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Synergistic effect of combining theophylline and drugs that potentially elevate serum creatine kinase

Junko Iwano*, Yoichi Nakamura†, Takashi Izumida*, Masayuki Yokota*, Yoshiharu Takiguchi*, Kazuo Minakuchi‡, and Saburo Sone†

*Department of Clinical Pharmacology, The University of Tokushima Faculty of Pharmaceutical Sciences, Tokushima, Japan ; and †Third Department of Internal Medicine, and ‡Division of Pharmacy, University Hospital, The University of Tokushima School of Medicine, Tokushima, Japan

Abstract : An increase in the serum creatine kinase (CK) level is one of the side effects of theophylline ; on rare occasions, the increase may be followed by rhabdomyolysis. Theophylline is often administered with drugs that potentially elevate the serum CK level (CK-elevating drugs) such as β-agonists and steroids. However, the effects of the combined treatment of theophylline and CK-elevating drugs have not been reported. We, therefore, retrospectively investigated the effects of combined treatment on the serum CK level, in 391 asthmatic outpatients.

In this study, the number and type of the CK-elevating drugs administered, and the serum levels of CK and theophylline, were investigated. The patients were divided into four groups : the theophylline-treated and CK-elevating drug-treated group, the theophylline-treated and non-CK-elevating drug-treated group, the non-theophylline-treated and CK-elevating drug-treated group, and the non-theophylline-treated and non-CK-elevating drug-treated group.

The theophylline-treated and CK-elevating drug-treated group showed about 100% higher serum CK levels (225 IU/L) than any other group (102-124 IU/L), and no increase in the serum theophylline level. This result indicates that there is a synergistic effect of theophylline and CK-elevating drugs on the serum CK level.

The combined treatment of theophylline and CK-elevating drugs induces a synergistic increase in the serum CK level, indicating not pharmacokinetic but pharmacodynamic interactions with these drugs. J. Med. Invest. 47 : 9-13, 2000

Key words : *theophylline, creatine kinase, drug interaction*

INTRODUCTION

Theophylline is used for the treatment of asthma and chronic obstructive pulmonary disease. The effective serum level of theophylline for asthma is over 5 μg/mL (1, 2). The toxic serum level is over 20 μg/mL, and may induce headache, nausea, vomiting, palpitations, insomnia, diarrhea, or rhabdomyolysis (3, 4). Furthermore, cardiac arrhythmias or seizures, which are sometimes fatal, may occur with more than 40 μg/mL (5, 6). Therefore, these adverse effects are generally induced by the increase in serum theophylline, which is often caused by an overdose of theophylline or some theophylline metabolism-inhibiting drugs such as macrolides, quinolones, cimetidine and so on (pharmacokinetic drug interaction) (7-9).

Rhabdomyolysis, the colliquation and necrosis of skeletal muscle, is one of the serious adverse effects of theophylline (10, 11). The symptoms include adynamia, pain and swelling of extremital muscles, numbness, myoglobinuria and acute renal

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Address correspondence and reprint requests to Masayuki Yokota, Department of Clinical Pharmacology, The University of Tokushima Faculty of Pharmaceutical Sciences, Shomachi 1-78, Tokushima 770-8505, Japan and Fax : +81-88-633-9516.

failure (12, 13). A high level of serum creatine kinase (CK) may serve as an index in diagnosing or predicting rhabdomyolysis (14, 15).

CK, a component of muscle cells, is present at high levels in serum in these conditions. This increase in CK results from damage to skeletal muscle or cardiac tissue, including acute myocardial infarction, muscular dystrophy, and polymyositis. It is also involved in trauma, seizures, hypothyroidism, rhabdomyolysis. The overdose of certain drugs including theophylline may also induce rhabdomyolysis (16, 17).

Theophylline is often administered together with drugs that potentially elevate the serum CK level (CK-elevating drugs) such as β-agonists, steroids, and antihyperlipidemics (18). However, the effects of this combined treatment, which may increase the serum CK level and possibly induce rhabdomyolysis, have not been reported. We retrospectively investigated the effects of this combined treatment on the serum CK level in 391 asthmatic outpatients.

PATIENTS AND METHODS

PATIENTS

The present study was performed on a total of 391 outpatients (female : 230, male : 161) with asthma ranging in age from 18 to 77 years (mean±SE : 55 ±1). They were examined at the Asthmatic Consultation of the Third Department of Internal Medicine, University Hospital, The University of Tokushima School of Medicine, from January 1995 to September 1997. We examined the number and kind of prescribed drugs and the CK and theophylline serum levels in these patients, retrospectively from their medical records.

The 391 patients were first divided into theophylline-treated (313 patients) and non-theophylline-treated (78 patients) groups. Of the theophylline-treated patients, 124 had been treated with CK-elevating drugs (theophylline-treated and CK-elevating drug-treated group), and 189 had not (theophylline-treated and non-CK-elevating drug-treated group). Of the non-theophylline-treated patients, 15 had been treated with CK-elevating drugs (non-theophylline-treated and CK-elevating drug-treated group), and 63 had not (non-theophylline-treated and non-CK-elevating drug-treated group) (Table 1).

