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## Immunoglobulin E Fluctuation in Thiopental Anaphylaxis

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Investigations have shown that immunoglobulin E (IgE) is the mediator of the human anaphylactic response<sup>1</sup> (Type I hypersensitivity). While the reported incidence of presumed anaphylactic responses to thiopental is rare but increasing,<sup>2</sup> the mechanism of these adverse reactions is unclear.<sup>3</sup> Basophil-degranulation testing of Fox *et al.* supports the classic Type I hypersensitivity nature of the response.<sup>4</sup> The existence of additional mechanisms of action, not necessarily Type I hypersensitivity, is found in the complement testing of Watkins *et al.*<sup>5,6</sup> Observations of fluctuations in serum IgE levels following adverse reactions to barbiturates have been difficult to interpret. They have been gathered during or after the event, with no control.<sup>6,7</sup> The case report below not only demonstrates the rare occurrence of this anaphylactic phenomenon, but also documents fluctuations in total serum IgE levels prior to, during, and after an intravenous challenge with thiopental. A method of verifying thiopental hypersensitivity is suggested, based on the involvement of IgE.

### REPORT OF A CASE

A previously healthy 20-year-old white woman was hospitalized immediately following a motor vehicle accident. Her initial evaluation took three hours, during which time vital signs and arterial blood-gas values were normal. Pathologic findings included a fractured right tibia, soft-tissue injury of the face, and a minimal hemoperitoneum (diagnosed by "mini"-laparotomy conducted with local lidocaine anesthesia). Only minimal intravenous colloid and crystalloid solutions were needed for replacement. The patient gave no history of drug allergy. Three previous occasions on which thiopental anesthesia had been used had been uneventful. The patient reported periorbital edema and nausea following seafood ingestion.

Anesthesia was needed for the correction of the injuries. A rapid-sequence technique for induction and intubation was performed using 1 mg pancuronium bromide, 250 mg thiopental, and 100 mg succinylcholine, iv. Induction and endotracheal intubation went smoothly. Immediately after intubation, a sinus

tachycardia of 180 beats/min developed. Blood pressure was unattainable by auscultation or palpation, there was intense bronchospasm, and a bright red cutaneous flush appeared. The erythema began on the chest but rapidly spread over the entire body. The skin was hot and dry, and within minutes became cyanotic. There was no urticaria. Rectal temperature was normal. Arterial blood-gas values at  $F_{I_{O_2}}$  1.0 now revealed marked hypoxia, hypercarbia, and acidosis ( $P_{a_{O_2}}$  36 torr,  $P_{a_{CO_2}}$  55 torr,  $pH$  7.26, base excess  $-3$  mEq/l).

Immediate resuscitative measures included controlled ventilation with 100 per cent oxygen, large-volume colloid and crystalloid infusion, and 15 mg ephedrine sulfate, iv. Within 30 min the pulse, blood pressure, skin color and ventilation had returned to normal. The only abnormal laboratory or radiographic findings were a decreased serum potassium (3.4 mg/l), a prolonged prothrombin time (16 sec with a 12 sec control), and a calculated base deficit of 5 mEq/l. The operation proceeded, and the five-hour operative experience was well tolerated. A balanced anesthetic technique of nitrous oxide-oxygen, pancuronium bromide, Innovar<sup>®</sup>, and fentanyl was employed. Recovery was uneventful. Five hours after the post-induction collapse, the following laboratory determinations were reported: slight leukocytosis (leukocyte count 13,700), with a differential of 84 per cent polymorphonuclears, 10 per cent bandcells, 3 per cent lymphocytes, 3 per cent monocytes, and no basophils or eosinophils. Total protein was decreased (4.8 g/dl), as were albumin and globulin (alpha 2, beta, and gamma fractions). Immunoglobulin electrophoresis revealed normal levels of IgG, IgA, IgM, and IgE.

Three weeks later, after informed consent had been secured from the patient and her family, minute incremental doses of thiopental were administered iv. Testing was performed with all resuscitative equipment and drugs readily available. Brachial-artery cannulation and electrocardiographic monitoring were done. Prior to thiopental injection, and after each set of incremental doses, serum immunoglobulin levels were determined. Initially, 1  $\mu$ g thiopental was injected per min for 10 min. This produced a slight pruritus of the left hand and arm (the injection site was an intravenous cannula in the right forearm). No other change was observed or volunteered by the patient. The next series of injections were 1 mg/min, again over a 10-min period. This dose produced pruritus over the left hand and face and a pruritic dermatographia on the abdomen and upper chest. The patient complained of palpitations; however, rhythm remained sinus rhythm at 90/min. Blood pressure was 110/70 torr, with a mean of 84 torr.

A series of 10-mg boluses of thiopental was then administered. Five injections were made at 5-min intervals. These administrations caused a non-progressive slight tachycardia (108 beats/min), a subjective increase in warmth of the skin, and increased pruritus of the neck, extremities and trunk. The patient claimed at this point that these subjective complaints were similar to her "allergic" reaction from eating seafood. Intravenous administration of thiopental was discontinued and the patient demonstrated no other clinical sequelae. Five hours after the last intravenous injection, serum immunoglobulin levels were again secured (table 1). The patient was advised to obtain a "medic alert" bracelet signifying her allergy to barbiturates, and in particular, to thiopental.

