Characterization of Sulfamethoxazole and Sulfamethoxazole Metabolite-Specific T-Cell Responses in Animals and Humans

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ABSTRACT

Sulfamethoxazole (SMX) is associated with hypersensitivity reactions. Identification of drug-specific lymphocytes from hypersensitive patients suggests involvement of the immune system. Lymphocytes from humans recognize SMX and nitroso-SMX (SMX-NO), whereas cells from sensitized rats recognize only SMX-NO. In this investigation, we study the nature of SMX-specific T cells in four species. Male rats, mice, and rabbits were immunized with SMX (50 mg kg\(^{-1}\)) or SMX-NO (1 mg kg\(^{-1}\)). Lymphocytes and/or splenocytes were isolated and incubated with SMX, SMX-hydroxylamine or SMX-NO and proliferation was measured. Lymphocytes were also isolated from SMX-hypersensitive patients (\(n = 3\)) and drug-specific proliferation was measured. In addition, rabbits were bled fortnightly for 4 months to determine whether SMX-NO-specific T cells cross-react with SMX. To confirm that SMX-NO responses were due to covalent binding and not cross-reactivity, cells were pulsed with SMX-NO and/or coincubated with glutathione. Splenocytes from mice, rats, and rabbits proliferated when stimulated with SMX-NO, but not SMX. A 2-h pulse with SMX-NO was sufficient for proliferation, whereas cells coincubated with SMX-NO and glutathione did not proliferate. Rabbit lymphocytes proliferated in the presence of SMX-NO and SMX-hydroxylamine, but not SMX. SMX-hydroxylamine was converted to SMX-NO in culture. The SMX-NO-specific response of rabbit lymphocytes was maintained for at least 4 months and the cells did not cross-react with SMX. Human lymphocytes from hypersensitive patients proliferated in the presence of SMX and both metabolites. These results highlight important differences in T-cell recognition of drug (metabolite) antigens in animals that have been sensitized against a drug metabolite and patients with hypersensitivity to the drug.

Administration of sulfamethoxazole (SMX) is associated with hypersensitivity reactions, the most common of which are cutaneous eruptions. These reactions range in severity from mild antibody-mediated urticarial reactions to the potentially fatal toxic epidermal necrolysis, which is T cell-mediated (Pichler et al., 2002). SMX is used in combination with trimethoprim, as cotrimoxazole, for the treatment of opportunistic infections associated with HIV infection. In these patients, hypersensitivity reactions are seen in 30% of individuals administered low-dose SMX for prophylaxis and 50% given SMX for treatment (Pirmohamed and Park, 2001).

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Due to the high incidence of SMX-hypersensitivity in patients with HIV infection there has been a resurgence of interest in the chemical and immunological mechanisms underlying these reactions.

Low molecular weight substances, including most allergenic drugs, are thought to become immunogenic by binding irreversibly to protein (Park et al., 1998). In the case of SMX, this involves P450 and myeloperoxidase-catalyzed metabolism (Cribb et al., 1990, 1995). The resultant hydroxylamine, which is not protein-reactive (Cribb et al., 1991; Naisbitt et al., 1996), circulates in the periphery (Gill et al., 1997). Further auto oxidation, under conditions of oxidative stress, generates the protein-reactive intermediate nitroso SMX (SMX-NO; Naisbitt et al., 1999, 2001; Reilly et al., 2000; Manchanda et al., 2002; Summan and Cribb, 2002; Fig. 1). In solution, SMX-NO is extremely unstable; degradation yields products of oxidation (nitro SMX), reduction (SMX, SMX hydroxylamine), and dimerization (azo and azoxy adducts) (Naisbitt et al., 2002). Patients with HIV infection have low

ABBREVIATIONS: SMX, sulfamethoxazole; HIV, human immunodeficiency virus; SMX-NO, nitroso sulfamethoxazole; MHC, major histocompatibility complex; DMSO, dimethyl sulfoxide; HBSS, Hanks’ balanced salt solution; SI, stimulation indices.
thiol levels and a decreased capacity to reduce SMX metabolites back to the parent drug (Walmsley et al., 1997; Naisbitt et al., 2000), which in turn is thought to contribute to the increased susceptibility to SMX hypersensitivity.

