

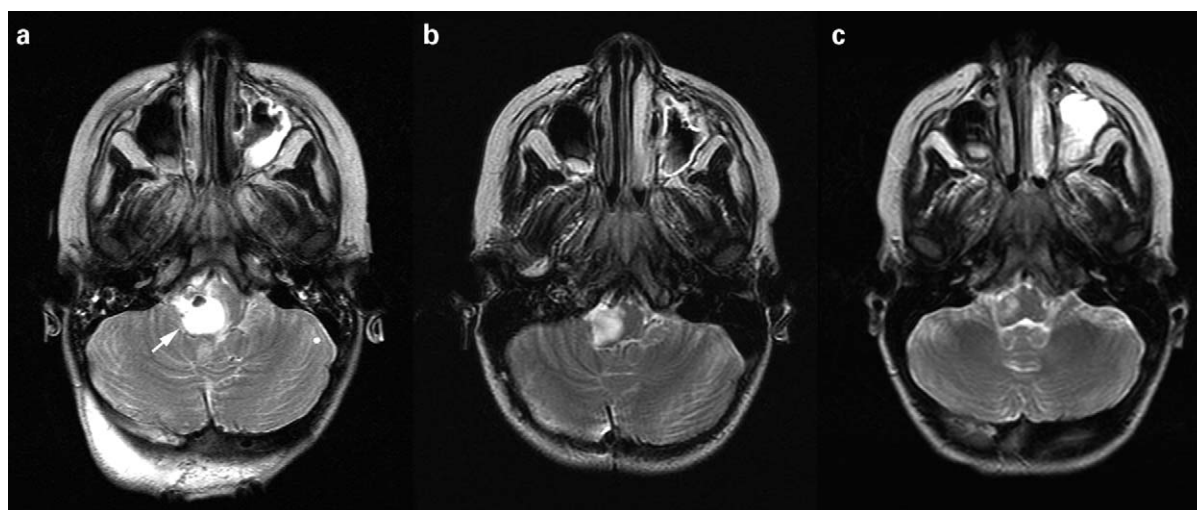


FIG 1. Sequential MRI demonstrating tumor size at baseline (A), at time of development of hypersensitivity (B), and after completion of chemotherapy made possible by desensitization to carboplatin (C).

breakthrough symptoms by premedicating and decelerating the dose escalation successfully improved tolerability. Avoidance of substantial morbidity associated with cranial irradiation and possibility of cure with chemotherapy justify the additional measures and risk involved in desensitizing repeatedly to carboplatin.

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Available online August 3, 2004.
doi:10.1016/j.jaci.2004.05.061

Recurrent anaphylaxis linked to pantoprazole

To the Editor:

Pantoprazole (Protonix/Wyeth-Ayerst, Madison, NJ), the fourth benzimidazole proton pump inhibitor to become available in the United States, has been increasingly used for the oral treatment of gastroesophageal reflux disease. There have been 2 case reports of anaphylactic reactions after administration of pantoprazole.^{1,2} We describe the case of a man with recurrent anaphylaxis induced by pantoprazole and investigate its relationship to cytochrome P450 polymorphisms.

A 47-year-old Hispanic male was referred to our clinic for evaluation of recurrent idiopathic anaphylaxis (urticaria, angioedema, substernal chest discomfort, orthostasis, and impaired consciousness) of 8 months' duration. He had no significant past medical history of atopy, drug allergy, or chronic medical conditions with the exception of gastroesophageal reflux disease treated with intermittent pantoprazole. Previous anaphylactic events occurred sequentially 24, 10, and 4 hours after pantoprazole, each after several days of uneventful use. The history was not compelling for provoking food ingestion, exercise, or another culprit before these episodes. With the exception of cockroach, results of serum IgE measurement to

