

Anaphylactic reactions associated with trimethoprim

A. M. H. BIJL*, M. M. VAN DER KLAUW*†, A. C. M. VAN VLIET* and B. H. CH. STRICKER†‡

*Drechtsteden Hospital, Dordrecht, †Drug Safety Unit, Inspectorate for Health Care, Rijswijk and ‡Department of Epidemiology & Biostatistics, Pharmaco-epidemiology Unit, Erasmus University Medical School, Rotterdam, The Netherlands

Summary

Background Anaphylactic reactions to cotrimoxazole are often ascribed to the sulphamethoxazole component of this antibacterial drug.

Objective To determine whether the trimethoprim component can be the cause of an anaphylactic reaction.

Methods An analysis was made of reports on anaphylaxis attributed to trimethoprim, as notified to the Drug Safety Unit of the Dutch Inspectorate for Health Care.

Results In the period between September 1981 and November 1995, 13 such reports were received. Nine were classified as probable anaphylaxis. Of these, the causal relationship between exposure to trimethoprim and anaphylaxis was classified as definite in three reports, and as probable in the other six. The remaining four reports were classified as possible anaphylaxis. In one of these, the causal relationship was classified as definite, and in three as probable.

Conclusion Although anaphylaxis due to trimethoprim seems to be rare, it may be more common than previously thought. Apparently, anaphylaxis to cotrimoxazole is not always caused by sulphamethoxazole.

Keywords: trimethoprim, anaphylaxis, reporting system, drug-induced, adverse reaction

Clinical and Experimental Allergy, Vol. 28, pp. 510–512. Submitted 3 April 1997; revised 3 November 1997; accepted 10 November 1997.

Introduction

Anaphylactic reactions associated with cotrimoxazole (a combination of sulphamethoxazole and trimethoprim) are a common phenomenon. Because sulphonamides are a frequent cause of allergy, reactions to cotrimoxazole are often attributed to the sulphamethoxazole component. Only few data exist on allergy to trimethoprim, a dihydrofolic acid inhibitor. Currently, trimethoprim is the antibiotic of first choice in general practice in the Netherlands for the treatment of urinary tract infections.

We describe the case-histories of 13 patients with anaphylactic reactions to trimethoprim alone, which were reported to the Drug Safety Unit of the Dutch Inspectorate for Health Care (DSU).

Materials and methods

Between September 1981 and November 1995, 13 cases of anaphylactic reactions attributed to trimethoprim were reported to the DSU. In these 13 cases, reporting physicians, patients, or patient's relatives were asked about the symptoms the patients had experienced, the temporal relationship between ingestion of the tablet and the occurrence of symptoms, the duration of symptoms, previous use of trimethoprim with or without symptoms, known allergies and other diseases and other medication used at the time of the anaphylactic reaction.

Reports were classified as described earlier [1], based on the occurrence of cardiovascular, gastrointestinal, dermatological and respiratory symptoms which are characteristic of anaphylaxis, and the onset within one hour after exposure [2].

The causal relationship between exposure to trimethoprim and anaphylaxis was classified as possible, probable

Correspondence: Dr B. H. Ch. Stricker, Drug Safety Unit, Inspectorate for Health Care, PO Box 5406, 2280 HK Rijswijk (ZH), The Netherlands.

Table 1. Characteristics of reports on trimethoprim-associated anaphylaxis

Patient	M/F*	Age (years)	Temporal relationship	Symptoms	Anaphylaxis	Causal relationship	Rechallenge**
A	F	22	15 min	hypotension, nausea, vomiting, angioedema	<i>Probable</i>	<i>Definite</i>	+
B	F	34	30 min	syncope, urge to defecate, erythema, oedema	<i>Probable</i>	<i>Definite</i>	+
C	F	37	45 min	hypotension, vomiting, diarrhea, urticaria	<i>Probable</i>	<i>Definite</i>	+
D	F	67	10 min	hypotension, stomach ache, erythema, dyspnoea	<i>Probable</i>	<i>Probable</i>	+
E	F	30	45 min	hypotension, nausea, vomiting, erythema	<i>Probable</i>	<i>Probable</i>	–
F	F	33	5 min	syncope, stomach ache, diarrhea, angioedema, dyspnoea	<i>Probable</i>	<i>Probable</i>	–
G	F	68	30 min	hypotension, rash	<i>Probable</i>	<i>Probable</i>	–
H	F	32	60 min	hypotension, bronchospasm	<i>Probable</i>	<i>Probable</i>	–
J	F	37	30 min	hypotension, urticaria, bronchospasm	<i>Probable</i>	<i>Probable</i>	0
K	F	29	3 h.	oedema, pruritus, bronchospasm	<i>Possible</i>	<i>Definite</i>	+
L	F	46	unknown	nausea, oedema, rash, dyspnoea	<i>Possible</i>	<i>Probable</i>	+
M	F	41	<5 h.	oedema, erythema, cough	<i>Possible</i>	<i>Probable</i>	0
N	M	62	unknown	erythema, bronchospasm	<i>Possible</i>	<i>Probable</i>	0

* M, male; F, female ** Rechallenge: + = symptoms after prior or repeated use; – = prior use without symptoms; 0 = no prior or repeated use.

or definite, also according to the method described earlier [1].

Results

Thirteen patients with an anaphylactic reaction to trimethoprim were reported (12 female, one male, age 22–68 years). Table 1 shows the relevant characteristics of patients and reactions.

