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Correlation between the adverse reactions to intravenous iodinated contrast media and IgE levels

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PURPOSE
The adverse reactions of the iodinated contrast media are believed to be non-IgE mediated and the result of triggering of the release of the mast cell mediators directly. However, the exact mechanism is still controversial and purpose of this prospective study is not only to determine any possible correlation of adverse reactions with total baseline blood IgE levels, but also to investigate the change of the IgE levels in the blood after the administration of the IV iodinated contrast media and correlate this with the various side effects.

MATERIALS AND METHODS
Blood samples were taken from 110 patients who underwent excretory urography just before the administration of the iodinated contrast media and on the 40th minute. Further blood samples were collected from 13 randomly selected patients out of the total 110, a week after the examinations. Total IgE levels were calculated in all samples using electrochemiluminescense immunoassay method.

RESULTS
IgE levels decreased statistically significantly using paired t test in all patients but one. The side effects were independent from the total baseline IgE levels according to the chi-square testing.

CONCLUSION
Results reveal that the measurement of the total baseline IgE levels can not be a prognostic factor for the adverse reactions to iodinated contrast media but the more a factor causes immuneglobuline to decrease after administration of iodinated contrast media, the less adverse reactions happen. Electrochemiluminescense immunoassay method ought to be scrutinized for the detection of IgE binded with iodinated contrast media.

Key words: contrast media • immuneglobuline E

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In radiological imaging, it is usually believed that the adverse reactions of intravenous (IV) iodinated contrast media (ICM) are non-IgE mediated anaphylactoid reactions, by the result of released vasoactive amines (histamine, serotonin, etc.) with the triggering of mast cells directly (1-10). But exact mechanism is still controversial. The purpose of this study is to investigate the variation of the IgE levels in the blood due to IV administration of ICM and to reveal the possible relation between total IgE levels in the blood and the reactions to ICM.

Materials and methods

From February 2002 to December 2003, 233 blood samples were taken from 110 patients between 5 to 80 years (mean, 40 years) of age who underwent intravenous pyelography (IVP). Blood samples were taken from 13 randomly selected patients first just before administration of IV ICM, then at the 40th minute following the examination and finally a week after the IVP. Total IgE levels in all the blood samples were calculated with Elecsys 2010 analyzer (Roche Diagnostics, Boehringer Mannheim Gmbh, Germany) by using electrochemiluminescence immunoassay (ECL) method.

The percentage of the variation of IgE level was symbolized as DD. The numbers and the types of ICM that were used in the examination are shown in Table 1. Since ICMs used in 12 patients were not noted, they were grouped as unknown.

Early and/or late reactions that were observed during the intravenous pyelography examination were classified as mild, moderate and severe according to Bush and Swanson's classification (2).

The nominal upper limit of IgE level was assumed as 100 IU/ml according to the reference values for children and adults given by Dati and Ringel (11).

The results were analyzed statistically by paired t test, chi-square test and t test.

Results

Adverse reactions that were observed in 13 patients were mild and moderate, and no severe reactions were observed in any patient. Observed adverse reactions in our study were found to be independent from total IgE levels in the blood according to chi-square test (p=0.88).

After the administration of IV ICM in 109 patients, IgE levels which were between 1.40% and 41.24%, with a mean value 15.58% have been noted to have decreased statistically significantly (paired t test). In only one patient, the level of IgE increased by 13.26 %.

As DD increased, the number of patients in whom the reactions were observed decreased statistically significantly according to t test (p=0.043). For instance, in 88 patients out of 110 (80%), DD was lower than 20%

and in 13 out of those 88 patients (14.70%) mild and moderate adverse reactions were observed (Table 2). In 22 out of 110 patients, DD was higher than 20% and no adverse reactions were seen in those patients.

In 13 patients whose blood samples were taken a week after from the IVP examination, IgE levels were found to be higher than those of the 40th minute level in 11 patients and higher than those of the beginning level in 7 patients.

Discussion

It has been accepted that the adverse reactions of radiographic ICM are independent from IgE and that these reactions are different from four types of hypersensitivity reactions. These reactions are evaluated as a subgroup like anaphylactic reactions. However, physiopathological mechanism has not been understood (1-9). For example, given that ICMs have a hapten molecular weight and specific antibodies are not shown clearly, it is accepted that the adverse reactions are not allergic reactions; however, occurrence of reactions more commonly in the patients with history of allergy is paradoxical (4,5).

Although there are lots of studies about adverse reactions related to the ICM, the cause of this mechanism has not been explained yet and the existing explanations about the mechanism are not beyond a hypothesis. Is histamine or other vasoactive mediators the major responsible actors in these reactions? Is histamine, which has been shown to increase in the adverse reactions due to ICM, released from mast cell and/or basophile cell? Is histamine release direct or IgE-mediated? What is the role of complement system? These kinds of questions could not be answered yet (1-8).

