Induction of tolerance after a serious trimethoprim-sulphamethoxazole reaction in an HIV-infected child

To the Editor: Trimethoprim-sulphamethoxazole (TMP-SMX) is highly effective for the prevention and treatment of *Pneumocystis carinii* pneumonia (PCP). Paediatric HIV infection is frequently complicated by PCP, a life-threatening, opportunistic infection. At present, between 11% and 12% of the South African population is infected with HIV-1. TMP-SMX is an important disease-modifying antimicrobial preparation, which reduces mortality and hospitalisation in HIV-infected children significantly.

Since being introduced in the 1930s, the sulphonamides have caused many adverse events. Before the HIV epidemic, less than 4% of adults experienced adverse reactions after TMP-SMX exposure. In contrast, approximately 60% of adults with HIV infection may react adversely, with most reactions consisting of mild drug eruptions.[1] There are few data on the proportion of HIV-infected children who experience adverse reactions to TMP-SMX therapy, but this is an uncommon clinical problem at Red Cross Children's Hospital (RXH). Inducing tolerance after TMP-SMX reactions is both safe and effective.[2,3] We report the successful induction of tolerance after a serious TMP-SMX reaction in an HIV-infected child.

A 9-month-old infant presented to RXH with severe laryngotracheo-bronchitis and pneumonia. An emergency intubation and subsequent tracheostomy were performed to secure an adequate airway, and she required assisted ventilation for hypoxaemia. She had generalised lymphadenopathy, hepatosplenomegaly, and dermatitis, features that are consistent with HIV infection, confirmed by P24 antigenaemia. Severe immunosuppression (CD4 count 0.568×10^9/l, CD4 percentage 14%) and pancytopenia (white cell count (WCC) 1.8×10^9/l, haemoglobin (Hb) 8.8 g/dl, platelet count 50×10^9/l) were present. Although the chest radiograph was not characteristic of PCP, an intravenous loading dose of TMP-SMX was administered. This was immediately followed by the development of generalised urticaria and angio-oedema. The patient was haemodynamically stable. Immunofluorescent stains were negative for PCP. No further TMP-SMX was administered during the first few days of hospitalisation.

On day 7 of the admission stavudine, lamivudine and ritonavir were commenced. The pancytopenia had largely resolved. Given the serious nature of the patient's underlying illness and the need for TMP-SMX prophylaxis, she was started on an oral TMP-SMX tolerance induction regimen. The starting daily dose was 1 ml (1:20 dilution of paediatric suspension), which contained 0.4 mg TMP and 2 mg SMX, and this was incrementally increased over 8 days when the recommended maintenance prophylactic dose was reached, and subsequently well tolerated (recommended prophylactic regimen in children: 150 mg TMP/m^2/day with 750 mg SMX/m^2/day administered either 3 times per week or 7 days per week). She recovered from the acute illness and remains in a satisfactory condition on antiretroviral therapy and TMP-SMX prophylaxis.

PCP causes considerable morbidity and mortality. The explosive HIV epidemic in southern Africa has led to increased use of TMP-SMX, the preparation of choice for both PCP prophylaxis and treatment. TMP-SMX is an inexpensive formulation that is included in the South African Essential Drugs List. In HIV-infected individuals, TMP-SMX also prevents a spectrum of bacterial infections, toxoplasmosis and isosporiasis.

Despite these therapeutic advantages, TMP-SMX may cause serious adverse events, as this report illustrates. Alternative drugs for preventing PCPinclude dapsone with or without pyrimethamine, pentamidine, sulfadoxine plus pyrimethamine and clindamycin plus primaquine.[4] These agents present variable challenges to paediatric practice including reduced efficacy, complicated routes of administration, lack of paediatric formulations, limited experience in children and limited accessibility. They may also cause adverse reactions.

Anaphylaxis is a syndrome of varied clinical presentation and severity. It is a potentially life-threatening event usually mediated by an immunoglobulin E (IgE) immune reaction, which is characterised by the sudden release of mast cell and basophil mediators. Anaphylactoid reactions by contrast are non-IgE-mediated events, which have a similar clinical presentation to anaphylaxis, e.g. cytotoxic reactions resulting from incompatible blood transfusions. There is no universally acceptable definition of anaphylaxis. Diagnosis is largely based on clinical considerations. The patient presented with features consistent either with anaphylaxis or an anaphylactoid reaction, urticaria and angio-oedema being common manifestations of both conditions.[5]

