

Allergic reactions to cyclophosphamide: Delayed clinical expression associated with positive immediate skin tests to drug metabolites in five patients

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Background: Cyclophosphamide (CP) is one of the relatively few drugs implicated in systemic allergic reactions for which the metabolites are well known. Formation of CP metabolites is a multistep, time-dependent process (hours) with significant interindividual differences. Although allergic reactions to CP have been recorded in 17 previous reports, skin testing with CP or its metabolites has been included in only five. We now describe five patients receiving monthly cycles of intravenous CP whose allergic reactions included clinical features of type I hypersensitivity but were atypical in their markedly delayed onset (i.e., 8 to 16 hours in patients 1 to 4 and 10 days in patient 5).

Objective: The objective was to investigate these late-developing clinical reactions by skin testing with CP and two of its major metabolites.

Methods: The five patients and a control group receiving intravenous CP uneventfully were studied by the same skin test protocol.

Results: The four individuals in the control group were unreactive to CP or its metabolites. All five patients with late-onset allergic reactions had positive immediate skin test results to CP metabolites but not to CP itself. We propose that the allergic reactions in patients 1 to 4 were mediated, wholly or in major part, by IgE antibodies reactive with allergens derived from time-dependent drug metabolites. The 10-day lag time in patient 5 is unexplained. Immunomodulation by the underlying malignancies or by the immunosuppressive drugs could have contributed.

Conclusion: IgE-mediated allergic drug reactions may have a delayed onset if the allergen is a time-dependent drug metabolite, illustrated in this study by CP. (*J ALLERGY CLIN IMMUNOL* 1996;97:26-33.)

Key words: Drug allergy; cyclophosphamide; allergy to drug metabolites; IgE antibody; anaphylaxis.

Cyclophosphamide (CP), a nitrogen mustard derivative synthesized in 1958, is used extensively in the chemotherapy of a variety of malignancies and in preparation for bone marrow transplantation. This alkylating drug is also being adminis-

tered to patients with a growing list of nonmalignant, immunopathologic conditions such as systemic vasculitis and systemic lupus erythematosus. Since 1976 a variety of apparent hypersensitivity reactions to CP have been reported.¹⁻¹⁷ These have included urticaria, angioedema, or both^{1, 3-5, 7, 9, 11, 12, 16} anaphylactic reactions with cu-

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Abbreviations used:

CP:	Cyclophosphamide
4-HPCP:	4-Hydroperoxycyclophosphamide
ID:	Intradermal
PM:	Phosphoramid mustard

taneous, respiratory, and vascular manifestations,^{2, 6, 8, 10, 14, 15, 17} and cutaneous vasculitis.¹³

We now report five reactions to intravenous CP that shared a delayed onset of allergic symptoms. Clinical features in these patients included elements of classical type I IgE-mediated reactions, but in several cases additional or atypical features were seen. Skin tests performed with CP and two of its known metabolites yielded positive immediate reactions only to drug metabolites in all five patients. This finding is discussed in relation to several previous reports in which allergic reactions occurring immediately after CP infusion were associated with evidence of IgE antibody reactive with CP itself.

METHODS

Skin testing

We used commercially available CP and ifosfamide, a closely related analogue of CP, both prepared for intravenous use (Mead Johnson and Co., Evansville, Ind.). Two CP metabolites, 4-hydroperoxycyclophosphamide (4-HPCP, as a surrogate for the unstable 4-hydroxycyclophosphamide) and phosphoramid mustard (PM), were synthesized by Dr. Richard F. Borch, University of Rochester Cancer Center and Department of Pharmacology.^{18, 19} For skin testing freshly prepared dilutions (10 mg/ml and 1 mg/ml) were made in sterile isotonic saline solution by the Strong Memorial Hospital Pharmacy for each patient and were used within 30 minutes of preparation. Initial prick tests were followed by intradermal (ID) testing, with observation of the test sites for 30 minutes. Grading of results involved a scale of 0 to 4+ as follows: 0, no reaction; 1+, erythema 0.5 to 2.5 cm diameter (prick), 1 to 2.5 cm (ID), with no wheal; 2+, wheal 0.1 to 0.2 cm (prick) or 0.1 to 0.4 (ID) plus erythema >2.5 cm; 3+, wheal >0.2 cm (prick) or >0.4 cm (ID), without pseudopods, plus erythema >2.5 cm; 4+, wheal diameter ≥0.5 cm with pseudopods and erythema >2.5 cm. Histamine (Center Laboratories, Port Washington, N.Y.) at 1 mg/ml (prick) and 0.1 mg/ml (ID) and isotonic saline solution served as positive and negative controls, respectively.

