Uncommon Vancomycin-Induced Side Effects

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Vancomycin has been used with increased frequency during the past 15 years and the most common toxicity with this drug is the "red man syndrome". Other adverse effects include neutropenia, fever, phlebitis, nephrotoxicity, ototoxicity, thrombocytopenia, interstitial nephritis, lacrimation, linear IgA bullous dermatosis, necrotizing cutaneous vasculitis and toxic epidermal necrolysis. Only two cases of vancomycin-induced Stevens-Johnson syndrome and one case of pancytopenia have been reported in the medical literature. The treatment for both situations is based on cessation of the vancomycin therapy; in cases of Stevens-Johnson syndrome, antihistamine and/or steroid agents can be used. This article reports a case of pancytopenia and a case of erythema major associated with neutropenia.
Key Words: Vancomycin, Stevens-Johnson, pancytopenia, reactions, thrombocytopenia.

Vancomycin, a glycopeptide antibiotic originally derived from *Streptomyces (Norcadia) orientalis*, is being widely used for severe Gram-positive bacterial infections, especially those caused by emerging strains of methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci [1]. In addition, vancomycin remains a major alternative for the treatment of bacterial endocarditis in penicillin-allergic patients and those patients with gram-positive penicillin-resistant infections.

Although known to be safe under therapeutic serum concentrations, vancomycin has been associated with adverse effects. The most common adverse reaction is the "red man syndrome", characterized by flushing of the upper body and pruritus due to histamine release. Chest pain, hypotension and muscle spasm may also occur. Other related-side effects include ototoxicity, neutropenia, fixed drug eruptions, fever, phlebitis, nephrotoxicity [1-3], thrombocytopenia [4] and rarely, pancytopenia and Stevens-Johnson syndrome [5,6].

We report two cases of uncommon vancomycin-related side effects and review literature through Medline from 1956 to 2000 (Key-words: vancomycin and pancytopenia, uncommon reactions, Stevens-Johnson, thrombocytopenia, effects, reactions).

Case Reports

Case 1. A 60-year-old woman was admitted for treatment of an infection in her left hip prosthesis, which had been reinserted in the previous year. Two months before her admission, she had spontaneous drainage of serous secretion and a worsening chronic pain. She reported an episode of rash after taking penicillin.

The prosthesis was removed and cultures of purulent secretion from surgery yielded negative-coagulase staphylococci resistant to methicilin. Vancomycin 1.0 g BID iv was initiated and the only drug used during this period was acetaminophen Exams are summarized in Table 1. On day 15 of vancomycin treatment, fever was noticed and chest X-ray and urine culture were negative. Despite the use of vancomycin, fever persisted on day 22. Neutropenia and relative eosinophylia were

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observed. LDH was 1215 U/L, SGOT was 70 U/L and ESR was 119 mm/hr. On day 25 of vancomycin treatment, rash appeared on her head and neck along with pruritus throughout her body, oral mucous necrosis, and persistent fever. Vancomycin was substituted by levofloxacin 500mg/day PO. Within 24 hours, the patient reported a decrease in pruritus and cutaneous erythema, and fever was not noticed any longer. Seventeen days after discontinuing vancomycin, the patient was discharged.

Case 2. A 38-year-old female patient was admitted due to infection in her right hip prosthesis, which had been reinserted 3 years before. Four months prior to admission, she reported a small quantity of a clean spontaneous drainage at the surgical site. She reported that she was allergic to penicillin.

Vancomycin 1.0 G BID IV was administered from day one and she was submitted to a hip drainage. Cultures yielded negative-coagulase staphylococci. Exams are summarized in Table 2. On day 5 of vancomycin treatment, fever was noticed and after 2 days she was worse and presented fever, malaise and paleness. Cefepime 2.0 g BID IV was added. The absolute neutrophil count (ANC) was decreasing and she was getting worse. Cefepime was changed for imipenem 500 mg q6h IV and her prosthesis was removed. On day 10 of vancomycin treatment she reported a rash on her body and on the next day she was sleepy. Neutropenia and thrombocitopenia were noticed. Vancomycin and imipenem were changed for levofloxacin 500 mg qd IV. Four days after discontinuing vancomycin she was better; her condition improved and she was discharged. No other drugs, except for acetaminophen, were used during this period.

Discussion

Adverse reactions to antibiotics are a common occurrence in hospitalized patients. Vancomycin is often prescribed for methicillin-resistant staphylococcal infections and acute hypersensitivity reactions to this drug have been described, consisting of flushing and pruritus, occasionally accompanied by hypotension ("red man syndrome"). The onset may occur within a few minutes and usually resolves over several hours, after completion of the infusion. It is often mistaken for an allergic or anaphylactoid reaction, but patients usually tolerate subsequent doses if the dilution and the period of infusion are increased. [1]. Vancomycin is one of the drugs that have the ability to directly release histamine from mast cells by nonimmunological processes. This has been demonstrated *in vitro* on normal human tissue and in volunteer subjects, in whom it was observed a correlation between histamine levels and symptoms. The red man syndrome is most likely a consequence of this vancomycin-associated histamine release.

