

# Effect of concomitantly used CYP3A4 inhibitors in patients treated with calcium channel blockers

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## Background:

As previously reported<sup>1)</sup>, we have established large database (ca 125,000 cases) on 19 marketed antihypertensive drugs, including calcium channel blockers (CCBs). This database was established using submitted data for Drug Use Investigations, conducted by pharmaceutical companies, under the Japanese Drug Re-examination System (Fig. 1). We now study using this database, from various points of view, aiming to enhance appropriate use of drugs, especially focused on safety information in depth.

## Objectives:

It is known that most CCBs are mainly metabolized by CYP3A4. We made observational study to see using our database, whether CYP3A4 inhibitors affect in the patients treated with CCBs. The effects of concomitantly used drugs were examined by comparing the frequency of adverse drug reactions (ADRs).

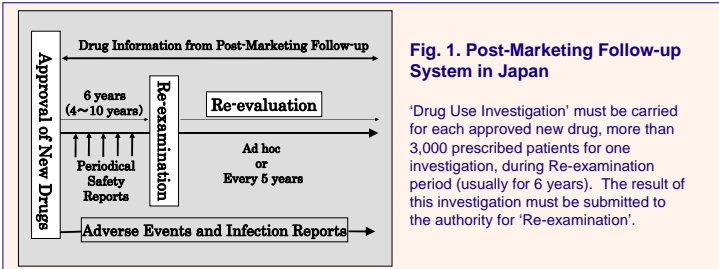


Fig. 1. Post-Marketing Follow-up System in Japan

'Drug Use Investigation' must be carried for each approved new drug, more than 3,000 prescribed patients for one investigation, during Re-examination period (usually for 6 years). The result of this investigation must be submitted to the authority for 'Re-examination'.

## Methods:

Out from the database, we picked out 17,430 patients who receive CCB. According to "the P450 Table of Indiana University"<sup>2)</sup>, we categorized them into 3 groups as follows: concomitantly used CYP3A4 enzyme-inhibitor including substrate of this enzyme (1,632 patients: 1,460+142+30), other concomitant agents (10,170 patients), and no concomitant (5,628 patients) (Table 1). The primary endpoint was the frequency of ADRs. Multiple regression analysis was performed to adjust sex, allergy, pre-medication, combination therapy, and period of administration. These statistical analyses were conducted by using Windows version of 'S'

Table 1. Univariate Analysis on CYP3A4 Inhibitors and ADR

	Total	Case	Freq.	O.R.	95%C.I.	P-Value
No Concomitant	5,628	189	3.4%	1		
Concomitant						
Others	10,170	380	3.7%	1.12	0.94-1.33	0.222 NS
Substrate (S) Only	1,460	65	4.5%	1.34	1.01-1.79	0.046 *
Inhibitor (I) Only	142	6	4.2%	1.27	0.55-2.91	0.573 NS
Both (S) + (I)	30	2	6.7%	2.06	0.49-8.69	0.327 NS
Total	17,430	642	3.7%			(* : p < 0.05, NS: p > 0.10)

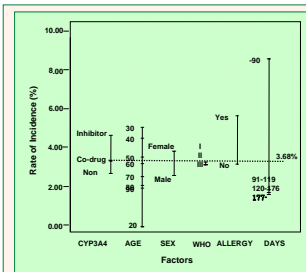


Fig. 2. Design Plot of ADR occurrence

Longitudinal axis is rate of incidence (%). Horizontal axis is suspected factors. Horizontal line of y=3.68 means the total average rate of incidence.

Various factors, such as CYP3A4 inhibitors, allergy patients, sex and the period of administration, might affect on the occurrence of ADR. On the other side, WHO classification on hypertension seems to be no co-relation on the occurrence of ADR.

Classification of Hypertension According to WHO			
Category	Systolic	Diastolic	
Grade 1 (mild)	140-159	90-99	
Grade 2 (moderate)	160-179	100-109	
Grade 3 (severe)	≥180	≥110	

Table 3. Typical ADRs (Top 10)

ADR	Total		No Conc.		Others		I and/or S	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Hot Flashes	209	1.20	72	1.28	84	0.83	22	1.95
Abnormal LFTs *	94	0.54	7	0.12	75	0.74	12	0.74
Headache	91	0.52	31	0.55	50	0.49	10	0.61
Palpitation	88	0.50	34	0.60	43	0.42	11	0.87
Dizziness	66	0.38	22	0.39	50	0.49	11	0.87
Nausea/Vomiting	25	0.14	5	0.09	17	0.17	3	0.18
Rash	21	0.12	5	0.09	13	0.13	2	0.12
Hypotension	19	0.11	4	0.07	10	0.10	5	0.31
Malaise	15	0.09	3	0.05	10	0.10	1	0.06
Abnormal KFTs *	15	0.09	0	0	14	0.14	1	0.06