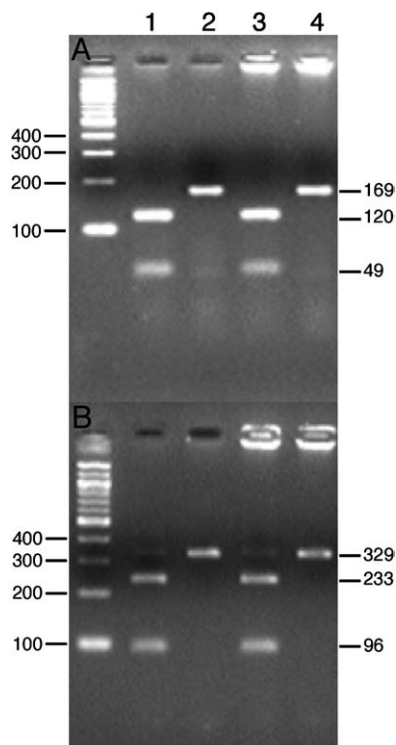


FIG 1. Genotyping test for the *CYP2C19**2 allele (**A**) and the *CYP2C19**3 allele (**B**) with gel analysis of *Sma*I-restricted and *Bam*HI-restricted PCR products, respectively, from genomic DNA of the patient (*lanes 1*, digested; *lanes 2*, undigested) and a control subject (*lanes 3*, digested; *lanes 4*, undigested).

common aeroallergens and foods were negative. The patient was prescribed an antihistamine, equipped with an EpiPen, and advised to report additional episodes.

One month later, the patient experienced another and more severe episode 3 hours after a 40-mg tablet of pantoprazole. He had not used the pantoprazole in the preceding month. A total tryptase level drawn at the time of evaluation in the emergency department was increased at 31 $\mu\text{g/L}$ (normal, <15.8 $\mu\text{g/L}$). A repeat total tryptase measurement was 5.7 $\mu\text{g/L}$ 2 months after the event.

Pantoprazole elicited a positive intradermal (wheal size, 8 mm) result by using a 0.02-mL concentrate (4 mg/mL solution) of pantoprazole. Three control subjects had no reaction to intradermal testing. We did not elect to perform an oral challenge because we believed the risks were considerable given the increasing severity of his reactions. On the basis of the history and supportive skin test, pantoprazole was identified as the likely cause of his anaphylaxis. Pantoprazole was discontinued with a benign 12-month course of follow-up.

Natsch et al¹ described the first case of anaphylaxis induced by pantoprazole. In their patient symptoms of urticaria, angioedema, and hypotension occurred within hours of ingestion of 40 mg of pantoprazole. This patient had received treatment 1 year earlier with pantoprazole, without a reported adverse event. Because of recurrent

dyspepsia, one of the remaining capsules was taken, after which an anaphylactic event occurred within an unspecified number of hours. Fardet et al² reported on a patient who had urticaria, angioedema, and hypotension within a few minutes of oral challenge with pantoprazole. In this patient the relationship between drug administration to symptom onset in 8 prior events was not described. In our patient the timing of the reaction to the dosing of pantoprazole was not originally suggestive of a causative role. We postulated that the unusual timing might be explained by variations in the metabolic pathways of pantoprazole. Interestingly, in Asian patients differences in pantoprazole clearance have been observed between poor versus extensive metabolizers of S-mephenytoin.³ The poor metabolizer phenotype, which is inherited in an autosomal recessive fashion in 2% to 5% of white populations, has been associated with several inactivating genetic polymorphisms in the *CYP2C19* gene.³⁻⁵ This gene encodes for the cytochrome P450 enzyme responsible for metabolism of S-mephenytoin and a number of other commonly used drugs, including pantoprazole. In poor metabolizers oral administration of pantoprazole resulted in a prolonged plasma half-life and decreased oral clearance of the drug.³ This could potentially result in an accumulation of drug with repeated dosing.

In poor metabolizers, CYP3A, an inducible enzyme, plays a more prominent role in pantoprazole metabolism.³ If the resulting sulfone metabolite was the more potent allergenic form of the drug, repeated dosing would theoretically result in a progressively accelerated appearance and higher level of the sulfone form. In fact, poor metabolizers have been shown to have higher peak serum levels of the sulfone form after a single oral dose.³ We investigated whether the timing of the anaphylactic events in our patient could be explained by a genotypic variance in the P450 pathway. We genotyped our patient along with a control subject for 8 defective mutation alleles (*CYP2C19**2, *2B, *3, *4, *5, *6, *7, and *8) by means of the PCR restriction enzyme analysis, as previously described.³⁻⁵ These mutations have been shown to account for more than 95% of the defective alleles in white poor metabolizers.⁵ In each case both the patient and the control subject were homozygous for the wild-type alleles (Fig 1).

