

Paracetamol (acetaminophen) hypersensitivity

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Background: Acetaminophen (paracetamol) is an analgesic antipyretic drug with no antiinflammatory effects and is widely used worldwide. Earlier clinical studies reported IgE-mediated adverse reactions to acetaminophen, but in vivo and in vitro tests have been inconclusive.

Objective: We propose to demonstrate an IgE-mediated mechanism in four patients with adverse reactions to acetaminophen (paracetamol). Tolerance to aspirin and other nonsteroidal antiinflammatory drugs are present in all patients.

Methods: We studied four patients with anaphylactic reactions to acetaminophen who tolerated aspirin and other nonsteroidal antiinflammatory drugs. Skin tests, oral challenges and immunoassay for allergen-specific IgE antibodies with acetaminophen were performed in all patients.

Results: All patients tolerated the aspirin oral challenge without adverse effects. In contrast, the oral challenge with acetaminophen produced adverse effects in all patients. Skin tests with acetaminophen were positive in two patients (3-mm wheal and flare) and IgE antibodies acetaminophen were detected in serum from two patients.

Conclusion: We describe four patients with adverse reactions to acetaminophen but with tolerance to aspirin and other nonsteroidal antiinflammatory drugs. Skin tests, oral challenges, and serum IgE results with acetaminophen suggest that an IgE-mediated mechanism is responsible for these reactions.

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INTRODUCTION

In 1893, Von Mering introduced acetaminophen (N-acetyl-*p*-aminophenol) to the market for medical purposes, but it was not widely used until 1950s. Today, acetaminophen (paracetamol) and fenacetine are the two most important coaltar derivative analgesic drugs because acetaminophen has less toxicity than fenacetine it is used more extensively.

Acetaminophen is readily absorbed from the gastrointestinal tract with peak plasma concentrations between 30 minutes to hours after ingestion. It is metabolized in the liver and excreted in urine mainly as the glucuronide and sulfate conjugates.¹ It is widely used by patients with gastrointestinal com-

plaints because it is readily tolerated with few adverse effects.

Side effects at therapeutic doses are usually mild but hematologic reactions, skin rashes, and other allergic reactions may occur. Acetaminophen overdose produces pallor, nausea, vomiting, anorexia, and abdominal pain. Liver damage, abnormalities of glucose metabolism, with metabolic acidosis and renal failure with acute tubular necrosis are often seen after overdose. Cardiac arrhythmias have also been reported.

Anaphylactoid adverse reactions to acetaminophen have been reported previously in the literature.^{2–9} In some cases an IgE-mediated mechanism has been suggested; however, to date, only two patients have demonstrated this mechanism by in vivo or in vitro tests.^{2,7} Elevated histamine levels have been reported during oral provocation with acetaminophen^{5,9} in two patients having shock as their manifestation. This reaction suggests that an IgE-me-

diated mechanism is responsible for acetaminophen (paracetamol) hypersensitivity.

Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) act by inhibiting the cyclooxygenase pathway; in contrast, acetaminophen is a weak inhibitor of the cyclooxygenase pathway. In acetyl salicylic acid-sensitive patients with asthma, however, the ingestion of high doses of acetaminophen may induce a fall in lung function similar to that with acetyl salicylic acid, supporting the idea of cross reactivity between these drugs in the human lung.¹⁰

The present report describes four patients with acetaminophen hypersensitivity with tolerance to acetyl salicylic acid and other nonsteroidal antiinflammatory drugs. Further, an IgE-mediated mechanism is suggested by in vivo and in vitro results.

MATERIALS AND METHODS

Patients

We studied four patients with adverse reactions to acetaminophen who attended our allergy department during an 8-month period.