To investigate the role of oxidative drug metabolism in SMX hypersensitivity, we developed a rat model of drug immunogenicity. Administration of SMX-NO, but not the parent drug, led to the production of metabolite-specific antibodies and T cells (Gill et al., 1997; Naisbitt et al., 2001). The T-cell receptor of SMX-NO-specific T cells was stimulated by an MHC-restricted, processed peptide derived from cellular protein haptenated with SMX-NO (Naisbitt et al., 2002). Chemical (thiol-depleting agents) and immunological (adjuvants) modulation, before SMX administration, confirmed that oxidative metabolism of SMX was required to stimulate a primary drug antigen-specific immune response in vivo. These observations are consistent with the demonstration of SMX metabolite-specific, but not SMX-specific, delayed-type hypersensitivity in mice (Choquet-Kastylevsky et al., 2001) and the original hapten hypothesis.

The belief that low molecular weight chemicals require covalent binding to be immunogenic has recently been challenged (Mauri-Hellweg et al., 1995; Schnyder et al., 1997; von Greayerz et al., 2001). T-cell clones isolated from hypersensi-
tive patients have shown that SMX can be presented directly in the apparent absence of drug metabolism. This form of drug recognition by T cells is MHC-restricted but does not require antigen processing (Schnyder et al., 1997). Further studies of SMX-hypersensitive patients with maculopapular- and bullous-type skin eruptions has confirmed that SMX can indeed be presented to T cells directly; however, it must be noted that T cells that proliferate in the presence of SMX-NO can also be isolated from most hypersensitive individuals (Schnyder et al., 2000; Burkhart et al., 2001; Nassif et al., 2002). Thus, the signal that stimulates the immune system is not known.

The aim of this project was to further address the nature of the SMX antigen recognized by T cells. To fulfill this aim, SMX- and SMX-NO-sensitized splenocytes from three animal species (mouse, rat, and rabbit) and lymphocytes from sensitized rabbits and hypersensitive humans were used. To delineate the potential of SMX-NO-specific T cells to cross-react with SMX with time, lymphocytes from SMX-NO-sensitized rabbits were collected fortnightly for 4 months and stimulated ex vivo with SMX and SMX-NO.

Materials and Methods

Chemicals. Dimethyl sulfoxide (DMSO), Hanks’ balanced salt solution (HBSS), L-glutamine, HEPES, penicillin, streptomycin, RPMI 1640 medium, human AB serum, transferrin, [3H]thymidine, fetal calf serum, and SMX were obtained from Sigma-Aldrich (Poole, Dorset, UK). SMX hydroxylamine and SMX-NO were synthesized according to the method of Naisbitt et al. (1996).

Cell Culture Media. Basal medium consisted of RPMI 1640 medium supplemented with L-glutamine (2 mM), HEPES (25 mM), streptomycin (100 μg ml\(^{-1}\)), and penicillin (100 μg ml\(^{-1}\)). For experiments with human cells this solution was supplemented with 10% human AB serum and transferrin (25 mg). In animal experiments, the basal media was supplemented with 10% fetal calf serum. All culture media was passed through a 0.45-μm filter before use.

Patient Details. Blood lymphocytes were obtained from three SMX-hypersensitive patients, three patients administered SMX without visible adverse effects, and three unexposed individuals. Of the SMX-hypersensitive patients, two were HIV negative and developed maculopapular rashes after treatment with cotrimoxazole. The third patient, who was HIV positive and was being treated with cotrimoxazole for prophylaxis for Pneumocystis carinii pneumonia, developed a rash and fever. All the patients had a positive rechallenge as part of their clinical care, and their symptoms improved after discontinuation of cotrimoxazole. Approval for the study was obtained from the local ethics committee and informed consent was obtained from each participant. Lymphocytes were isolated from venous blood by density centrifugation using Lymphoprep. Purified cells were washed with culture media and the yield was assessed using an improved Neubauer hemocytometer (Weber Scientific, Int.). Viability, which was consistently greater than 95%, was monitored by trypan blue dye exclusion.

