

CASE REPORT

Urticaria During Triple Therapy for *Helicobacter pylori* Infection

Clinical Implications

GEORGES DELPRE, MD, ELLA LIVNI, PhD, and YARON NIV, MD

KEY WORDS: urticaria; adverse drug effects; *Helicobacter pylori*; omeprazole.

The widespread use of an ever-increasing number of drugs is responsible for the multiple adverse reactions observed by the clinician. Current practice advocates eradication of *Helicobacter pylori* infections, and this is achieved quite well by the use of triple therapy (1). However, a survey of the recent literature revealed that the safety of such regimens has often been discussed but never properly investigated (1–3). We describe a case in which adverse effects were noted to each of the three components of therapy.

CASE REPORT

A 54-year-old woman was referred because of heartburn that had recently become worse. The past history was unremarkable except for allergic rhinitis and recurrent sinusitis. Biopsies obtained during gastroscopy from an inflamed area revealed superficial chronic active gastritis with intestinal metaplasia and the presence of *H. pylori*. The patient received a two-week treatment schedule: omeprazole 20 mg $\times$ 2/day and amoxicillin 500 mg $\times$ 4/day, to be given for the full 14 days, with the addition of tinidazole 500 mg $\times$ 2/day from day 5. On day 7 of this regimen, there was an onset of malaise and pruritus, and shortly thereafter the patient noticed the appearance of hives.

On her own initiative, the patient began to take an antihistaminic drug (chlorpheniramine maleate 2 mg twice daily), which somewhat relieved her symptoms and permitted her to continue with the triple drug therapy for an additional five days. However, on the morning of day 12, there was an intense eruption, and she discontinued all medications. Two days after cessation of treatment, all symptoms disappeared completely.

On follow-up one week later, the physical examination

was unremarkable, and no abnormalities were revealed on the biochemical tests except for mild eosinophilia (7%). Two months later specific immunologic tests were performed for the three drugs taken (Table 1). A macrophage migration inhibition factor (MIF) assay (4), performed by interacting the patient's lymphocytes with macrophages of normal guinea pigs, was positive for omeprazole and tinidazole (migration index: 0.60 and 0.69, respectively, where ≤ 0.80 is positive). A mast cell degranulation (MCD) test was performed according to a modification of the previously described method (5), in light of the recent work demonstrating that sensitization of rat mast cells by human IgE and IgE antibodies, or human serum and specific allergens, results in a biologic response of their degranulation and histamine release (E Livni and R Tamir, unpublished data). Determination by ELISA of histamine release from the rat mast cells in the presence of the patient's sera alone and with the suspected offending drug yielded a strong positive value only for amoxicillin (2430 nmol/liter histamine as compared to 470 nmol/liter in the serum alone) (Table 1).

The same two techniques were also performed in three control patients with *H. pylori* infection shortly after termination of treatment with the three identical drugs to which they did not exhibit any adverse side effects. The results of their tests were negative.

Three months later a [^{14}C] urea breath test was performed in the patient, and the results were positive for *H. pylori*. Six months later there was still marked sensitivity to omeprazole, as evidenced on repeated MIF assay and MCD test (Table 2). For the other two drugs, all tests were negative. Leukocyte count was 6300 mm^3 with 3% eosinophils.

DISCUSSION

Helicobacter pylori is now recognized as the causative agent of chronic active gastritis (1). A high rate of eradication is obtained with triple-drug therapy consisting of a proton pump inhibitor and two antibiotics (1–3).

In the evaluation of such regimens, when side effects are mentioned at all, it is only in regard to their

Manuscript received July 9, 1996; accepted December 17, 1996.

From the Department of Gastroenterology and Laboratory of Drug Allergy, Rabin Medical Center, Beilinson Campus, Petah Tiqva and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Address for reprint requests: Dr. G. Delpre, Institute of Gastroenterology, Rabin Medical Center, Beilinson Campus, Petah Tiqva 49 100, Israel.

TABLE 1. RESULTS OF INITIAL SPECIFIC IMMUNOLOGICAL ASSAYS

Drugs tested	MIF*				MCD†	
	1st assay	2nd assay	3rd assay	Mean MI	Serum + drug (a)	Serum alone (b)
Omeprazole	+	+	—	+	—	—
	0.35	0.63	0.82	0.60	480	470
Tinidazole	—	+	+	+	—	—
	0.81	0.64	0.64	0.69	510	470
Amoxicillin	—	—	—	—	+	+
	0.85	0.86	0.99	0.90	2430	470

* MIF: macrophage migration inhibition factor; MI: migration index. Results are expressed as MI (MI ≤ 0.80 is positive; MI > 0.80 is negative); Concentrations of drugs used (in the assays) are: 1st assay = 10; 2nd = 50; 3rd = 100 µg/ml of culture.