The proton pump inhibitors lansoprazole and omeprazole have also been associated with anaphylactic reactions.⁶⁻⁸ Several of these reports describe anaphylactic symptoms occurring within minutes of ingestion of omeprazole, which is suggestive of an IgE-mediated event.^{6,7} Additionally, cross-reactivity among proton pump inhibitors has been reported. Galindo et al⁸ described a patient who had anaphylaxis within minutes of a 40-mg omeprazole infusion. Skin testing showed reactivity to omeprazole, as well as lansoprazole, suggesting cross-reactivity. Natsch et al¹ reported a patient who had anaphylaxis 45 minutes after 40 mg of oral omeprazole and, subsequently, 45 minutes after 30 mg of oral lansoprazole. Gonzalez et al⁹ described a case of urticaria 30 minutes after oral omeprazole and anaphylaxis within

45 minutes of an oral challenge of lansoprazole in the same patient. Skin testing results were positive to omeprazole, lansoprazole, and pantoprazole, and similar to findings in our patient, the tryptase level was increased 3 hours after lansoprazole challenge. These reports would contrast with the report from Fardet et al,² in which the reaction appeared specific to pantoprazole and not cross-reactive with an alternative proton pump inhibitor.

In our patient the positive skin test response and increased tryptase level are consistent with prior case reports of proton pump inhibitor anaphylaxis and suggest an immediate hypersensitivity mechanism. The specific mechanism of anaphylaxis to this class of drugs, however, remains to be definitively established. Although mutations in the *CYP2C19* gene were not identified, the timing of anaphylactic events invokes the possible involvement of modifying pharmacogenetic factors, variations in relative levels of drug-specific IgE, or both. Pantoprazole should be considered in the differential diagnosis of idiopathic anaphylaxis.

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Available online August 3, 2004.
doi:10.1016/j.jaci.2004.05.068

Alterations of stress-induced expression of membrane molecules and intracellular cytokine levels in patients with atopic dermatitis depend on serum IgE levels

To the Editor:

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease that can be divided into an allergic form, among others characterized by high serum IgE baseline levels, and a nonallergic form.¹ AD results from an interaction between various genetic, environmental and immunologic factors.² As we previously reported, patients with AD respond to mental stress immunologically differently compared with healthy controls (HC).³ To our knowledge, differences between subtypes of AD concerning the immunologic responsiveness to mental stress have not yet been measured. Therefore, we used serum-specific IgE (CAP RAST FEIA-System, Pharmacia, Uppsala, Sweden) to identify specific IgE antibodies. Thereby, we reanalyzed previously published data dividing the group of AD patients into 2 subgroups, discriminating patients with high serum IgE baseline levels (IgE^{high}; n = 6) and patients with low serum IgE baseline levels (IgE^{low}; n = 9) (cutoff, 1000 kU/L).

Significant psychological arousal, indicated by an increase of heart rate and blood pressure,^{3,4} was observed in all 3 groups equally. However, in contrast to our previous results, no significant stress-induced increase of the absolute number of CD8⁺ T lymphocytes was observed in any group. Nevertheless, stress induced a significant increase of CD8⁺ T lymphocytes with intracellular IL-4 ($P_{\text{Baseline-Stress}} [P_{\text{T-B-S}}] < .05$ for time effect; Fig 1), as well as an increase of IL-4 in the supernatant of stimulated PBMCs ($P_{\text{T-B-S}} < .05$) only in IgE^{high}. In contrast, no significant increase was found in IgE^{low} for HCs for both CD8⁺ T lymphocytes with intracellular IL-4 and IL-4 in the supernatant of stimulated PBMCs. Furthermore, no significant effect was detectable for CD4⁺ and CD8⁺ T lymphocytes with intracellular IL-4. Stress induced an increase of CD4⁺ T lymphocytes with intracellular IL-5 immediately after the stress procedure ($P_{\text{T-B-S}} < .05$) only in IgE^{high} (Fig 1). Furthermore, 2×3 ANOVA revealed a significant group effect for CD4⁺ ($P < .01$) and CD8⁺ T lymphocytes with intracellular IL-5 ($P < .05$) because of an increased number of these cells in IgE^{high} compared with the other groups. There were no significant changes for CD4⁺ or CD8⁺ cells or CD8⁺ T lymphocytes with intracellular IFN- γ detectable in any group.

Stress induced a significant increase in CLA⁺/CD8⁺ lymphocytes in all 3 groups (2×3 ANOVA; $P_{\text{T}} < .01$). A further differentiation revealed that this increase was obviously resulting from a significant increase in the CLA⁺/CD8⁺ T-lymphocyte subpopulation in IgE^{high}