In addition to the five patients with allergic reactions, we also tested a control group of four patients with hematologic malignancies receiving intravenous CP uneventfully. These studies were approved by the University of Rochester Research Subjects Review Board.

CLINICAL SUMMARIES

Case 1

A 55-year-old white woman with undifferentiated lymphocytic lymphoma was receiving single monthly doses of intravenous CP and vincristine plus oral prednisone (100 mg) 5 days a month. (The first dose of prednisone was in the evening after the intravenous chemotherapy.) Approximately 8 to 9 hours after the fourth intravenous treatment she felt "feverish" and had dyspnea and mild wheezing. These symptoms occurred at home and resolved gradually during a several day period without therapy. Eight to 9 hours after the fifth treatment, she had chills (without rigor), again felt "feverish," and had a generalized, raised, blotchy, highly pruritic skin rash, marked edema of the face, lips, and periorbital regions, nausea, vomiting, and urinary and fecal incontinence. In the hospital emergency department she had hallucinations and was found to be borderline hypotensive (96/70), orthostatic (80/60), febrile (38.3° C), and to have dysphagia and hoarseness. Neither stridor nor wheezing were described. A history of environmental, food, or medication allergy was denied. The patient immediately received diphenhydramine, methylprednisolone (125 mg intravenously), and intravenous fluids and was admitted to the hospital. The blood pressure stabilized without vasopressors, and other symptoms gradually resolved during a 5- to 6-day period while the patient continued to receive oral steroids and antihistamines. Skin tests performed 3 months after the reaction revealed significant reactions to PM and 4-HPCP and a less vigorous response to ifosfamide (Table I).

Comment

The clinical features are consistent with systemic anaphylaxis except for the chills (without rigor) and low-grade fever. The chills might be attributable simply to abnormal thermal regulation caused by the extensive rash and capillary dilatation, or an additional pathogenetic mechanism such as cytokine release might have induced chills and fever.

Case 2

A 47-year-old white woman with stage III chronic lymphocytic leukemia was receiving monthly cycles of intravenous CP and vincristine, with 5 days of oral prednisone as in case 1, and prophylactic allopurinol. One week after the third course she noted a diffuse, pruritic skin rash involving the trunk, extremities, and buttocks that lasted 2 to 3 days and was not observed by her physicians. Allopurinol was discontinued. Approximately 16 hours after the fourth course she had fever, a widespread, apparently nonpruritic rash, headache, unusual fatigue, and dyspnea, all of which worsened as the day progressed. In the emergency department she had fever (40.1° C), hypotension (85/45), marked dyspnea (respiratory rate, 35 to 40/min), and nonproductive cough without wheezes, stridor, or pulmonary rales, pedal cyanosis, and a diffuse, macular, erythematous

TABLE I. Results of skin testing*

Compound tested†	Case 1	Case 2	Case 3	Case 4	Case 5	Controls‡
Cyclophosphamide (CP)	0/0	0/0	0/0	0/0	0/0	0/0
4-Hydroperoxy-CP	1+/3+	1+/4+	0/0	0/3+	0/1+	0/0
Phosphoramidate mustard	1+/4+	2+/4+	0/3+	0/4+	0/3+	0/0
Ifosfamide	1+/2+	0/0	0/0	0/0	0/0	0/0

*Prick tests are recorded in the numerator, ID tests in the denominator.