Immunizing Protocols. The rat was chosen as a model because SMX metabolism has been studied previously and been shown to be similar to humans (Gill et al., 1997). The immunogenicity of SMX and SMX-NO was studied in mice because of their decreased capacity to metabolize SMX to SMX-NHOH (Naisbitt, unpublished data). Metabolism of SMX in rabbits has not been investigated. However, experiments with rabbits allowed us to study the kinetics of the SMX-NO-specific proliferative response and investigate whether SMX-NO-specific T cells cross-react with SMX with time. Male Wistar rats (8–12 weeks, 175–225 g), male CD1 mice (6–9 weeks, 20–30 g), and New Zealand White rabbits (10–12 weeks, 2–2.5 kg) were purchased from Charles River UK Ltd. (Kent, UK). All animals were immunized with SMX (50 mg ml\(^{-1}\)) or SMX-NO (1 mg kg\(^{-1}\)) in DMSO i.p. (rats and mice, 100 μl/injection; rabbits, 200 μl/injection) 4 times weekly for 2 weeks using established methodology (Naisbitt et al., 2001). Control animals were administered DMSO alone. Seven days after completion of the immunization protocol, animals were sacrificed and the spleen was removed using aseptic technique. In separate experiments, blood (7 ml) was taken from the ear of SMX-NO-sensitized rabbits. This procedure was repeated every 2 weeks for 16 weeks. After the 2-week immunization protocol, the rabbits were not exposed to SMX-NO.

Red cell-depleted splenocytes and/or lymphocytes were isolated by density centrifugation using Lymphoprep. Purified cells were washed with culture media and the yield was assessed using an improved Neubauer hemocytometer (Weber Scientific, Int.). Viability, which was consistently greater than 95%, was monitored by trypan blue dye exclusion.

Determination of the ex Vivo Proliferative Response of Blood Lymphocytes and Splenocytes to Sulfamethoxazole and Its Metabolites. Isolated human and rabbit lymphocytes and animal splenocytes (mouse, rat, and rabbit) and rabbit incubated SMX were assessed (1.5 × 10\(^5\)) in 96-well U-bottomed cell culture plates with SMX (190–250 μg m\(^{-1}\)) or SMX-NO (1–25 μg ml\(^{-1}\)) at 38°C, 5% CO\(_2\). In separate experiments rabbit lymphocytes were incubated with SMX (1–25 μg ml\(^{-1}\)), SMX-hydroxylamine (0.5–100 μg ml\(^{-1}\)), or SMX-NO (0.5–100 μg ml\(^{-1}\)). SMX hydroxylamine was added in the presence and absence of glutathione (1 mM), which is thought to prevent the oxidation of SMX hydroxylamine to SMX-NO. After 2 days (for animal experiments) or 5 days (for human experiments), proliferation was measured by the addition of [3H]thymidine (0.5 μCi) for the final 8 h of culture. Three and 5 days represent optimal proliferation for animal and human cells, respectively (data not shown). Cells were harvested and incorporated radioactivity was measured as counts per minute on a beta counter (PerkinElmer Life Sciences, Cambridge, UK). Proliferative responses were calculated as stimulation indices (SI; cpm in drug-treated cultures/cpm in cultures containing DMSO alone).
sured by assessment of [3H]thymidine incorporation. The extent of 
covalent binding was measured by flow cytometry using a previously 
described protocol (Naisbitt et al., 1999). Briefly, drug-treated cells 
were stained with a hapten-inhibitable anti-SMX IgG antibody 
(1:500, v/v; 40 µl) and a phycocerythrin-conjugated and IgG second-
ary antibody. The number of cells staining positive for covalently 
bound SMX was taken to be equivalent to the difference in fluo-
rescence intensity between drug-treated cells and cells incubated with 
DMSO alone.

