000).
27) Thomson A. H., Whiting B., *Clin. Pharmacokinet.,* **22**, 447–467 (1992).
28) Kasahara H., Shinozaki T., Nukariya K., Nishimura H., Nakano H., Nakagawa T., Ushijima S., *Jpn. J. Psychiatry Neurol.,* **48**, 1–12 (1994).
29) Garcia M. J., Alonso A. C., Maza A., Santos D., Matesanz C., Dominguez-Gil A., *J. Clin. Pharm. Ther.*, **13**, 375–380 (1988).
30) Gaulier J. M., Boulieu R., Fischer C., Mauguiere F., *J. Pharm. Pharmacol.*, **49**, 734–736 (1997).
31) Yamanoue T., Okabayashi K., Ikeda H., Iwasaki Y., Kitaura T., Unei H., Inoue T., Wada S., Kihira K., Ohtani M., *J. Jpn. Soc. Emer. Med.*, **3**, 438–441 (2000).