

## Commentary

# Red man syndrome

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### Abstract

Vancomycin can cause two types of hypersensitivity reactions, the red man syndrome and anaphylaxis. Red man syndrome has often been associated with rapid infusion of the first dose of the drug and was initially attributed to impurities found in vancomycin preparations. Even after improvement in vancomycin's purity, however, reports of the syndrome persist. Other antibiotics (e.g. ciprofloxacin, amphotericin B, rifampicin and teicoplanin) or other drugs that stimulate histamine release can result in red man syndrome. Discontinuation of the vancomycin infusion and administration of diphenhydramine can abort most of the reactions. Slow intravenous administration of vancomycin should minimize the risk of infusion-related adverse effects.

**Keywords** antibiotics, antihistamines, red man syndrome, vancomycin

The incidence of nosocomial infections in hospitalized patients varies between 5 and 15% [1]. Nosocomial infection can lead to complications in 25–33% of those patients admitted to intensive care units. Vancomycin is often used in intensive care units. It is the drug of choice for the treatment of infections due to methicillin-resistant staphylococci, *Corynebacterium jeikeium*, and resistant strains of *Streptococcus pneumoniae*. Vancomycin is an alternative drug for serious staphylococcal and streptococcal infections, including endocarditis, when allergy precludes the use of penicillins and cephalosporins.

Vancomycin can cause two types of hypersensitivity reactions, the red man syndrome and anaphylaxis [2]. Red man syndrome is an infusion-related reaction peculiar to vancomycin [3]. It typically consists of pruritus, an erythematous rash that involves the face, neck, and upper torso. Less frequently, hypotension and angioedema can occur. Patients commonly complain of diffuse burning and itching and of generalized discomfort. They can rapidly become dizzy and agitated, and can develop headache, chills, fever, and paresthesia around the mouth. In severe cases, patients complain of chest pain and dyspnea. In many patients, the syndrome is a mild, evanescent pruritus at the end of the infusion that goes unreported.

Signs of red man syndrome would appear about 4–10 min after an infusion started or may begin soon after its completion. It is often associated with rapid (< 1 hour) infusion of the first dose of vancomycin. The reaction may not be of the same severity with successive exposures, but it can occur for the first time after several doses or with a slow infusion [4]. Delayed reactions at or near the end of a 90 or 120 min infusion have been seen in patients who had been on vancomycin therapy for longer than 7 days without prior incident [5]. Most of the hospital protocols require vancomycin to be infused over 60 min, as a minimum [5,6]. Sporadic reports of red man syndrome following the administration of vancomycin via routes other than intravenously are also on the increase. Red man syndrome has been linked to intraperitoneal and oral administration of vancomycin [7].

Red man syndrome was in the past attributed to impurities found in vancomycin preparations, earning the drug the nickname 'Mississippi mud'. But reports of the syndrome persisted even after improvements in the compound's purity [5]. Studies have shown that an unknown percentage of the population may be prone to releasing a large amount of histamine in response to vancomycin [6]. The hypersensitivity reactions that can arise due to vancomycin are due to its

effect on the mast cells. In tissue culture, vancomycin causes degranulation of peritoneal mast cells in rats [8]. The anaphylactic reaction is mediated by IgE. Red man syndrome, an anaphylactoid reaction, is caused by the degranulation of mast cells and basophils, resulting in the release of histamine independent of preformed IgE or complement. The extent of histamine release is related partly to the amount and rate of the vancomycin infusion. Clinical studies have shown that the plasma tryptase levels were not significantly elevated in confirmed anaphylactoid reactions, so they can be used to distinguish chemical reactions from immunologic reactions [9].

The most common hypersensitivity reaction associated with vancomycin is red man syndrome. The incidence varies between 3.7 and 47% in infected patients [2]. Studies of vancomycin also show that the most severe reactions occur in patients younger than the age of 40, particularly in children [6]. Other research has found that between 30 and 90% of healthy volunteers receiving vancomycin developed red man syndrome, while only about 47% of those with infections had the reaction [10]. One explanation for these results is that an infection induces some histamine release as part of the natural immune response. Having a higher histamine level to begin with is thought to downregulate vancomycin's effect on mast cells and basophils. It occurs in 5–13% of patients, especially when the infusion is given over less than 1 hour [11]. Polk and colleagues [12] observed the reaction during a 1 hour infusion of 1 g vancomycin in nine of 11 volunteers (82%), which was associated with a rise in plasma histamine levels. No reaction occurred with a 500 mg dose. Healy and colleagues [13] noted symptoms in eight of 10 volunteers (80%) given 1 g vancomycin over 1 hour, but in only three of 10 volunteers (30%) given the same dose over 2 hours. Total histamine release was greater with the faster infusion.

Antibiotics such as ciprofloxacin, amphotericin B, rifampicin and teicoplanin [14] can potentially cause red man syndrome. Like vancomycin, they are capable of causing direct degranulation of mast cells and basophils. Red man syndrome is amplified if these antibiotics are combined with vancomycin or with each other [10]. Red man syndrome is also magnified in patients receiving vancomycin and opioid analgesics, muscle relaxants, or contrast dye because these drugs can also stimulate histamine release.

The effects of red man syndrome can be relieved by antihistamines. Pretreatment with hydroxyzine can significantly reduce erythema and pruritus [15]. Administration of diphenhydramine to patients before starting vancomycin infusion (1 g over 1 hour) can prevent the occurrence of red man syndrome with the first dose of vancomycin [16]. Other studies have shown that combining an H<sub>1</sub> receptor blocker with an H<sub>2</sub> receptor blocker such as cimetidine may help to prevent or reduce the risk of red man syndrome [5].

If red man syndrome appears then the vancomycin infusion should be discontinued immediately. A dose of 50 mg diphenhydramine hydrochloride intravenously or orally can abort most of the reactions. Once the rash and itching dissipate, the infusion can be resumed at a slower rate and/or at a lesser dosage. Hypotension will require intravenous fluids and, if severe, vasopressors may be needed. Hypotension can be troublesome if it occurs during anesthesia following the use of vancomycin for surgical prophylaxis [17,18]. Therapy with a  $\beta$ -blocker before surgery has been found to be protective against hypotension caused by vancomycin infusion [19].

In summary, each intravenous dose of vancomycin should be administered over at least a 60 min interval to minimize the infusion-related adverse effects [20]. Longer infusion times should be used in patients receiving doses considerably larger than 1 g vancomycin. Studies have shown that vancomycin is much better tolerated when it is given in smaller and more frequent doses [20]. In clinical situations where prolonged infusion times are often impractical, as in the intensive care unit or an operative setting, especially ambulatory orthopedic or emergency procedures, pretreatment with antihistamines combined with an H<sub>2</sub> receptor blocker can offer protection against this infusion-related reaction with vancomycin [5].

## Competing interests

None declared.

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