Statistics. All data are expressed as mean ± S.D. The Mann-
Whitney U test was used for comparison of control and test values, 
accepting P < 0.05 as significant.

Results

Administration of Nitroso Sulfamethoxazole to Mice, 
Rat, and Rabbits Stimulates a Potent Drug-Metabolite-
Specific Cellular Immune Response. Splenocytes from 
SMX-NO-sensitized mice, rats, and rabbits proliferated after 
ex vivo stimulation with SMX-NO (Fig. 2). Proliferation was 
observed at SMX metabolites concentrations that are seen in 
humans after high doses of SMX (Gill et al., 1996; Mitra et 
al., 1996). The strength of the SMX-NO-specific proliferative 
response was greater in rabbits when mice, rats, and rabbits 
were compared (mouse, 4.3 ± 1.6; rat, 14.5 ± 2.2; rabbit, 
32.8 ± 3.0; P < 0.05; 10 µg ml⁻¹ SMX-NO). Concentrations 
of SMX-NO above 5 µg ml⁻¹ inhibited mouse splenocyte prolif-
eration. Splenocytes from rat and rabbit were less sensitive to 
the toxic effects of SMX-NO. In these species, SMX-NO 
concentrations above 25 µg ml⁻¹ inhibited proliferation (data 
not shown). Splenocytes from animals administered SMX or 
SMX-NO did not proliferate after ex vivo exposure to SMX. 
Splenocytes from control mice, rats, and rabbits did not prolif-
erate after ex vivo exposure to SMX or SMX-NO.

To show that formation of a SMX-NO cellular hapten was a 
prerequisite for SMX-NO-specific proliferation of mouse, 
rat, and rabbit splenocytes, cells from SMX-NO-sensitized 
animals were pulsed with SMX-NO, washed, and cultured for 
the remainder of the incubation period in the absence 
of soluble drug. We have previously shown that covalent bind-
ing of SMX-NO to cellular protein is rapid; cellular conjugates 
can be detected as little as 3 min (Naisbitt et al., 2001). In addition, in separate experiments, SMX-NO-sensi-
tized splenocytes were cultured with SMX-NO and glutathi-
one. Mouse, rat, and rabbit splenocytes proliferated after a 
2-h pulse with SMX-NO (Fig. 3); the extent of proliferation 
was similar to that seen with soluble SMX-NO. In contrast, 
no proliferation was seen when splenocytes were coincubated with 
SMX-NO and glutathione (Fig. 3).

Proliferation of Lymphocytes from Sulfamethox-
azole-Hypersensitive Humans and Sulfamethoxazole 
(Metabolite)-Sensitized Rabbits. Lymphocytes from sulf-
amethoxazole-hypersensitive patients, with and without 
HIV infection, proliferated in the presence of SMX, SMX 
hydroxylamine, and SMX-NO (n = 3; Table 1). Figure 4 
shows SMX-, SMX hydroxylamine-, and SMX-NO-specific 
proliferation of lymphocytes from HIV-positive hypersensi-
tive patient 1. The response to SMX and SMX hydroxyl-
amine was concentration-dependent, whereas SMX-NO-specific 
proliferation was detectable at each concentration tested 
(1–25 µg ml⁻¹; Fig. 4). Lymphocytes from patients exposed to 
SMX without adverse effects and unexposed individuals did 
not proliferate with SMX or SMX-NO.