Next, in the theophylline-treated and CK-elevating drug-treated group (124 patients), we examined the serum theophylline levels of 77 patients and divided them into two groups, namely, the CK-elevating drug-treated and theophylline-elevating drug-treated group (23 patients) and the CK-elevating drug-treated and non-theophylline-elevating drug-treated group (54 patients). In the theophylline-treated and non-CK-elevating drug-treated group (189 patients), we examined the serum theophylline levels of 92 patients and similarly divided them into two groups, namely, the non-CK-elevating drug-treated and theophylline-elevating drug-treated group (19 patients) and the non-CK-elevating drug-treated and non-theophylline-elevating drug-treated group (73 patients) (Table 2). Theophylline-elevating drugs were defined as drugs that elevate the serum

Table 1. Characteristics of asthmatic outpatients

	Theophylline-treated			Non-theophylline-treated			Total
	CK-elevating drug			CK-elevating drug			
	(+)	(-)	Total	(+)	(-)	Total	
Number of outpatients							
female	80	98	178	12	40	52	230
male	44	91	135	3	23	26	161
total	124	189	313	15	63	78	391
Age (Mean±SE)	55±1	54±1	55±1	64±3	51±2	54±2	55±1
range	(22-77)	(18-76)	(18-77)	(49-73)	(22-73)	(22-73)	(18-77)
CK-elevating drugs							
β-agonist	80			4			84
steroid	54			7			61
antihyperlipidemic	25			3			28
others	20			1			21
total	179			15			194

Table 2. Characteristics of theophylline-treated asthmatic outpatients whose serum theophylline levels were examined

	CK-elevating drug-treated			Non-CK-elevating drug-treated			Total
	Theophylline-elevating drug			Theophylline-elevating drug			
	(+)	(-)	Total	(+)	(-)	Total	
Number of outpatients							
female	12	37	49	11	35	46	95
male	11	17	28	8	38	46	74
total	23	54	77	19	73	92	169
Age (Mean±SE)	55±1	54±1	54±1	62±3	55±2	56±1	55±1
range	(39-70)	(30-74)	(30-74)	(41-76)	(20-75)	(20-76)	(20-76)
Theophylline-elevating drugs							
macrolide	12			14			26
allopurinol	13			10			23
others	4			11			15
total	29			35			64

theophylline level ; the elevation was probably due to the inhibition of theophylline metabolism.

METHODS

The serum CK levels were measured by UV spectral analysis using the autoanalyzer 736 (Hitachi, Japan) for 391 patients. The serum theophylline levels were measured with an enzyme-multiple immunoassay technique using the analyzer 7150 (Hitachi, Japan) for 169 patients.

Statistics

ANOVA and Fisher's PLSD test for multiple comparisons were used to compare the serum levels of CK or theophylline between two groups. Differences were considered significant at $P<0.01$.

RESULTS

Serum CK levels

Some 179 CK-elevating drugs were used (1.4 drugs/person on average) in the theophylline-treated and CK-elevating drug-treated group. One drug was used for each patient (1.0 drug/person on average) in the non-theophylline-treated and CK-elevating drug-treated group. β-agonists, steroids and anti-hyperlipidemics were used as CK-elevating drugs (Table 1).

The mean (±SE) serum CK level of the 313 theophylline-treated patients was 164±11 IU/L. This was significantly higher ($P<0.0001$) than that of the 78 non-theophylline-treated patients (102±7 IU/L).

As shown in Fig.1, the mean (±SE) serum CK level of the theophylline-treated and CK-elevating drug-treated group (124 patients) was 225±25 IU/L, significantly higher than the value for any other group ($P<0.01$). The mean serum CK level of the theophylline-treated and non-CK-elevating drug-treated group (189 patients) was 124±6 IU/L, that of the non-theophylline-treated and CK-elevating drug-treated group (15 patients) was 102±14 IU/L, and that of the non-theophylline-treated and non-CK-elevating

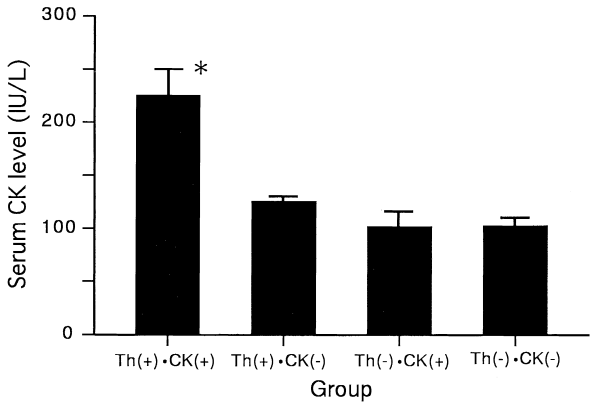

Fig. 1. Serum CK levels (mean±SE) of asthmatic outpatients. Patients were divided into four groups, namely Th(+)·CK(+) (theophylline-treated and CK-elevating drug-treated group), Th(+)·CK(-) (theophylline-treated and non-CK-elevating drug-treated group), Th(-)·CK(+) (non-theophylline-treated and CK-elevating drug-treated group), and Th(-)·CK(-) (non-theophylline-treated and non-CK-elevating drug-treated group).
*$P<0.01$ compared with Th(+)·CK(-), Th(-)·CK(+) and Th(-)·CK(-).