All were women, aged 21 to 65 (mean age 41), who described allergic symptoms after ingesting acetaminophen (650 mg) that they received for different diseases. Their reactions included local (forehead) urticaria in patient 4, generalized urticaria and angioedema in patients 1 and 3, and anaphylaxis in patient 2. They all had previously tolerated aspirin and other nonsteroidal antiinflammatory drugs. Only patient 1 was atopic with hay fever, a positive skin test to grass pollen and an elevated total IgE level. The other three had no history of atopy or adverse reactions to any other drug. None of them described any previous urticaria or ana-

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Table 1. Summary of Patient Characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Age (yr)	21	24	54	65
Sex	female	female	female	female
Atopy	yes	no	no	no
Tolerates NSAID	yes (ibuprophen)	yes (ibuprophen)	yes (metamizole)	yes (ketorolaco)
Reaction	Generalized urticaria and angioedema	Anaphylaxis (hypotension, angioedema)	Generalized urticaria and angioedema	Local urticaria (forehead)
Time interval after ingestion	20 min	30 min	60 min	10 min
Reason for ingestion	dismenorrhea	dismenorrhea	headache	arthritis
Time between last reaction and the study	2 months	1 month	4 months	18 months

phylaxis. A summary of their clinical data are shown in Table 1.

Written informed consent was obtained from all patients before the study.

Skin Tests

Duplicate skin prick tests were performed by the same physician on the volar aspect of the forearm. Skin tests were performed with a solution of acetaminophen (Apiretal gotas) diluted in saline 0.9% at a concentration of 100 mg/mL. Histamine phosphate (10 mg/mL) and saline (0.9% commercial source) were used as positive and negative controls, respectively. All four patients and the 30 individuals that formed the control group were tested. Results were considered positive if the prick elicited a wheal and flare of at least 3mm bigger than the negative control.^{11,12}

Oral Challenge

Single-blind oral challenges were performed with aspirin, 250 mg and 500 mg, in a cumulative fashion at 1-hour intervals. All patients tolerated the challenge without adverse effects. Oral challenges with acetaminophen were performed on different day. Patient 1 received 75 mg of acetaminophen and the other three received 650 mg in a single dose. (Because a different physician performed the challenge on patient 1, this patient received a lower dosage.) The oral challenge was not performed in the control group because

all subjects had previously tolerated acetaminophen without adverse effects.

Serum IgE Antibodies for Acetaminophen

Specific IgE determination for acetaminophen was performed as follows:

First, commercial acetaminophen was conjugated with human serum albumin (commercial Sigma HSA); afterwards, cyanogen-bromide-activated filter paper disks (Pharmacia, Uppsala, Sweden) were coupled with acetaminophen bound to HSA, following the method of Ceska.¹³ The disks were incubated for 24 hours with 50 mL of patient serum (in duplicate) at room temperature (disk A). As a control for nonspecific binding, HSA disks (Pharmacia, Uppsala, Sweden) were incubated with 50 mL of patient serum for the same time and conditions (disk B).

The disks were then washed three times with phosphate-buffered-saline-tween 20 (PBS-tween) and 50 mL of I¹²⁵-labeled antihuman IgE (Pharmacia, Uppsala, Sweden) was added. After 24 hours the disks were washed three times with PBS-tween, a 10-minute interval separating each of the three washings. Finally, the activity on the disks was counted in a gamma scintillation counter.

Ten individuals with total serum IgE levels less than 2000 U/L were used as control group. Specific IgE reactions to acetaminophen were

considered positive using a ratio criterion: mean counts per minute for disk A double the mean counts per minute for disk B (ratio cpm = acetaminophen – HSA/HSA $\geq$ 2).

RESULTS

Skin prick tests with acetaminophen were positive in two of the four patients (patients 1 and 2). A 3-mm wheal with erythema was obtained in both of these patients, with no reaction to the saline. Skin prick tests were negative in patients 3 and 4 and in the control group (n = 30).