In some instances, vancomycin produces immunologically mediated adverse reactions such as interstitial nephritis, lacrimation and linear IgA bullous dermatosis [1], exfoliative erythroderma, necrotizing cutaneous vasculitis and toxic epidermal necrolysis [6].

Isolated reports of vancomycin-associated neutropenia are found in the medical literature, as well as cases of agranulocytosis, thrombocytopenia [4], and only 2 cases of Stevens-Johnson syndrome [5,6].When it was introduced into clinical use, a retrospective study of 85 patients who had received vancomycin showed a 2% incidence of neutropenia. This was thought to be related to impurities in the drug formulation and newer methods of preparing this antibiotic were developed in order to avoid such a problem. However, a new study of 98 patients treated with vancomycin from 1974 to 1981 still showed a 2% incidence of neutropenia [3]. Nowadays neutropenia associated with vancomycin therapy has been reported at a rate of 2% to 8% [1,4,7]. This usually occurs in the absence of other symptoms or signs of drug toxicity and the interval till the onset of the neutropenia ranges from 9 to 30 days. Rapid and complete recovery of the patient's white blood cell count ensues once the vancomycin was discontinued.

The cause of this reaction is still unclear. Nevertheless, bone marrow suppression is not thought to be the mechanism responsible because examination of bone marrow biopsy specimens from patients with

Table 1. Exams during hospitalization (Case1)

Exam/Day	2d	17d	23d	25d	27d	35d
Ht	23	24	21	31	31	32
HB	7.6	8.0	7.3	10.7	10.9	11.1
WBC	9400	2500	1600	2300	3100	14400
BAND	6	22	2	1	11	3
META	0	0	0	0	0	0
LINPH	23	23	50	42	40	21
EOS	2	10	32	28	33	3
NEUT	66	56	10	6	18	66
PLT	141	155	142	200	263	292

Table 2. Exams during hospitalization (Case 2)

Exams/Day	5d	9d	10d	14d
Ht	35	25	24	26
HB	11.6	8.3	7.9	8.8
WBC	2600	1700	1300	3700
META	0	2	0	0
BANDS	32	25	25	4
NEUTR	91	75	72	54
EOS	0	0	0	0
LIMPH	6	21	23	37
PLT	165	86	68	178

this adverse effect has shown both hypoplasia and hyperplasia of the granulocyte series. A peripheral destructive effect of vancomycin might play a role in reducing the neutrophil count, but again there is conflicting evidence in the literature [7].

It has been postulated that an immunologically mediated mechanism is responsible for reactions to vancomycin and the finding of vancomycin-dependent antibodies to the patients' neutrophils supports this theory. Weitzman et al. detected serum opsonizing antineutrophil antibodies in 3 patients receiving vancomycin plus a cephalosporin; however, this was not confirmed in 2 different assays. Adrouny et al. reported a case of agranulocytosis caused by vancomycin and they proposed a hypersensivity-mediated mechanism as a cause of neutrophil destruction, because of reports of associated rashes and eosinophilia. Isolated cases of vancomycin-induced thrombocytopenia have been reported and the mechanism is probably related to immunological destruction, as strongly suggested by its association with a drug-dependent antiplatelet antibody [4].

Stevens-Johnson syndrome is an acute mucocutaneous process characterized by severe exfoliative dermatitis and mucosal involvement of the gastrointestinal tract and conjunctiva. It has a less severe variant called erythema multiform minor. Both are characterized by "target" or "iris" lesions and a great number of etiological agents have already been described as the trigger of these processes, such as viral infections, mycoplasmal infection, neoplasia, collagen vascular disease, endocrine agents, X-ray therapy and numerous drugs. Their pathogenesis still remains unclear, but an immunological mechanism, probably cell-mediated, has been suggested as the real cause. Clinical diagnosis of Stevens-Johnson syndrome is based on the presence of "target" or "iris" lesions involving the skin and erosive lesions of two or more mucosal surfaces [6]. Associated findings include extensive dermal exfoliation, nephritis, lymphadenopathy, hepatitis, and multiple serologic abnormalities. The treatment consists of cessation of vancomycin and administration of antihistamine alone or associated with steroid agents [5].

Because all drugs have the potential for adverse reactions, the risk/benefit ratio must be considered before they are administered. The white cell count should be monitored in all patients receiving vancomycin and it appears to be prudent to discontinue vancomycin therapy as soon as this hematological abnormality is detected.

There are few options for patients receiving vancomycin in whom a serious adverse reaction occurs. Sanche et al. have reported a successful case where vancomycin was replaced by teicoplanin [8,9] in order to complete the treatment of a patient that presented neutropenia. Other options that may be found in literature are the use of granulocyte colony-stimulating factor [7] and rechallenge with vancomycin [10]. Despite the lack of literature reports, linezolide and streptogramins may be other alternatives whenever vancomycin is the treatment of choice and the patient presents serious adverse reactions. One must also keep in mind the possibility of other antibiotics, based on antibiogram information , such as quinolones and SMX/TMP.

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