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CASE REPORT

Severe anaphylaxis caused by orally administered vancomycin to a patient with *Clostridium difficile* infection

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Abstract We report the first case of anaphylaxis to oral vancomycin in a cystic fibrosis patient with severe and relapsing *Clostridium difficile* infection (CDI) refractory to metronidazole. The patient's colitis has been successfully treated with a combination of intravenous metronidazole and tigecycline.

Keywords *Clostridium difficile* · Anaphylaxis · Tigecycline · Oral vancomycin

Enteral vancomycin is the first agent recommended by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA) [1], and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [2] for the treatment of severe or relapsing *Clostridium difficile* infection (CDI). Oral vancomycin is often considered to be innocuous, given its presumed trivial systemic absorption, independently of the colitis severity and the creatinine clearance [3]. Nevertheless, and perhaps contrary to general misconception, a drug's immunogenicity is not dependent on systemic absorption, albeit potentiated by it. Very few allergic reactions have been reported with the oral administration of vancomycin. Among them, Osawa et al. [4] report a case of urticarial rash after two doses of 250 mg following a protocol of desensitization in a CDI patient with suspected allergy to vancomycin. Other authors have described the occurrence of red man syndrome (RMS), attributable to oral vancomycin in one adult [5] and one infant [6]. To our knowledge, this is the first reported case of anaphylaxis caused by oral vancomycin.

Case presentation

A 35-year-old male with cystic fibrosis was admitted for diarrhea and severe abdominal pain. The patient had undergone lung transplantation 5 years previously and was currently immunosuppressed with tacrolimus 1 g bid, mycophenolate 750 mg bid, and prednisone 10 mg bid. His other drugs included salbutamol, inhaled budesonide with tobramycine, desloratadine 5 mg daily if needed, pantoprazole, and azithromycin and cotrimoxazole three times a week in prophylaxis. There was no beta-blocker or angiotensin inhibitor. Several possible IgE-mediated hypersensitivity reactions were documented in his charts, namely, bronchospasm and laryngeal edema with cefepime, piperacillin, and latex, and an anaphylactic shock to ciprofloxacin. Eight years previously, the patient also had a history of pruritic erythematous rash on the upper trunk and face during intravenous vancomycin infusion. Apart from a slight face edema, the reaction was not accompanied by any dyspnea, wheezing, or hypotension, and was described as an anaphylactoid RMS in his medical records.

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Six weeks before the episode, the patient had been treated on an outpatient basis for a pulmonary infection and mild CDI, confirmed by cytotoxicity assay, with linezolid and oral metronidazole for 14 days. Symptoms recurred some days later with abundant loose stools (>4 per day), worsening abdominal cramps, chills, and rectal temperature at 38.4 °C. Upon arrival, the arterial pressure was 122/69 mmHg, the pulse was 92 beats/min, and the abdomen was diffusely tender without defense. His white cell count (WCC) was 20,100 cells/mm^3, and serum creatinine and albumin were within normal ranges. Vancomycin 500 mg was given orally at the emergency and, 35 min later, symptoms of throat tightness and dyspnea developed, along with tachycardia (140 bpm), face erythema, and laryngeal edema. Intramuscular adrenaline, intravenous diphenhydramine, methylprednisolone, ranitidine, and 1 L of 0.9 % NaCl bolus were given and the symptoms subsided. No other medication had been given before the reaction and precautions for latex allergy have been respected. Symptoms resumed 45 min later with respiratory distress, stridor, and decreased oxygen saturation measured with pulse oximetry from 100 to 92 %. Vaponephrine inhalations and a second dose of adrenaline were given, which relieved the stridor. Vancomycin was discontinued immediately after this reaction, and, given the CDI severity (maximum WCC 39,000 cells/mm^3, sustained fever at 39 °C, severe abdominal pain, and partial ileus necessitating an evaluation in surgery), the patient was given intravenous tigecycline (100 mg loading dose, followed by 50 mg bid), a single dose of intravenous polyclonal immunoglobulins (400 mg/kg), and intravenous metronidazole (500 mg IV tid). CDI was confirmed on the following day by cytotoxicity assay. The patient had a favorable evolution, and was treated with 14 days of tigecycline and metronidazole (switched to oral formulation), with a rapid decline of blood leucocyte count, stool frequency, and abdominal pain.