Several immunological assays may be used to identify drug-specific antibodies, drug-specific T-lymphocytes or mediators elaborated by activated inflammatory cells. Tests available in South Africa include skin prick tests, Immuno-CAP RAST (Pharmacia, Uppsala, Sweden) and the CAST (Bühlmann, Basel, Switzerland). As IgE-mediated mechanisms are not always involved in drug reactions, negative results do not necessarily exclude drug-induced hypersensitivity. Serum tryptase (β-tryptase plus alpha-proto-tryptase) is concentrated selectively in the granules of human mast cells, and correlates with the clinical severity of anaphylaxis.[6] If the clinical presentation is equivocal, measuring serum tryptase may be helpful in differentiating anaphylaxis from non-anaphylactic

reactions, e.g. anaphylaxis versus acute severe asthma. Serum tryptase cannot distinguish between an anaphylactic or anaphylactoid reaction, as tryptase levels are elevated regardless of the mechanism of mast cell activation. Tryptase was not measured in the patient because there was a clear causal relationship between TMP-SMX administration and the development of symptoms. The tryptase assay is available at the Allergology Unit, University of Cape Town.

Although tolerance can be induced in 33 - 100% of HIV-infected individuals, neither the mechanism of TMP-SMX hypersensitivity nor the immunological events underpinning tolerance are understood.[3] The term desensitisation implies that the underlying mechanism is IgE-mediated. As the mechanism of TMP-SMX hypersensitivity has not been fully elucidated, the terms 'graded challenge', 'test dosing' or 'tolerance induction' are preferred in the context of a TMP-SMX reaction.[2] Common features of TMP-SMX hypersensitivity such as erythematous or maculopapular eruptions, leucopenia and fever suggest a cell-, IgM- or IgG-mediated reaction. Evidence supporting the role of IgE in the pathogenesis exists, i.e. skin prick and intradermal skin test responses to sulphonamide determinants have been documented in patients who have had adverse events.[7] Non-immune mechanisms may also contribute to TMP-SMX reactivity.[8] Additional factors that may predispose HIV-infected individuals to TMP-SMX reactions include the slow acetylator phenotype, high TMP-SMX dosages, severe immunosuppression and polypharmacy.[9] It is likely that several mechanisms may precipitate these reactions.

In conclusion, a number of approaches have been used to induce tolerance. If PCPtherapy is urgently required, a 6-hour graded TMP-SMX challenge may be used.[3] Where minor reactions have occurred, cautiously 'treating through' the event will allow patients to tolerate TMP-SMX.[2,10] When TMP-SMX prophylaxis is needed a more gradual approach may be adopted as demonstrated in this case. Induction of tolerance should only be undertaken at institutions that have the facilities to manage severe adverse reactions, particularly anaphylaxis.

George du Toit
Louis Reynolds
Brian Eley

Department of Paediatrics and Child Health
Red Cross War Memorial Children's Hospital and
University of Cape Town

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Cytotoxicity of pregnancy-related traditional medicines

To the Editor: The thalidomide tragedy is witness to the fact that great care needs to be exercised in the administration of drugs to pregnant women. Approximately 80% of Zulu and Xhosa women in South Africa use traditional medications during pregnancy, so a knowledge of the toxicity of plants commonly chosen by traditional healers for pregnant women is of vital importance in assessing the potential impact they might have on the health of both the mother and the developing fetus.

The primary function of *isihlambezo* is to ensure adequate fetal growth and wellbeing and to promote general maternal health and a quick uncomplicated labour. However, there have been reports raising concern about the toxicity of some of the approximately 60 plant species used in *isihlambezo* mixtures. *Rhoicissus tridentata* extracts have been linked to a number of fatalities caused by central nervous system (CNS) depression and respiratory failure.[1,2] Animal deaths[3] have also been attributed to this species. Although the fruits of the genus *Combretum* are widely regarded as toxic, and are not consumed by wild animals or used by healers,[4] there is only one case in which the toxicity of the fruit has been clinically proven.[4] In 1996 it was reported that 5 women in Zimbabwe died after vaginal insertion of material from *Combretum erythrophyllum*, from the same genus of the Combretaceae family as *C. kraussii*.[4] The butanol extract from *C. kraussii* was found to be toxic to brine shrimp.[4] However the organic solvent butanol is not used by healers, who extract plants with boiling water. The toxicity of several other species has also been reported.[5]

We carried out a study in order to establish whether *Gunnera perpensa* (*uqobo* in Zulu), *C. kraussii Hochst* (*umdubu* in Zulu) and *R. tridentata* subsp. *cuneifolia* (*isinwazi* in Zulu), exhibited