In the literature, there are no *in vivo* studies that investigate correlation between adverse reactions of ICM and total IgE levels in the blood. This is due to the fact that the adverse reactions were accepted as non-IgE mediated anaphylactic reactions (1-8). In only one study, total IgE levels were evaluated in patients with ischemic heart disease after coronary angiography (9). Since the reactions are of anaphylactic type, we expected that IgE levels due to ICM would not change or would increase consistently with the literature (9, 10). However, we observed that IgE levels decreased at various degrees in all patients except one.

According to our study, the more decreased the IgE levels (increased DD), the fewer patients have experienced adverse reactions. For example, DD was lower than 20% in all the patients in whom the reactions were seen and DD was higher than 20% in all patients with no reactions. DD values are given in Figure 1. We observed that there is a direct relationship between the decrease in IgE levels (DD) after the administration of ICM

Table 1. Distribution of contrast media used in the study

Type	Number	Contrast media	Brand name
Ionic monomer	8	Ioxithalamate	Telebrix 350, 50 ml
Nonionic monomer	21	Iopromide	Ultravist 370, 50 ml
	19	Iopamidol	Iopamiro 370, 50 ml
	6	Iomeprol	Iomeron 400, 50 ml
	12	Iobitridol	Xenetix 300, 50 ml
	3	Ioxilan	Oxilan 350, 50 ml
	18	Iohexol	Omnipaque 350, 50 ml
Nonionic dimer	11	Iodixanol	Visipaque 320, 50 ml
Unknown	12	?	?

Table 2. The distribution of reaction and IgE threshold value in 88 patients whose ΔD level was under 20%

	Reaction (+)	Reaction (-)	n_{Σ}
$n_{IgE > 100\ IU/ml}$	5	36	41
$n_{IgE \leq 100\ IU/ml}$	8	39	47
n_{Σ}	13	75	88

ΔD: percentage of change in the IgE level.

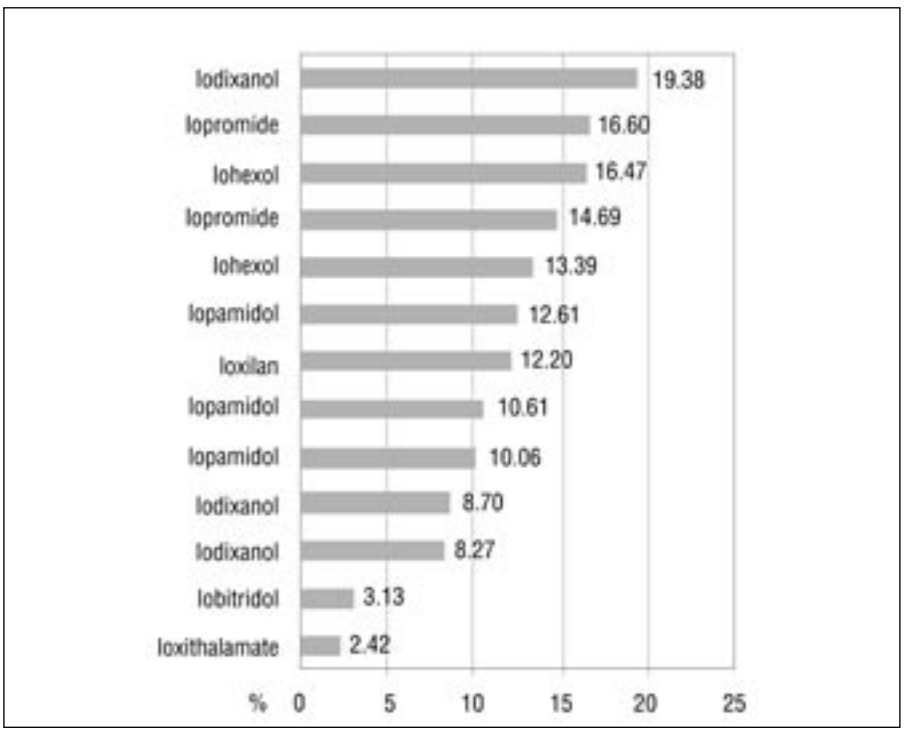

Figure 1. ΔD levels in patients with reactions and the iodinated contrast media used in these patients (ΔD: percentage of change in the IgE level).