†Only tests with 10 mg/ml concentrations are shown; results of tests with 1 mg/ml concentrations were uniformly negative.

‡Four patients with hematologic malignancies receiving intravenous cyclophosphamide uneventfully.

rash affecting the face, arms, trunk, and thighs and described as "sunburn-like" or "erythroderma." Palms, soles, and mucosal surfaces were spared. Arterial blood obtained after initiation of nasal oxygen by cannula (4 L/min) yielded pH 7.47, $p\text{CO}_2$ 24 mm Hg, $p\text{O}_2$ 86 mm Hg, and O_2 saturation 94%. (Assuming an FIO_2 of 35%, the A-a gradient was elevated to approximately 130 mm Hg.) The initial chest film revealed mild infiltration or edema at both lung bases, which was more extensive in a second film 12 hours later. The heart size was normal in these and subsequent films, and an electrocardiograph result was normal except for sinus tachycardia. Physical examination of the chest remained negative, but dyspnea and tachypnea persisted. Initial treatment included increased oxygen delivery, intravenous fluids, dopamine infusion, high-dose intravenous methylprednisolone, diphenhydramine, and ranitidine, and transfer to the intensive care unit. Intravenous antibiotics were also given until blood and cerebrospinal fluid cultures were definitely negative. The patient rapidly became afebrile. Dopamine could be discontinued after 24 hours and oxygen after 48 hours in concert with rapid radiographic clearing of the pulmonary parenchyma. However, small bilateral pleural effusions, left greater than right, appeared at this time. The rash faded without desquamation. Hepatic and renal function were well maintained throughout the patient's course. Other laboratory data obtained during the acute reaction revealed (1) a white blood cell count of 23,000 with 79% neutrophils and 12% bands, and (2) low normal C3 and slightly low hemolytic complement (CH50) titer. These same complement assays yielded significantly higher values 3 weeks later at her next admission (see following).

The CP metabolites for skin testing were not available at this time. The hematology service believed that CP was a mainstay of the patient's treatment and that vincristine rather than CP might have induced the allergic reaction. Therefore the patient was rehospitalized 3 weeks later and was challenged with increasing oral doses of CP (1 mg, 10 mg, and 100 mg on successive days). Seven hours after the 100 mg dose was administered, a fall in systolic blood pressure from 120/70 to 92/70 was the first sign of a reaction. Within 2 hours blood pressure was 80/55, and the patient's temperature rose progressively to a maximum of 39.2° C, with subsequent appearance of eyelid swelling and mildly pruritic, bilateral lower leg and pedal edema but no rash. The

respiratory rate increased to 24/min, but significant respiratory distress did not develop, and physical examination of the chest remained negative. The chest film, however, which was completely clear on admission, now showed bilateral infiltrates at both lung bases (interpreted as interstitial edema), small bilateral pleural effusions, and normal heart size. A transient neutrophilic leukocytosis (26,000) recurred. Complement (CH50, C4, C3) assays and ^{125}I -Clq-binding assay for immune complexes showed no change from normal admission values. Treatment was with intravenous fluids, diphenhydramine, and acetaminophen, and the patient recovered gradually during a 48-hour period. Skin testing 7 months later yielded positive reactions to both 4-HPCP and PM (Table I).

Comment

This patient's complex systemic reaction and positive clinical challenge are more difficult to categorize. Of interest are certain similarities of these clinical features to those reported in acute systemic reactions to sulfa drugs.²⁰

Case 3

A 47-year-old white woman with fallopian tube adenocarcinoma with extension to the uterus and peritoneal cavity was being treated with monthly intravenous carboplatin and CP. Twelve hours after her second course, she had a diffuse, nonpruritic, erythematous, macular rash involving her face, neck, chest, arms, and legs. The rash subsided during a 3- to 4-day period with oral diphenhydramine. Subsequent therapy with etoposide and carboplatin was uneventful. Skin testing 4 weeks later revealed a positive reaction to PM (Table I).

