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Anaphylaxis and hypersensitivity syndrome reactions in increasing severity following repeated exposure to tinidazole

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Sir,

Anaphylaxis is a potentially life-threatening immunological reaction that results from the sudden release of mast-cell-derived and

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basophil-derived mediators into the circulatory system.

Hypersensitivity syndrome reactions (HSR) include cutaneous eruptions like erythema multiforme and Steven-Johnson syndrome, and are commonly induced by drugs. Erythema multiforme (EM) is an acute, usually self-limiting mucocutaneous disorder characterised by unique iritis or target lesions such as macules, papules, vesicles and bullae. Severe erythema multiforme with predominantly extensive bullous eruption of the skin and mucous membrane, sudden onset, high fever and prostration is termed Stevens Johnson syndrome. We report here an interesting case of a 30-year-old male who developed erythema multiforme, laryngeal oedema, anaphylaxis and **Stevens-Johnson syndrome** [More Details](#) following repeated exposure to tinidazole. The patient presented with diarrhoea and was prescribed a combination of norfloxacin 400 mg and tinidazole 500 mg. After ingesting a few tablets, he developed dull red erythematous oral mucosal lesions over a period of few days and stopped the treatment on his own. The lesions were thought to be coincidental to drug intake and a probable diagnosis of drug-induced adverse dermatological reaction was not considered at that period of time.

Five months later, the patient had diarrhoea and on his own, he ingested one tablet of the same combination (norfloxacin 400 mg and tinidazole 500 mg) that had been prescribed earlier. Within four hours, he developed anaphylactic reaction characterised by tachycardia, bronchospasm and laryngeal oedema. Oral mucosal lesions also developed within the following two days. The lesions were erythematous, well circumscribed, tender and more severe as compared to those that had occurred earlier. Treatment was stopped and a diagnosis of a possible drug-induced anaphylaxis and erythema multiforme was made. It is interesting to note that earlier, the patient was prescribed metronidazole for diarrhoea on a few occasions, but he had developed no adverse drug reaction (ADR). As tinidazole belongs to the same nitroimidazole group of drugs as metronidazole, the cause of anaphylaxis was thought to be norfloxacin and the patient was advised not to use norfloxacin or related fluoroquinolone-containing combinations in the future.

Eighteen months later, the patient had diarrhoea and the physician aware of his past allergy to norfloxacin type of drugs prescribed only tinidazole (a dose of 500 mg twice daily). The patient, however, was reluctant to take any drug due to his earlier experience, and ingested only half a tablet of tinidazole. Within an hour, he developed severe anaphylaxis characterised by severe bronchospasm, laryngeal oedema, tachycardia, hypotension and difficulty in talking and swallowing. He had to be hospitalised for treatment. The next day, he developed severe oral and genital

mucosal lesions. A diagnosis of tinidazole induced anaphylaxis and Steven-Johnson syndrome was made.

Severe potentially life-threatening reactions to tinidazole are uncommon. However urticaria, facial and laryngeal oedema, hypotension, bronchospasm and dyspnoea have been rarely reported.[1] McEwen has reported six cases of anaphylactic reaction in which epinephrine was needed and all the patients recovered. All these patients had reaction following a dose of 2g or more.[2] Our patient developed moderate anaphylactic reaction first to 500 mg of tinidazole and severe anaphylaxis was seen after a 250 mg dose of tinidazole was administered,(edit team to check inclusion of drug name)following a repeat exposure one-and-a-half-years later. It is well-known that in patients who have been exposed before, subsequent reactions have occurred faster with increasing severity.[3] This increased risk of ADR in patients with history of previous episode is primarily as a result of activation of mast cells and basophils via cell bound allergen specific IgE molecules.[4] Our reaction has a score of 9 on the Naranjo algorithm for ADR causality assessment, thus considering tinidazole as a highly probable cause for this ADR.[5] Although Erythema multiforme to tinidazole has been reported rarely, literature survey has failed to report a well-established case of Stevens-Johnson syndrome to tinidazole in the past.[1] Both metronidazole and tinidazole belong to 5-nitroimidazole group and cross-allergy is expected. However in our patient, there was no ADR to metronidazole after repeated use. Unlike metronidazole which is 2-methyl-5-nitromidazole-1-ethanol, tinidazole is 1-[2- (ethylsulfonyl) ethyl]-2-methyl-5-nitroimidazole.[1] As our patient showed hypersensitivity only to tinidazole, it seems likely that the ethylsulfonyl group present in the tinidazole structure is primarily responsible for the hypersensitivity syndrome reactions and anaphylaxis.

This case is unique in many aspects-

- a)Anaphylaxis, although reported following the use of tinidazole, is extremely rare and standard textbooks of pharmacology do not mention it as a possible ADR.
- b)To the best of our knowledge, Steven-Johnson syndrome due to tinidazole has not been reported in literature, and such immediate onset (within a day) is again, rare.
- c) No cross-allergy to structurally similar compound metronidazole has been seen.
- d) Different types of ADRs are reported in the same patient,

following the use of the same drug at the same time.

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