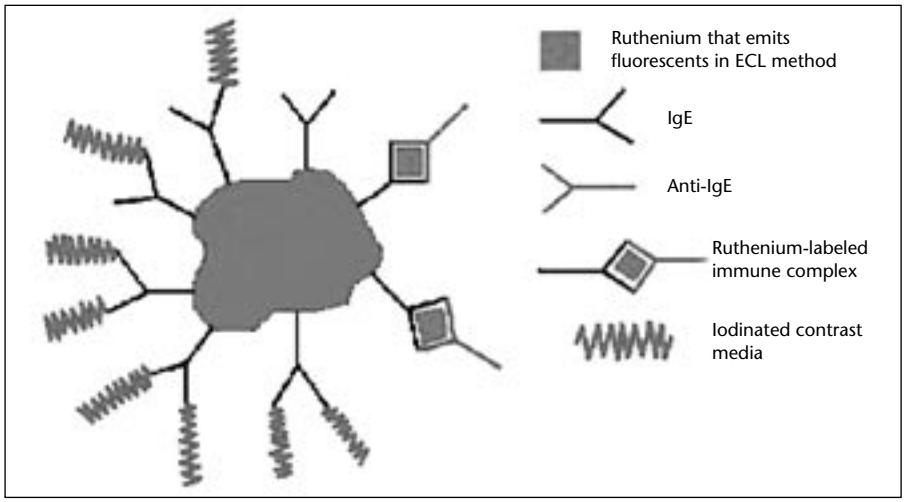

Figure 2. Simplified drawing of the cause of decrease in IgE level following the administration of IV ICM due to ECL immunotest method. In order to measure IgE levels using ECL, ruthenium-labeled anti-IgE and IgE should form immune complex. Iodinated contrast media prevent the measurement by affecting the formation of these complexes.

and the adverse reactions. However, the possible cause of decrease in IgE levels should be clarified since it was expected to increase or not to change at all.

We thought that the reason of decrease in IgE levels was due to ECL technique (Figure 2). Elcsys 2010 analyzer works based on competitive, sandwich and bridging principles (Roche Diagnostics Elcsys 2010 Immunoassay System Reference Guide V3.0). In ECL technique, ruthenium-labeled anti-IgE antibodies bind to IgE and the appearing fluorescent light is detected and measured by the analyzer. Lasser et al. claim that the ICMs act like pseudoantigens (4). Following administration of intravenous ICM, hapten ICM molecules, which cause pseudoantigen affect by binding onto bounded or free IgE's Fab endings, prevent the binding of anti-IgE antibodies used in the ECL technique and thus prevent the detection of IgEs. As a result, IgE levels could not be calculated, thus it is observed as a decrease in IgE levels in the blood following the administration of ICM (Figure 2). We would like to emphasize that Elcsys 2010 analyzer has been checked by an authorized service and the results of IgE have been stated as total IgE.

Whether it is caused by a mistake of ECL technique or is an exceptional case, how can the relationship between the decrease in IgE levels due to IV ICM and adverse reactions be explained? One of the results of our study is that adverse reactions, also accepted in the literature following the administration of ICM, is independent from IgE levels in the blood. But this result should not be interpreted as if there is prevention of the binding of IgE with antigens/pseudoantigens. If IgE binds more substances of such kind, the amount of antigens /pseudoantigens that encounter mast cells and/or basophile cells will decrease and a kind of neutralization will occur. In parallel, less reaction will be observed especially after IV administrations of ICMs, which cause reactions by directly affecting mast cell and/or basophile cell.

There are some limitations of our study. Adverse reactions were observed in a few numbers of patients; severe reactions were not observed at all; intravenous ICM was given manually and thereby a non-homogeneous injection occurred; and Ig G levels were not evaluated simultaneously with IgE. The frequency of adverse severe reactions also are rare in the literature, between 0.04%-0.22% (9) and therefore the probability of encountering one in daily practice is very low (8, 9).

We thought that the cause of increase in IgE levels in only one patient was related to measurement error or patient's medical history. The patient was 38 years old and he had bilateral nephrolithiasis. Before lithotripsy (ESWL) and surgery, he had undergone multiple IVP examinations where he had had multiple IV administrations of ICM. Two months later, findings of left renal atrophy were observed during the follow-up.

In this study, our purpose was not to compare the types of ICM that cause reactions. A larger patient population is necessary to obtain statistically significant results for this kind of study. Moreover, there are numerous such studies in the literature.

In summary, four main results were obtained in our study: adverse reactions of ICM are independent from total IgE levels; non-specific total IgE levels in the blood increase after the administration of IV ICM, while they are expected not to change or increase; as the decrease percentage increases, the probability of adverse reactions decrease; ECL immunotest method must be revised due to expected mistake or exception on ICM binded IgE measurements.

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