Comment

These clinical features are not strongly suggestive of type I hypersensitivity; nevertheless, a positive immediate skin reaction was elicited to a CP metabolite, and readministration of carboplatin provoked no reaction.

Case 4

A 37-year-old white woman with a history of breast cancer was evaluated. After undergoing a left modified radical mastectomy, she was treated with intravenous CP, 5-fluorouracil, and oral compazine in monthly cycles of 5 days. Twelve hours after her fourth course she had

urticaria, which subsided during a several day period on antihistamine therapy. Eleven hours after her fifth course, however, she had a much more severe episode consisting of generalized urticarial lesions and facial angioedema lasting approximately 36 hours in spite of antihistamine and corticosteroid therapy. She did not have respiratory symptoms or hypotension. Eighteen months later the patient was reevaluated for possible intensive chemotherapy preceding bone marrow transplantation for metastatic disease. Skin testing revealed positive reactions to PM and 4-HPCP (Table I), and CP was not used in her treatment.

Comment

This clinical reaction clearly fits type I IgE-mediated allergy except for the delayed onset.

Case 5

A 28-year-old white woman with poorly differentiated lymphocytic lymphoma completed six cycles of intravenous CP, vincristine, and oral prednisone uneventfully. Ten months later her lymphoma recurred, and she was begun on a new monthly chemotherapeutic regimen with intravenous CP, adriamycin, vincristine, and oral prednisone. Twelve days after completion of the first course in the new cycle, the patient had an urticarial rash over the face and trunk; it subsided gradually on an antihistamine. Ten days after completing her second cycle, she had a more intense and extensive urticarial rash, a sense of tongue swelling, and oral ulcerations. The patient had no systemic symptoms and was found on examination to be normotensive and without wheezing, dyspnea, objective evidence of angioedema, lymphadenopathy, or joint symptoms. Several small buccal ulcers were described. When skin tested 6 weeks later, the patient was sensitive to PM (Table I). The patient was switched to alternative chemotherapy and ultimately underwent successful bone marrow transplantation.

Comment

The urticarial reaction per se would fit IgE-mediated hypersensitivity, but the 10-day lag time from CP administration to clinical symptoms is not readily explained. Classic features of serum sickness were lacking. The patient denied taking other drugs during the 10-day interval. It is unclear whether the oral ulcers represent CP-induced "mucositis" or are a component of the allergic reaction.

RESULTS

Each of the five patients who had had allergic reactions displayed positive immediate skin test results to 10 mg/ml concentrations of one or both of the available CP metabolites but not to CP itself (Table I). Patient 1 also reacted mildly to the related alkylating drug, ifosfamide. The four CP-treated patients in the control group were unreactive to the same reagents (Table I). Several other

known metabolites of CP were not available for inclusion in our skin testing protocol.

DISCUSSION

Data from other reports of allergic reactions to CP are summarized in Table II. Both immediate and delayed-onset reactions have been observed. A few occurred during oral therapy, but most were associated with intravenous administration. Occasional patients have had seemingly allergic reactions, including systemic anaphylaxis, during their first exposure to CP (Table II).

In the present series all five adverse reactions shared a delayed onset after intravenous administration of CP, 8 to 16 hours in cases 1 to 4 and 10 days in case 5. Previous exposures to intravenous CP ranged from two to seven cycles. Although the immunopathogenic mechanism(s) are not completely clear in all cases, the allergic nature of these adverse reactions is supported by the major clinical features, by the occurrence of two allergic episodes of escalating intensity in cases 1, 4, and 5 and the clearly positive rechallenge in case 2, and by positive immediate skin tests in all five patients and negative skin test results in four CP-treated patients in the control group (Table I).