† MCD: mast cell degranulation. Results, measured by histamine release (determined by ELISA), are expressed in nanomoles per liter. a, histamine values in the presence of the patient's sera and tested drugs; b, histamine values in the presence of the patient's sera alone. Positive test is indicated by the formula: $(a - b/b) \times 100 > 30\%$.

incidence and severity (1–3). To the best of our knowledge, precise identification of the offending drug(s) has not been performed in patients with adverse reactions to *H. pylori* therapy. In four such cases reported recently, the authors attributed the rash that developed to amoxicillin alone, and not to the other components, but failed to provide supporting evidence (6, 7). Allergic skin disorders have also occasionally been reported with omeprazole (8) and, more rarely, with tinidazole (9). The patient presented here had no prior drug allergy. The urticaria that appeared during the triple-drug therapy continued to increase in severity until all three drugs were discontinued.

Acute urticaria is a classic manifestation of IgE-mediated hypersensitivity. Degranulation of the mast cells by the offending drug in the presence of the patient's serum indicates an immediate type I hypersensitivity of the humoral immune response (5), since mast cells have receptors for IgE antibodies. In our patient, the first MCD test showed that this type of immediate hypersensitivity was strongly elicited by amoxicillin, and a subsequent MCD test showed this

was true also for omeprazole. The initial marked positive MIF responses to both omeprazole and tinidazole also indicated lymphocyte activation as part of the delayed hypersensitivity type reaction and illustrated the possible activation of cell-mediated immunity in a state of humoral IgE-dependent allergy (5, 10).

In summary, it should be noted that the use of two specific immunologic tests (MIF and MCD) for drug allergy permitted us to demonstrate that all three drugs, each with its own specific immunogenicity and mechanisms, were implicated in the urticaria. Our negative results in three control patients emphasize the reliability of these tests and their potential as aids in the clinical decision to perform drug rechallenge. In cases in which there is a persistent *H. pylori* infection, the recognition of allergy will enable the clinician to avoid the use of the offending medications in further therapy. Lansoprazole (1) would be an appropriate alternative to omeprazole in view of the absence of cross-sensitivity between these two drugs (G Delpre, E Livni, and Y Niv, unpublished data).

TABLE 2. RESULTS OF INITIAL (I) AND REPEATED (II) (AFTER 6 MONTHS) TESTS*

Drugs tested	MIF I (mean MI)	MIF II (mean MI)	MCD			
			Test I		Test II	
Omeprazole	+	+	—	—	+	+
	0.60	0.53	480a	470b	987a	603b
Tinidazole	+	—	—	—	—	—
	0.69	0.81	510a	470b	610a	603b
Amoxicillin	—	—	+	+	—	—
	0.90	1.0	2430a	470b	415a	603b

* See Table 1 legends for definitions and abbreviations.

SUMMARY

Triple therapy, which includes a proton pump inhibitor and two antibiotics, is currently being used in the eradication of *Helicobacter pylori*. We report a patient who developed malaise and urticaria while she was being treated with omeprazole, amoxicillin, and tinidazole. On withdrawal of the three drugs, the clinical symptoms promptly resolved. Tests for allergy demonstrated that the adverse effects were related to the three drugs and that both cellular and humoral mechanisms were involved. It is stressed that the precise identification of the offending drug(s) and assessment of the mechanisms involved are of importance in the management of patients who remain infected by *Helicobacter pylori*. This is especially true when considering patients with omeprazole sensitization.

REFERENCES

1. O'Morain C, Lamouliatte H: Eradication. *Curr Opin Gastroenterol* 10 (suppl 1):46–52, 1994
2. Thijs TC, Van Zwet AA, Oey HB: Efficacy and side effects of a triple drug regimen for the eradication of *Helicobacter pylori*. *Scand J Gastroenterol* 28:934–938, 1993
3. Bell GD, Powel KU, Barridge SM, et al: *Helicobacter pylori* eradication: Efficacy and side effect profile of a combination of omeprazole, amoxicillin and metronidazole compared with four alternative regimens. *Q J Med* 86:743–750, 1993
4. Delpre G, Lapidot M, Lipschitz A, Livni E, Kadish U: Hyperprolactinemia during famotidine therapy. *Lancet* 342:868, 1993
5. Aderka D, Livni E, Sharon CR, Pinchas J: The migration inhibition factor test for identification of hypersensitivity reactions to drugs. *Ann Allergy* 56:342–344, 1986
6. Barette A, Glapszynski Y, De Prez C: Evaluation of various multidrug eradication regimens for *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 4:817–823, 1991
7. Labenz J, Gyenes E, Ruhl GH, Borsch G: Omeprazole plus amoxicillin: Efficacy of various treatment regimens to eradicate *Helicobacter pylori*. *Am J Gastroenterol* 88:491–495, 1993
8. Wilde MI, McTavish D: Omeprazole—an update of its pharmacology and therapeutic use in acid-related disorders. *Drugs* 48:91–132, 1994
9. Mishra D, Mobashir M, Zaheer M: Fixed drug eruption and cross-reactivity between tinidazole and metronidazole. *Int J Dermatol* 29:740, 1990
10. Livni E, Halevy S, Stahl B, Joshua H: The appearance of macrophage migration inhibition factor in drug reactions. *J Allergy Clin Immunol* 80:843–849, 1987