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TABLE 1. Immunoglobulin Fluctuations during Thiopental Challenge

	Prior to Intravenous Challenge	After 10- microgram Injection	After 10- milligram Injection	After 50- milligram Injection	5 Hours after Injection	Normal Range
IgG (mg/dl)	1,010	1,060	910	960	1,050	564-1,765
IgA (mg/dl)	192	214	224	214	250	85-385
IgM (mg/dl)	238	226	204	238	263	53-375
IgE (units/ml)	66	12	84	180	330	<160

## DISCUSSION

This patient's response conforms to the accepted clinical syndrome of human anaphylaxis<sup>9</sup> (Type I hypersensitivity), as well as to published descriptions of presumed acute hypersensitivity to thiopental.<sup>4,10-17</sup> The marked tachycardia, hypotension, bronchospasm, flushing of the skin, and cyanosis, combined with arterial hypoxemia, hypercarbia and acidosis, leave little doubt as to the severity of the initial reaction. The patient's specific hypersensitivity to thiopental was clinically confirmed by her response to minute quantities of drug administered by intravenous challenge.

The pattern of fluctuation in this patient's total serum IgE levels supports the classic anaphylactic nature (Type I hypersensitivity) of the response. IgE, the reagent alluded to by Prausnitz and Küstner, has been isolated and purified. The IgE antibody exists in nearly all human beings, regardless of allergy history, but is found in relatively high levels in patients who have clinical allergy. The major sites of synthesis are the lymphoid tissues of the respiratory and gastrointestinal tracts. IgE is cytophilic, that is, once produced, the majority of this immunoglobulin attaches itself to receptor sites on the cell membranes of mast cells and basophils. The immunoglobulins then can combine with antigen to mediate the secretion of various biologically active substances by the mast cells and basophils.<sup>18</sup> To date, histamine, slow-reacting substance of anaphylaxis (SRSA), eosinophil chemotactic factor of anaphylaxis (ECF-A), platelet-activating factor (PAF), basophil kallikrein of anaphylaxis (BK-A), and neutrophil chemotactic factor of anaphylaxis (NCF-A), have all been shown to be released during the IgE-antigen-mediated response.<sup>19</sup> These substances are responsible for the signs and symptoms commonly associated with an acute anaphylactic response. The magnitude and spectrum of the response are thought to be related to quantities and varieties of substances secreted. Current evidence supports that secretion is mediated intracellularly by cyclic AMP levels and is dependent, at least in part, on the presence of a bivalent cation, usually calcium.

The scope of this response varies from individual to individual. Only a small amount of total IgE exists freely in the serum.<sup>18</sup>

In a previously sensitized individual, the initial response to antigen exposure is a sharp reduction in circulating antibody levels. This can be accounted for by the complexing of antibody with the newly injected antigen.<sup>20</sup> Our data would seem to demonstrate this phenomenon. The IgE levels decreased from 66  $\mu$ /ml to 12  $\mu$ /ml after 10  $\mu$ g thiopental. The time required for this reduction was 40 min.

Low levels of serum IgE after thiopental and methohexital in patients with clinical hypersensitivity have been reported.<sup>6-8</sup> These measurements were taken at widely varying time intervals during or after marked adverse reactions. There were many variables, and control levels were not established. These circumstances were also present in our measurement of a normal IgE level, five hours after the patient's initial collapse. Our intravenous challenge had but one variable, and documented a normal pre-challenge control level of IgE.

Immediately after the reduction in antibody levels, the body responds to the antigen with marked elevations in circulating antibody levels.<sup>20</sup> This response could be seen in our patient's increasing total serum IgE levels on three subsequent determinations. The last total serum IgE level showed a fivefold increase over the pre-challenge control level, but also a 27-fold increase over the patient's lowest documented level.

During thiopental challenge, the patient's IgG, IgA, and IgM levels were unchanged. This consistency could be considered a control within this study, arguing against the possibility of artifactual IgE level fluctuation due to hemoconcentration or hemodilution.

All IgE levels were determined by radioimmunoassay (RIA). The testing was done in the same laboratory at the same time, using the same lot of reagents, constituting another form of control.

IgE and antigenic reactivity are highly specific.<sup>18</sup> The only variable was the presence or absence of

thiopental, which strongly suggests that the variance in total serum IgE levels was secondary to the thiopental stimulus, and that the phenomenon of thiopental-induced anaphylactoid reaction in this instance was in fact one of true reagin or IgE-mediated anaphylaxis (Type I hypersensitivity).

We do not suggest that each suspected incidence of thiopental anaphylaxis should be investigated with such an elaborate and involved method. From the information gathered concerning the role played by IgE in this response, a simple, quick and relatively noninvasive method of investigation is suggested.

IgE-thiopental specificity could be determined more efficiently through a radio-allergosorbent test (RAST). This method of testing was developed by Wide, Bennich and Johansson<sup>21</sup> and suggested for testing thiopental hypersensitivity by Brown.<sup>15</sup> In the RAST, a specific antigen is conjugated with an insoluble polymer. This combination is added to the sample of serum to be studied. The polymer antigen complex is "washed" and IgE not specific for the antigen polymer is removed. The remaining combination is then added to a quantity of radioactively labeled antihuman IgE and, after an appropriate time to complex, is again "washed." The level of radioactivity of the complex correlates with the level of specific IgE present in the tested serum. This can be accurately quantified and expressed in standard units. RAST testing requires only a few milliliters of the patient's blood, and its results are available within 24 hours. At present, this test does not exist for the antigen thiopental, and its development could be time-consuming and possibly technically difficult. Currently we are exploring the feasibility of developing the RAST for thiopental. Potential exists not only for better delineating the mechanism of adverse drug reactions, but also for a quick and relatively noninvasive method of identifying patients at risk.

This case of an adverse reaction to thiopental provides clear evidence of the classic anaphylactic nature (Type I hypersensitivity) of this phenomenon. Variations in serum IgE levels suggest that RAST testing might provide an excellent method of diagnosis and study.

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