In our cases 1 to 4, positive immediate skin reactions were obtained with one or both of the available CP metabolites but not with CP itself. We propose that the 8- to 16-hour lag time before onset of symptoms reflects, at least in significant part, the time required for generation of the metabolite-dependent allergens, as initially proposed by Kim et al.⁹ It also seems plausible that these patients' IgE antibodies possess a narrow specificity for hapten-generated epitopes unique to CP metabolites. The mean plasma half-life of CP in adults is 7 to 8 hours but with a fairly broad range of 5.5 to 12 hours.²¹ During this time most of the administered CP is converted by hepatic microsomes to 4-hydroxy CP, which functions as the transport molecule to tissues in which alkylation takes place.^{21,22} The latter compound is in equilibrium with its open-ring tautomer, aldophosphamide, which can be transformed by many tissues either to inactive metabolites or to the active alkylating agent, PM, and acrolein.²¹⁻²³ Even though the latter transformation occurs intracellularly, plasma levels of PM are measurable for hours after a single intravenous dose of CP.²³ Formation of the complete metabolite-derived allergen (e.g., with PM or 4-hydroxy-CP) would then presumably involve coupling of these haptens to

TABLE II. Summary of reported allergic reactions to cyclophosphamide

Reference	First author/ year	Age (yr)/ sex	Underlying disease	Route	Reaction observed during	Clinical reaction	Timing of reaction	Skin testing
1	Lakin 1976	6 M	Sarcoma	IV	7th Course	Urticaria	Immediate	(+)P-K test:CP
2	Karchmer 1977	66 F	Non-Hodgkins lymphoma	IV	15th Course	Anaphylaxis	Immediate	NT
3	Ross 1977	29 M	Hodgkins lym- phoma	IV	1st Course; pre- viously sensi- tive to mechloreth- amine	Angioedema	10 hr	NT
4	Krutchik 1978	48 F	CA breast	IV/PO	1st PO course; but before IV Rx	Urticaria	7 hr	NT
5	Legha 1978	61 F	CA lung	IV	3rd Course	Urticaria	Immediate	NT
6	Murti 1979	2 M	Retino-blas- toma	IV/PO	17th Course	Anaphylaxis	Immediate	NT
7	Anku 1982	56 M	CA lung	IV	1st Course	Urticaria	Immediate	NT
8	Aulbert 1983	25 ?	Hodgkins lym- phoma	IV	4th Course	Anaphylaxis	Immediate	(+):CP
9	Kim 1985	48 M	Myeloma	IV/PO	1st IV Course, but before PO Rx	Urticaria, chills, fever	8 hr	(+):PM
10	Kath 1986	64 F	Hodgkins lym- phoma	IV	1st Course	Anaphylaxis	Immediate	NT
11	Kritharides 1987	32 F	Mycosis fun- goides	IV/PO	1st Course IV; also reacted to PO	Urticaria	4 hr	NT
12	Grosbois 1987	45 ?	Myeloma	IV	1st Course	Urticaria	Hours	NT
		55 ?	Myeloma	IV	3rd Course	Urticaria	Hours	NT
13	Green 1989	55 M	CLL	PO	2nd Course	Vasculitis	6 hr/day	NT
14	Jones 1989	36 F	CA Breast	IV	2nd Course	Anaphylaxis	Immediate	NT
15	Salles 1991	85 F	Non-Hodgkins lymphoma	IV	1st Course	Anaphylaxis	Immediate	NT
16	Cromar 1991	37 F	Sarcoid	IV	8th Course	Urticaria	Immediate and 6 hr	(+):CP, 4-HPCP, PM
17	Knysak 1994	27 F	SLE	IV	9th Course	Anaphylaxis	Immediate	(+):CP, 4-HPCP
	This report	55 F	Non-Hodgkins lymphoma	IV	5th Course	Anaphylaxis	8-9 hr	(+):4-HPCP, PM, IF
		47 F	CLL	IV	4th Course	Severe systemic reaction	16 hr	(+):4-HPCP, PM
		47 F	Genital CA	IV	2nd Course	Skin rash	12 hr	(+):PM
		37 F	CA Breast	IV	4th Course	Urticaria; Angioedema	11 hr	(+):4-HPCP, PM
		28 F	Non-Hodgkins lymphoma	IV	7th Course	Urticaria	10 days	(+):PM