Discussion

We report the first case of anaphylaxis to oral vancomycin. While the first reaction could be confused with RMS, the recurrence and the severity of the episode with a predominance of respiratory distress and stridor in a previously sensitized patient to vancomycin favored the hypothesis of anaphylaxis. Conversely, RMS is a non-IgE-mediated reaction typically occurring with the rapid infusion of intravenous vancomycin, and its incidence may be lower by prolonging the intravenous infusion time over 60 min. The serum tryptase level, which might be high in drug anaphylaxis and barely elevated in RMS [7], was not obtained.

This case emphasizes the clinical relevance of IgE-mediated hypersensitivity to minute amounts of antigens, as may occur with poorly absorbed drugs and even topical antimicrobials such as neomycin, bacitracin, and rifamycin SV [8–11]. The literature on food IgE-mediated hypersensitivity reactions showed that anaphylaxis thresholds vary upon individual and molecule immunogenicity. The ingested lowest provoking doses of many food allergens are inferior to 1 mg [12] and, indeed, airborne particles of fish might be sufficient to trigger such a reaction [13]. In contrast, the literature on poorly or non-absorbed antimicrobials' immunogenicity is sparse and clinicians may consequently overlook the risk of provoking anaphylaxis with these drugs. In the case of oral vancomycin, only a few papers report detectable serum vancomycin, while data from the largest studies investigating its pharmacokinetics do not support consistent systemic absorption [3]. However, in the light of this case, one can hypothesize that vancomycin may have a very high immunogenicity potential in predisposed patients and only small absorption or even contact with the intestinal mucosa, especially if inflamed, could be sufficient to cause anaphylaxis. On the other hand, clinicians should also be aware of patients' susceptibility to drug allergies. Cystic fibrosis raises the incidence of antibiotic allergy, likely because of prolonged and repeated courses of therapy that increase the risks of sensitization and recurrent infections favoring antibiotic haptenization [14]. Similarly, the patient could suffer from multiple drug allergies syndrome with many antecedents of different and severe reactions to structurally and pharmacologically unrelated drugs. While this syndrome is a controversial entity, multiple drugs allergies and intolerances could predispose patients to develop adverse reactions to other drugs [15]. We, therefore, advocate that clinicians be highly vigilant while using presumably unabsorbed allergenic compounds such as oral vancomycin, especially in individuals susceptible to drug allergies, such as patients with cystic fibrosis.

Very few clinical data are available on tigecycline for the treatment of severe or relapsing CDI, and the most recent guidelines have not formulated recommendations regarding this agent [1]. Apart from this case, only seven other cases have been reported with severe and refractory CDI successfully treated with a monotherapy regimen of tigecycline [16, 17] or in combination with metronidazole [18] or rifaximin [19], without recurrence of the colitis. Conversely, Kopterides et al. [20] described a case of a critically ill patient with severe CDI that failed to improve after 18 days of tigecycline. While these few reports should be interpreted carefully in the absence of clinical trials, they support tigecycline use as a third line agent of treatment when metronidazole and vancomycin have failed and/or cannot be administered to the patient.

New therapeutic options with lower impact on fecal microbiota are currently studied. Patients treated with fidaxomicin have recently shown an important decrease in recurrences when compared with vancomycin in two multicenter randomized trials [21, 22]. It is hypothesized that its favorable effect on fecal flora might contribute to a lower recurrence rate [23]. This new agent, apart for improving patients' CDI outcomes, might decrease the risk of acquisition and overgrowth of vancomycin-resistant enterococci (VRE) [24] when compared with vancomycin. Even if the association between vancomycin and acquisition of VRE intestinal colonization is not consistently reported [25], the latter might have deleterious consequences in predisposed patients [26].

Conclusion

Clostridium difficile infection (CDI) is the main cause of nosocomial diarrhea and, with the recent higher rates of treatment failure and recurrences with metronidazole, oral vancomycin has become widely used as the first-line treatment. The incidence of oral vancomycin allergies is, therefore, expected to increase, and clinicians should be aware of these reactions, especially among people with risk factors to antibiotic allergies, such as cystic fibrosis patients. We report, herein, the first case of anaphylaxis to oral vancomycin. It should be emphasized that, in the instance of drug allergies, whether absorbed or not, alternative treatment or prompt desensitization must be undertaken. Clinical trials should be undertaken to assess the efficiency and security of tigecycline as an alternative treatment in severe or relapsing *C. difficile*, as this agent might be useful in patients who are refractory or allergic to vancomycin.

Conflict of interest None.

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