SMX-NO-sensitized rabbit lymphocytes proliferated strongly in the presence of SMX-NO and SMX hydroxyl-
amine, but not the parent drug (Fig. 4). The concentrations of 
SMX hydroxylamine and SMX-NO that caused proliferation 
were similar to that seen in hypersensitive humans. SMX 
hydroxylamine-specific proliferation was concentration-de-
pendent, whereas the response to SMX-NO was seen at each 
concentration tested. Lymphocytes from untreated rabbits 
did not proliferate with SMX or SMX-NO.

Lymphocytes from SMX-hypersensitive humans and SMX-
NO-sensitized rabbits proliferated when pulsed with SMX-
NO, washed, and resuspended in drug-free media for the 
remainder of the incubation period. In contrast, lymphocytes 
pulsed with SMX did not. The addition of glutathione had no 
effect on SMX-specific proliferation of human lymphocytes, 
whereas SMX-NO-specific proliferation of rabbit and human 
lymphocytes was inhibited (data not shown).

Proliferation of rabbit lymphocytes to SMX hydroxylam-
line was inhibited by the addition of glutathione at low concen-
trations; however, proliferation was seen with higher concen-
trations of SMX hydroxylamine (Fig. 5a). Proliferation of
human lymphocytes with SMX hydroxylamine and glutathione was not studied because they proliferate in the presence of covalently and noncovalently bound SMX. The response of rabbit lymphocytes to SMX hydroxylamine is intriguing because the above-mentioned data seem to suggest that the response can be directed against noncovalently bound drug (metabolite) as well as a drug haptenated protein. To study whether SMX hydroxylamine is converted to SMX-NO in culture, we measured the formation of SMX covalent adducts by flow cytometry. In the absence of glutathione, SMX hydroxylamine bound rapidly to cells (Fig. 5b). Covalently bound SMX was detectable on cells after 4 h in culture at 37°C. In the presence of glutathione, which is thought to prevent oxidation of SMX hydroxylamine (Gill et al., 1996), covalent binding was delayed, but not inhibited. Covalently linked SMX cellular adducts were seen after 48 h (Fig. 5c).

### Nitroso Sulfamethoxazole-Specific Rabbit Lymphocytes Are Long Lasting in Vivo and Do Not Cross-React with Sulfamethoxazole

To study the duration of the SMX-NO-specific immune response in vivo and to see whether SMX-NO-specific T cells cross-react with SMX with time, SMX- and SMX-NO-specific proliferation of lymphocytes from rabbits sensitized with SMX-NO was assessed for 4 months. It is important to note that, on completion of the 2-week immunization protocol, rabbits were not exposed to either SMX or SMX-NO. Data presented in Fig. 6 show that although the extent of SMX-NO-specific lymphocyte proliferation declined with time, significant proliferation was seen after 4 months. In addition, SMX-NO-specific lymphocytes did not cross-react with SMX.

### Discussion

Drug hypersensitivity reactions are a major clinical problem. Identification of drug-specific T cells in the peripheral circulation and skin, at the time of the reaction, provides evidence that the immune system is involved in the development of clinical symptoms (Mauri-Hellweg et al., 1995; Schnyder et al., 1997, 2000). Despite this, the nature of the drug antigen that stimulates hypersensitivity reactions is a matter of debate. From the current state of knowledge, there are three possible mechanisms as to how drugs might stimulate T cells. First, protein-reactive drugs such as penicillin bind covalently to protein, which is then recognized by the immune system (Padovan et al., 1996). Second, many drugs are not chemically reactive per se and do not seem to be immunogenic. They may however become chemically reactive after drug metabolism (Naisbitt et al., 2001, 2002). Finally, in vitro studies have demonstrated that certain chemically inert drugs can form sufficiently strong noncovalent bonds with MHC molecules to stimulate T cells directly (Schnyder et al., 1997, 2000).