M, Male; F, female; IV, intravenous; NT, not tested; CP, cyclophosphamide; 4-HPCP, 4-hydroxyperoxy-cyclophosphamide; PM, phosphoramidate mustard; IF, ifosfamide; CLL, chronic lymphocytic leukemia; SLE, systemic lupus erythematosus.

one or more host carrier proteins such as plasma proteins or cell-associated proteins.^{21, 24} These derivatized proteins may then require buildup to a threshold concentration to trigger sufficient mediator release from specifically sensitized mast cells, basophils, or both to produce the clinical reaction.

Whether this postulated sequence fully accounts for the 8- to 16-hour lag time in patients 1 to 4 is not clear. Significant interindividual variation in the pharmacokinetics of CP metabolism, which is increasingly recognized,²³ may be relevant. Nevertheless, reactions delayed for 11 to 16 hours may reflect additional, undefined factors. We do not think the delayed reactions are attributable to prednisone therapy. Patients 3 and 4 did not receive corticosteroids, but both had 11-hour lag times. In patients 1 and 2 the first dose of prednisone was taken hours after the infusion of CP had been completed, and potentially allergenic metabolites were already being formed. The CP given in cycles prior to the reaction failed to suppress IgE antibody formation, judging from the clinical events and subsequent skin tests. In patients 1 to 4 it is difficult to envision a mechanism by which either prednisone (taken hours after the CP infusion) or the CP itself could alter the timing of the allergic reaction without suppressing it.

To examine further the idea that immediate versus delayed onset of allergic reactions to CP may be related to the specificity of the patient's IgE antibodies, we compared in Table II (last two columns) the reported lag time (from CP infusion to onset of reaction) and skin test results in the relatively few reports in which they are available. In case reports 1, 8, and 17 the allergic reactions were immediate, and evidence was presented for the presence of IgE antibody reactive with CP itself (in report 1 this was by P-K passive transfer). In report 9 the clinical reaction began 8 hours after CP infusion, and skin testing was positive only to PM. Report 16 seems particularly instructive. The patient had both an immediate reaction and a second reaction at 6 hours; her skin tests were positive both with CP itself and with two metabolites, PM and 4-HPCP, which is a stable surrogate for 4-hydroxy CP.^{18, 19, 21}

In fairness, it should be noted that in reports 1 and 8 (Table II) CP metabolites were not tested and that in report 17 skin testing was also positive to 4-HPCP (and to CP itself), but the patient did not have a delayed reaction. In the latter case treatment for this severe immediate reaction may have been continued long enough to abort a second reaction (details not given). Another pos-

sible interpretation is that 4-hydroxy CP may bind to potential carrier proteins less efficiently than PM, which is thought to be the principal alkylating agent in CP therapy.²¹⁻²³ All of the patients with delayed-onset reactions in our own series (Table I) and in reports 9 and 16 (Table II) had positive skin test results to PM, with or without reactivity to 4-HPCP. Finally, the possibility exists that IgG-blocking antibodies are formed by certain patients (e.g., to CP itself or to 4-HPCP) and thus might attenuate a reaction to one drug hapten but not to another, for example, PM. Therefore correlating immediate reactions with IgE antibody reactive with CP itself and late reactions with antibody to a metabolite may prove to have some general validity but is likely to be oversimplified.

We also considered that cases 1 to 4 might represent atypical examples of (1) the late-phase reaction that may occur 3 to 8 hours after classical immediate hypersensitivity reactions to a variety of allergens,²⁵ or (2) biphasic anaphylaxis.²⁶ Our patients, however, did not have an immediate clinical reaction, and none of our patients had secondary (late-phase) cutaneous reactions at positive test sites.