Number of Cases  
Total 17,430  
No Conc. 5,628  
Others 10,170  
I and/or S 1,632

\* LFT: Liver Function Test  
\* KFT: Kidney Function Test

Table 2. Multivariate Analysis on CYP3A4 Inhibitors and ADRs

	Total	Case	O.R.	95%C.I.	p-Value
<b>Concomitant Drugs</b>					
No Concomitant	5,628	189	1		
Concomitant with					
· Inhibitors and/or					
Substrates	1,632	73	1.34	1.01~1.80	0.045 *
· Others	10,170	380	1.17	0.97~1.41	0.111 NS
<b>Sex</b>					
Male	8,421	233	1		
Female	9,007	409	1.68	1.42~1.99	0.000 *
Unknown	2	0			
<b>Age (year)</b>					
	17,430	642	0.98	0.97~0.99	0.000 *
<b>Classification of Hypertension According to WHO</b>					
Grade 1	7,988	258	1		
Grade 2	4,837	138	0.91	0.73~1.13	0.384 NS
Grade 3	1,378	48	1.14	0.73~1.13	0.432 NS
Unknown	3,229	198	2.73	1.71~4.34	0.000 *
<b>Allergy</b>					
No	14,664	554	1		
Yes	297	23	1.55	0.97~0.99	0.066 +
Unknown	2,469	65	0.93	0.60~1.45	0.745 NS
<b>Pre-medication</b>					
No	5,697	143	1		
Yes	5,980	243	1.73	1.38~2.15	0.000 *
Unknown	5,759	256	0.78	0.49~1.25	0.302 NS
<b>Period of administration (day)</b>					
	17,430	642	0.98	0.98~0.99	0.000 *

(\*: p < 0.05, +: p < 0.10, NS: p > 0.10)

## Results and Discussion:

In our abstract, most of the CYP3A4 inducers were classified as steroids and anti epileptic drugs. In this report, we eliminate the CYP3A4 inducers group, because backgrounds of these patients concomitantly used CYP3A4 inducers might be very much different from those of the ordinary hypertensive patients.

From the results of univariate analysis (Table 1), relative risks for CYP3A4 inhibitors only, substrates only, and CYP3A4 inhibitors and substrates against no-concomitant were calculated as 1.235, 1.324, and 1.971, respectively. Since the number of patients of CYP3A4 inhibitors only, and CYP3A4 inhibitors and substrates were very small, we gathered these two groups with CYP3A4 substrates (CYP3A4 inhibitors and/or substrates group). As a result of univariate analysis, sex, allergy, pre-medication, combination therapy, and the period of administration seemed to be confounding factors (Fig. 2). We adjusted these factors in multivariate analysis.

Comparing with no-concomitant group, the odds ratio of concomitantly use with CYP3A4 inhibitors and/or CYP3A4 substrates was 1.34 (p=0.045), use with others (non-influential drugs to CYP3A4) was 1.17 (p=0.111) (Table 2).

Typical ADRs appeared in patients who administrated CCBs were listed in Table 3. Compared to no-concomitant group, the frequencies of 'Abnormal Liver Function Tests' and 'Hypotension' were increased in CYP3A4 inhibitors and/or substrates group. On the contrary, 'Rash' was not affected by concomitant drugs, since the mechanism of this ADR might be dose independent, allergic reaction.

## Conclusions:

Our studies outcome shows that the group of concomitantly receiving CYP3A4 inhibitors and/or substrates showed higher tendency of ADR in comparison to the group of no-concomitant use.

We tried to use our database for the hypothesis generation and/or strengthen. As a result of this study, it was revealed our database might be useful for this purpose. Since, there is no available large-scale database of post-marketing drugs in Japan, we believed our database of Drug Use Investigations might be a valuable database for risk/benefit assessment of post-marketing drugs. We would like to make an effort to enlarge our database continuously.

## No conflict of interest was declared

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Astra Zeneca K. K.	Chugai Pharmaceutical Co., Ltd.	Daichi Pharmaceutical Co., Ltd
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## Literature cited

- Fujita, et al. Pharmacoepidemiology and Drug Safety 2005; 14: 41-46
- "The P450 Table of Indiana University"  
<<http://medicine.iupui.edu/flockhart/table.htm>>

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