Nine reports were classified as probable anaphylaxis. Of these, six patients experienced gastrointestinal symptoms like vomiting or urge to defaecate, eight had skin symptoms, mainly urticarial rash and angioedema. Four had respiratory symptoms, such as dyspnoea and wheezing and all experienced hypotension. The temporal relationship between ingestion of the tablet and the start of symptoms varied from 5 to 60 min. Of these nine patients all but one were known to have used trimethoprim or cotrimoxazole before, three of them reported symptoms such as itch or general discomfort on previous exposure, whereas four had used the drug before without problems.

Four patients were classified as anaphylaxis possible because they had symptoms characteristic of or compatible with anaphylaxis, but a temporal relationship between exposure and anaphylaxis which was either unknown or longer than 1 h. One patient reported similar symptoms after previous use of cotrimoxazole.

Out of 13, five patients used other drugs which were continued without problems. Furthermore, five patients had known allergies to allopurinol, acetylcysteine, latex, ferro

fumarate, nitrofurantoin, penicillin and grass pollen, respectively.

The causal relationship was classified as definite in four patients because they had experienced allergic symptoms on more than one occasion during use of trimethoprim or cotrimoxazole. In one patient IgE-antibodies against trimethoprim were demonstrated. In the other patients these tests could not be performed.

Discussion

Thirteen patients with an anaphylactic reaction attributed to trimethoprim were reported to the DSU. Ten patients reported earlier use of trimethoprim or cotrimoxazole, five of them with symptoms. Unfortunately, most patients did not remember which symptoms they had developed, or information was unobtainable. Of the 13 patients, five had known allergies to other substances. We did not find evidence in literature for a cross-allergy between these substances and trimethoprim.

There can be no doubt that trimethoprim may cause anaphylaxis. The incidence of this effect, however, remains unknown, as voluntary reporting schemes give no insight into the frequency of adverse reactions, due to underreporting and reporting bias.

Little is found in the medical literature on anaphylactic reactions to trimethoprim alone. Although hypersensitivity reactions have been reported, i.e. toxic epidermal necrolysis [3], pneumonitis [4], fixed drug eruption [5–7], vasculitis [8], and photosensitivity reactions [9], anaphylactic reactions were only rarely reported [10–12].

Harle *et al.* described eight patients with an anaphylactic reaction to cotrimoxazole of whom one had antitrimethoprim-IgE with a positive RAST-inhibition test [10]. In another report three case-histories were described, two of patients with anaphylactic reactions, and one with generalized urticaria after use of cotrimoxazole, who had positive skin-prick tests and rechallenge-tests to trimethoprim, and negative skin prick and intradermal tests and rechallenge tests to sulphamethoxazole. No significant levels of specific IgE to trimethoprim could be detected [11]. One other report discussed a patient with an anaphylactic reaction to cotrimoxazole, who had a positive skin-prick test and specific IgE with a positive RAST-inhibition to trimethoprim, while skin-prick and intradermal tests to sulphamethoxazole were negative and no IgE against sulphamethoxazole could be found [12].

In conclusion, anaphylactic reactions to cotrimoxazole should not be attributed too easily to the sulphamethoxazole-component, since anaphylaxis to trimethoprim may not be as uncommon as previously thought.

References

- 1 Van der Klauw MM, Wilson JHP, Stricker BHCh. Drug-associated anaphylaxis: 20 years of reporting in the Netherlands (1974–94) and review of the literature. *Clin Exp Allergy* 1996; 26:1355–63.
- 2 Wasserman SI, Marquardt DL. Anaphylaxis. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds *Allergy: principles and practice*, 4th edn. St. Louis: C.V. Mosby 1993; 1525–35.
- 3 Nwokolo C, Byrne L, Misch KJ. Toxic epidermal necrolysis occurring during treatment with trimethoprim alone. *BMJ* 1988; 296:970.
- 4 Higgins T, Niklasson PM. Hypersensitivity pneumonitis induced by trimethoprim. *BMJ* 1990; 300:1344.
- 5 Lim JTE, Chan HL. Fixed drug eruptions due to co-trimoxazole. *Ann Ac Med* 1992; 21:408–10.
- 6 Gibson JR. Recurrent trimethoprim-associated fixed skin eruption. *BMJ* 1982; 284:1529–30.
- 7 Hughes BR, Holt PJA, Marks R. Trimethoprim associated fixed drug eruption. *Br J Dermatol* 1987; 116:241–2.
- 8 Holt RIG, Ebrahim SBJ. Trimethoprim-induced vasculitis. *Postgrad Med J* 1992; 68:391.
- 9 Chandler MJ. Recurrence of phototoxic skin eruption due to trimethoprim. *J Infect Dis* 1986; 153:1001.
- 10 Harle DG, Baldo BA, Wells JV. Drugs as allergens: detection and combining site specificities of IgE antibodies to sulphamethoxazole. *Molec Immunol* 1988; 25:1347–54.
- 11 Alonso MD, Marcos C, Davila I et al. Hypersensitivity to trimethoprim. *Allergy* 1992; 47:340–2.
- 12 Cabañas R, Caballero MT, Vega A, Martin-Esteban M, Pascual C. Anaphylaxis to trimethoprim. *J Allergy Clin Immunol* 1996; 97:137–8.