The acetaminophen oral challenge was positive in all patients, eliciting immediate hypersensitivity responses consisting of generalized urticaria/angioedema in patients 1, 2, 3 and local urticaria in patient 4. All patients had good responses to therapy with antihistamines and corticosteroids. Patient 2 required treatment with epinephrine.

Elevated IgE levels to acetaminophen were detected in patients 2 and 3; in patients 1 and 4 the ratio of counts bound to acetaminophen versus counts bound to HSA was < 2. The control group had a mean ratio of 1.07.

These results are summarized in Table 2.

DISCUSSION

Acetaminophen (paracetamol) is a widely used analgesic-antipyretic drug with no antiinflammatory effects.

Table 2. Summary of In vitro and In Vivo testing with Acetaminophen

	Patient 1	Patient 2	Patient 3	Patient 4	Control Group
Acetaminophen (100 mg/mL) skin test	+(3mm)	+(3mm)	No reaction	No reaction	No reaction (n = 30)
Oral Challenge and dosage	Generalized U/AE 75 mg	Anaphylaxis 650 mg	Generalized U/AE* 650 mg	Local urticaria 650 mg	Not tested
RAST ratio	1.4	2.3	2.1	1.9	From 0.9 to 1.5, mean value = 1.07
Total IgE (U/L)	894	87	11	135	All less than 2000 U/L (n = 10)

* U/AE is an abbreviation for urticaria and angioedema.

The mechanism for sensitivity to aspirin and other nonsteroidal antiinflammatory drugs involves the inhibition of prostaglandin synthesis. Acetaminophen is a weak inhibitor of prostaglandin synthesis. The existence of some patients having anaphylactoid reactions to acetaminophen, but with tolerance to aspirin and other nonsteroidal antiinflammatory drugs suggests an immunologic mechanism responsible for these reactions.^{3,7,8} In some of these patients oral challenges gave positive results^{2,8} but prick tests were positive only in one patient.⁷ Specific IgE determination failed to show positive results in all patients.

All of our patients tolerated the ingestion of aspirin, therefore inhibition of prostaglandin synthesis does not seem to play a role in these reactions.

Positive skin prick tests in 2 of 4 patients suggests an IgE-mediated mechanism. The test solution with acetaminophen, 100 mg/mL, could be a potential irritant, but one of the control group showed a wheal or erythema response. Skin prick tests were negative in two of four patients but this is common in drug hypersensitivity.

The reproducibility of symptoms after oral challenge in all patients who were tolerant to nonsteroidal antiinflammatory drugs suggests a selective acetaminophen hypersensitivity.

Using an IgE binding ratio of two is a method to assess hapten-specific IgE binding. This ratio of two has a high sensitivity and has been used satisfactorily in another drug hypersensitivity

study to demonstrate an IgE mechanism, as shown by Karol et al.¹⁴

In general, a patient's level of total serum IgE may affect the RAST ratio results, particularly when this level is >150 U/L. This occurs only in patient 1, who is also the only atopic patient. We therefore make the assumption that the total levels of IgE do not interfere with our results.

We are unable to explain the discordance between the skin test results and the specific IgE antibodies levels in patient 1, who had a positive skin test, but specific IgE similar to the control group. The negative skin test and specific IgE results in patient 4 may be explained by a metabolite of acetaminophen acting as an hapten and not present in specific IgE results or skin test.

More than 10 individuals in the control group for specific IgE levels to acetaminophen could be desirable in this study.

We also tested the commercial formula Apiretal in the skin test and Gelocatil in the oral challenge. The possibility of an excipient playing a role in these reactions have been rejected because different commercial formulations were ingested for the original reactions in each patient.

In this report we demonstrate results that appear consistent with an IgE-mediated mechanism being responsible for the reactions to acetaminophen. Our report is the first to show elevated specific IgE antibodies to acetaminophen. We conclude that for a drug very

commonly used, the few anaphylactoid reactions to acetaminophen reported worldwide cannot be considered significant, therefore acetaminophen is a safe drug.

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