SMX is a dihydropteroate synthetase inhibitor that is effective in the treatment of opportunistic diseases associated with the progression of HIV infection. Unfortunately, SMX administration is associated with the development of hypersensitivity reactions in 30 to 50% of patients with HIV, some of which can be severe and cause deaths (Firmohamed and Park, 2001). SMX is not chemically reactive and does not bind covalently to protein (Cribb et al., 1991, Naisbitt et al., 1996). However, CYP2C9-mediated hydroxylation of the terminal amine residue of SMX generates SMX hydroxylamine (Cribb et al., 1995), which under conditions of oxidative stress, is converted to the protein-reactive metabolite...
SMX-NO (Naisbitt et al., 1999, 2001; Reilly et al., 2000; Manchanda et al., 2002; Summan and Cribb, 2002). CYP2C9 is expressed in liver, skin, and macrophages (Cribb et al., 1995; Baron et al., 1998; Saeki et al., 2002) and indeed Reilly et al. (2000) have recently shown that cultured human keratinocytes metabolize SMX to SMX hydroxylamine. The aim of our study was to investigate the nature of the SMX antigen presented to drug-specific T cells in four species: mice, rats, rabbits, and humans.

Splenocytes from mice, rats, and rabbits sensitized with SMX-NO were found to proliferate in vitro after stimulation with SMX-NO, but not the parent drug (Fig. 2; Table 1). Similarly, lymphocytes from SMX-hypersensitive patients proliferated with SMX-NO; however, in contrast to the ani-
Statistical analysis compares drug-treated splenocytes with cell variation was consistently less than 20% and has been removed for clarity. Statistical analysis compares drug-treated splenocytes with cell incubations containing DMSO alone (+, P < 0.05).

Imortantly, lymphocytes from hypersensitive patients were tested for their ability to proliferate against drug (metabolite) antigens several months or even years after the development of hypersensitivity, whereas sensitized animals were tested 4 to 7 days after drug administration. Thus, to study the nature of the drug antigen in SMX-hypersensitive patients and sensitized animals directly, lymphocytes from rabbits sensitized with SMX and SMX-NO were cultured with SMX and SMX metabolites every 2 weeks for 4 months. Results obtained were essentially the same as that seen with rabbit splenocytes: cells from SMX-NO-sensitized rabbits proliferated in the presence of SMX-NO but not SMX, whereas administration of SMX did not stimulate a cellular response. The response to SMX-NO declined slowly with time, but was still significant 4 months after completion of the sensitization protocol (which represents approximately 5 years in a human life), and there was no cross-reactivity with SMX (Fig. 6). These data clearly indicate that the nitroso metabolite of SMX is extremely immunogenic. SMX- and SMX-NO-specific proliferation of human lymphocytes indicates that the T-cell repertoire in humans seems to be significantly different to that seen in animals. There are two possible explanations for the observed results. First, there is a difference in drug presentation by the antigen presenting cells in hypersensitive patients; and second, the receptor system is more readily triggered in T cells from hypersensitive patients, thus overriding the need for covalent binding in vitro. However, because the number of antigen molecules required to stimulate T cells is incredibly low [Irvine et al. (2002) estimate that T cells can be stimulated when as little as 10 ligands are present], they are below the limits of chemical detection at present. In view of the relative lack of sensitivity of currently available analytical techniques, it is unknown whether there is ongoing metabolism within immune cells. One possibility of overcoming this would be to use transfected autologous cells expressing high levels of P450 isoforms such as CYP2C9; this is being investigated.

It must be noted that animals sensitized with SMX-NO do not develop SMX hypersensitivity. It is possible that animals administered soluble SMX-NO do not receive the appropriate antigenic signal to cause pathology. In this respect, systemic administration of SMX-NO generates an exogenous antigen by direct cell surface haptenation (Naisbitt et al., 1999; Manchanda et al., 2002), whereas in patients administered SMX it is possible that SMX-NO would be formed intracellularly (Cribb et al., 1999; Cribb et al., 1995; Reilly et al., 2000). Protein binding at the site of metabolic activation generates an endogenous antigen that might stimulate a more potent cellular immune response.