Our fifth patient had urticaria and oral ulceration approximately 10 days after the last CP infusion, an interval distinctly different from that in the other four cases, and is not readily explained. Yet, this patient exhibited positive immediate skin reactions to PM and, minimally, to 4-HPCP (Table I). Clinical features of a serum sickness-like reaction were lacking. It should be noted, however, that one of the previously reported allergic reactions to CP (13, Table II) consisted of cutaneous vasculitis.¹³ It is noteworthy that our patient 2 had a diffuse, pruritic rash 1 week after her third CP course. Then the next CP treatment was followed in 16 hours by a life-threatening systemic reaction to the next CP treatment. Is the 10-day reaction in patient 5 analogous to the "prodromal" reaction occurring 1 week after CP in patient 2? Finally, immunomodulation by the underlying malignancy or by the drug-induced immunosuppression could have contributed to the 10-day delay, but this does not really explain why patient 5 differed from the others.

The severe reaction in case 2 included hypotension plus at least three features that are atypical for classical anaphylaxis: high fever, marked respiratory distress without airway obstruction, and neutrophilic leukocytosis. Sepsis and toxic shock syndrome, both major initial concerns, were ruled out. Although an echocardiogram was not obtained,

the patient had no clinical, radiographic, or electrocardiographic evidence of underlying heart disease before or after this reaction. The available data suggest that the relatively brief increase in alveolar-arterial oxygen gradient and the rapidly resolving pulmonary radiographic changes were most consistent with noncardiogenic interstitial edema reflecting acute, reversible changes in pulmonary capillary permeability. A contribution from transient myocardial dysfunction^{27, 28} cannot, however, be excluded.

Although this patient's overall reaction includes elements that are atypical for systemic anaphylaxis,²⁹⁻³¹ it seems plausible that IgE antibodies to CP metabolites (PM, 4-HPCP, or both) contributed to the pathogenesis. However, the mediators producing the atypical features listed previously and their cellular source remain to be defined. Serum complement depletion appears to have occurred during the major reaction in case 2 but not during the milder reaction to the oral challenge. Complement depletion has been observed in human anaphylaxis.^{30, 32} Of interest are certain similarities of this patient's reaction to the severe, systemic reactions to trimethoprim-sulfamethoxazole in patients infected with the human immunodeficiency virus.²⁰ These authors proposed that such reactions represent a combination of type I hypersensitivity plus massive release of cytokines such as tumor necrosis factor.²⁰ The adverse reactions to trimethoprim-sulfamethoxazole have been particularly noted in patients in whom treatment was interrupted and restarted,²⁰ a feature mimicked perhaps by monthly pulses of CP. The strong association of the trimethoprim-sulfamethoxazole reactions with immune deficiency may also be mirrored to some degree by an altered immune status in occasional patients with lymphoid malignancies.

The occurrence of urticaria or anaphylaxis with the first known exposure of a patient to CP in both immediate and delayed time frames (reports 7, 10, 11, 12, and 15 in Table II) invites speculation that preexisting antibodies to other antigens may sometimes cross-react with CP or with a CP metabolite. Unfortunately, none of these reports provided skin test data. Alternatively, nonimmune mediator release by CP or a CP metabolite could occasionally occur in patients. Moreover, Cromar et al.¹⁶ have reported that in one of three volunteers in a control group who had never received cytotoxic drugs, PM induced a positive immediate skin reaction. Nonspecific skin reactions to PM were not found in the four patients in our control group, all of whom had received previous CP therapy.

At this medical center, where four of the five allergic episodes occurred, a total of 1904 courses of intravenous CP were given during the 2-year span in which these cases were collected. Although allergic reactions to CP are rare, the observations in our first four patients illustrate a clinical point of broader significance, that is, that the clinical expression of an IgE-mediated allergic drug reaction may be delayed beyond the expected time interval if the allergenic hapten is a time-dependent drug metabolite. CP is one of relatively few drugs implicated in systemic allergic reactions for which the metabolites are well known. Elucidation of allergic reactions to many other drugs would in all likelihood be advanced if their metabolites were available for testing.

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