Table 3. Serum theophylline level of asthmatic outpatients treated with theophylline

	CK-elevating drug-teated			Non-CK-elevating drug-treated		
	Theophylline-elevating drug			Theophylline-elevating drug		
	(+)	(-)	Total	(+)	(-)	Total
Serum theophylline level (μg/mL) (Mean±SE)	11.2±1.1	9.1±0.5	9.7±0.5	8.7±1.3	8.7±0.5	8.7±0.5

Not significantly different between any two groups.

drug-treated group (63 patients) was 102±8 IU/L. No significant difference was obtained between any two of these three groups.

Serum theophylline levels

As shown in Table 3, the mean (±SE) serum theophylline level of the CK-elevating drug-treated and theophylline-elevating drug-treated group (23 patients) was 11.2±1.1μg/ml, that of the CK-elevating drug-treated and non-theophylline-elevating drug-treated group (54 patients) was 9.1±0.5 μg/ml, that of the non-CK-elevating drug-treated and theophylline-elevating drug-treated group (19 patients) was 8.7±1.3 μg/ml, and that of the non-CK-elevating drug-treated and non-theophylline-elevating drug-treated group (73 patients) was 8.7±0.5μg/ml. No significant difference was obtained between any two groups.

DISCUSSION

In the present study, the relationships of the number and kind of drugs used in combination with theophylline and the serum levels of CK and theophylline were investigated in outpatients with asthma. Theophylline was used in combination with many kinds of drugs, such as β-agonists, steroids, antihyperlipidemics, macrolides, and allopurinol (Table 1, 2). These drugs potentially affect the serum level of CK or theophylline (7-9). Although investigators have reported that the serum CK level elevated as a result of theophylline administration (17, 19, 20), the effects of the combined therapy of theophylline and CK-elevating drugs have not been reported. In the present study, a higher level of serum CK was observed only in the patients treated with both theophylline and the CK-elevating drugs, without an increase in the serum theophylline level (Fig. 1, Table 3). However, the elevated CK level (225 IU/L ; normal range : under 180 IU/L) was not as high as that associated with rhabdomyolisis (3-fold the normal limit) (21).

First, we compared the serum CK level of the theophylline-treated patients (164 IU/L) with that of the non-theophylline-treated patients (102 IU/L). This significant difference was suggested to be due to the CK-elevating effect of theophylline. However, this effect could have been caused by the combination of CK-elevating drugs with theophylline.

Therefore, we examined the effects of theophylline in combination with and without the CK-elevating drugs on the serum CK level. The CK levels might be elevated by either theophylline or the CK-elevating drugs, but were not increased in the present study probably because the doses were not high enough. As shown in Fig.1, the combined treatment of theophylline and the CK-elevating drug produced about 100 IU/L higher levels than any other treatment. While 1.0 CK-elevating drug per person was used in the non-theophylline-treated and CK-elevating drug-treated group, 1.4 CK-elevating drugs per person were used in the combined treatment group. This could have caused the higher serum CK level. For the combined treatment, however, the serum CK level of the patients treated with just one CK-elevating drug was almost the same as that of the patients treated with two or more CK-elevating drugs (data not shown).

Neither the single use of theophyline nor that of the CK-elevating drug significantly affected the CK level, compared with the value for the non-theophylline-treated and non-CK-elevating drug-treated group. The combined treatment of theophylline and the CK-elevating drug increased the serum CK level, probably via a synergistic effect (Fig.1). However, this effect might be due to the higher level of serum theophylline in the combined treatment group than in any other group.

Therefore, we examined the serum theophylline levels in 169 out of the theophylline-treated patients (Table 3). The mean serum theophylline level of the 23 patients treated with both the CK-elevating drug and theophylline-elevating drug appeared to be higher than that of any other group, however,

no significant difference was obtained. Accordingly, the increase in serum CK level with the combined treatment of theophylline and the CK-elevating drug is independent of the serum theophylline level. Furthermore, theophylline has not been reported to increase the serum level of any CK-elevating drug.

In conclusion, our results showed that treatment with theophylline and CK-elevating drugs in combination increases the serum CK level, while their single use does not. Furthermore, this synergistic effect is not caused by an increase in the serum theophylline level, which seems to indicate a pharmacodynamic drug interaction. This synergistic effect may be associated with adverse reactions, but further studies are required to confirm its clinical implications.

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