The mechanism by which the chemically inert, proreactive metabolite SMX-hydroxylamine stimulates T cells is not fully understood. This is of particular importance because approximately 2% of an oral dose of SMX is excreted in urine as the hydroxylamine (Gill et al., 1997). Likewise, the altered redox status in plasma of patients with HIV infection (Walmsley et al., 1997) is known to favor the conversion of SMX hydroxylamine to SMX-NO and the generation of covalently bound drug-protein adducts (Naisbitt et al., 2000). The results of our present study show that oxidation of SMX hydroxylamine stimulates lymphocytes from SMX-NO-sensitized animals and hypersensitive patients (Fig. 5). Glutathione inhibited SMX hydroxylamine-mediated lymphocyte proliferation at low metabolite concentrations (Fig. 5); however, proliferation was still seen with higher, supratherapeutic concentrations of SMX hydroxylamine. This was intriguing, because glutathione is thought to prevent the oxidation of SMX hydroxylamine to SMX-NO (Naisbitt et al., 1999). We initially considered the possibility that the proliferative response might have been due to a noncovalent interaction between SMX hydroxylamine and the T-cell receptor. However, flow cytometric analysis of cell culture incubations revealed that although oxidation of the hydroxylamine was delayed, oxidation and covalent binding of SMX hydroxylamine was seen after 48 h (Fig. 5). These data highlight the fact that maintenance of levels of sulfhydryl-containing compounds such as glutathione plays a critical role in inhibiting the conversion of SMX hydroxylamine to SMX-NO. In patients with a disturbed redox balance as is seen with HIV infection (van der Ven et al., 1995), increased generation of SMX-NO may be one factor that contributes to the increased incidence of drug hypersensitivity.

The reasons why all SMX-hypersensitive patients have T cells that proliferate in the presence of both SMX and SMX-NO are not known. It is possible that oral exposure to a drug antigen may lead to the generation of T cells that proliferate in the presence of the parent drug; however, there is no obvious scientific rationale for this. Factors that determine the nature of individual susceptibility will be also important (Fig. 7). To this end, studies have shown that NAT2
and GST polymorphisms are not determinants of individual susceptibility (Pirmohamed et al., 2000; O’Neill et al., 2002). Polymorphisms in other drug-metabolizing enzymes such as myeloperoxidase may be important but have not been investigated. It seems that all patients administered SMX will be exposed to both the parent drug and SMX-NO. The factors determining whether antigen formation results in a hypersensitivity reaction are unknown, but could include the following. First, it is possible that T-cell receptor engagement per se is insufficient to lead to tissue damage and in the absence of costimulation tolerance or immunological ignorance may supersede; these phenomena have been reported to occur in patients exposed to the contact allergen nickel (Cavani et al., 1998). Second, the ability of a drug (metabolite) to stimulate an immune response that leads to tissue damage might be directly related to the presence of complementary bidirectional drug binding domains within MHC and the T-cell receptor. The expression of these binding domains is under genetic control and therefore differs from individual to individual. Recent studies using the HIV-1 nucleoside-analog reverse transcriptase inhibitor abacavir as a paradigm have shown that HLA-B57 was present in 78% (Mallal et al., 2002) and 46% (Hetherington et al., 2002) of abacavir-hypersensitive patients versus 2 and 4% of abacavir exposed controls. Similarly, in SMX hypersensitivity, Ozkaya-Bayazit and Akar (2001) have reported a link between the HLA-B22 haplotype and susceptibility to SMX hypersensitivity. The relationship between the expression of specific T-cell receptors and drug hypersensitivity has not been studied; however, most drug-specific T cells isolated from the blood of individuals with hypersensitivity to the drugs carbamazepine (Naisbitt et al., 2003a), lamotrigine (Naisbitt et al., 2003b) and phenobarbital (Hashizume et al., 2002) have been shown to express the Vβ chain 5.1. Although these data are preliminary, there seems to be a correlation between the expression of immunological receptors and the phenotypic features of drug hypersensitivity.

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References


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