International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-2, 2014 ISSN No: 2277 - 7873

CASE STUDY

Vancomycin Induced Fever & Chills in Pediatrics: A Rare Adverse Effect

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Manuscript No: IJPRS/V3/I2/00304, Received On: 11/06/2014, Accepted On: 24/06/2014

ABSTRACT

Vancomycin, a glycopeptide antibiotic originally derived from *Streptomyces (Norcadia) orientalis*, is a widely used antibiotic for severe Gram-positive bacterial infections, especially those caused by emerging strains of methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci. Initial preparations of Vancomycin contained many impurities frequently associated with adverse effects. The most common adverse reaction is the "red man syndrome". Chest pain, hypotension and muscle spasm may also occur. Other related-side effects include ototoxicity, neutropenia, fixed drug eruptions, fever, phlebitis, nephrotoxicity. There is a reduction in the incidence of adverse effects currently due to well controlled drug administration. Here we report two cases of Vancomycin induced fever and chills developed after treating with constant intravenous infusion. In both these cases patient were admitted with septic arthritis and were treated with Vancomycin infusion. In both the cases 'drug induced fever & chills' was confirmed based on increase in temperature noted in temperature chart. Though Vancomycin induced fever & Chills is a rare adverse effect and can be well managed with administration of paracetamol (acetaminophen) without causing any further complications, careful and constant monitoring should be implemented and such adverse effects must be reported properly. Each intravenous dose of Vancomycin should be administered over at least a 60 min interval to minimize the infusion-related adverse effects. Longer infusion times should be used in patients receiving doses considerably larger than 1 g Vancomycin.

KEYWORDS

Vancomycin, Drug Induced Fever & Chills, Rare Adverse Effect

INTRODUCTION

Vancomycin, a glycopeptide antibiotic originally derived from *Streptomyces (Norcadia) orientalis*, in 1956 and introduced into medical practice in 1958, is a widely used antibiotic for severe Gram-positive bacterial infections, especially those caused by emerging strains of methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci[1,2]. It has many mechanisms of action, the best known and probably most important being the inhibition of cell wall synthesis in bacteria[3]. 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. Two features of Vancomycin are of great interest in medical practice: the low level of bacterial resistance to the antibiotic, and the negligible -incidence of cross reactions with other antibiotics[4-7]. Although known to be safe under therapeutic serum concentrations, Vancomycin has been associated with adverse effects[1,8,9]. Initial preparations of Vancomycin contained many

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impurities frequently associated with adverse effects. Today, with drug purification, the number of patients who experience toxic effects is very small. Furthermore, well controlled drug administration, according to technical standards, has also contributed to a reduction in the incidence of adverse effects[4-7]. 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[1,8,9], thrombocytopenia[10] and rarely, pancytopenia and Stevens-Johnson syndrome[11,12]. Fever and chills are rare adverse effects; they were more commonly observed with initial preparations of the antibiotic[13-15]. After intravenous administration, Vancomycin is distributed into various body fluids. Many factors influence the drug's pharmacodynamics, including age. Total body clearance of Vancomycin increases with age. Due to the complex pharmacokinetics of the drug, the monitoring of the antibiotic concentration in plasma is recommended to assure successful therapy[4-7]. Here we report two cases of Vancomycin induced fever and chills developed after treating with constant intravenous infusion.

Case 1

A 10 month old female baby weighing 7 kg was admitted in pediatric intensive care unit on 15/02/2014 with complaints of fever (not associated with chills & rigors) and swelling of left knee. Baby was asymptomatic before 3 days but suddenly developed fever of high grade which was not relieved by medication. Knee swelling also developed suddenly but not associated with discharge. On examination baby was conscious, coherent, febrile, no PICCKLE (Pallor, Icterus, Cynosis, Clubbing, Koilonychia, Lymphadenopathy, Edema), cardiovascular sound S1 & S2 heard & no murmer, bilateral air entry was normal & no abnormal sound was present on respiratory examination, per abdomen was soft. Her lab report shows; erythrocyte sedimentation rate 25 mm in 1st hour & 48mm in 2nd hour, WBC 20.9 x 10^3 / mm^3, hemoglobin 8.5 gms %, total count 8900 cells/mm^3, differential count; polymorphs 69%, lymphocytes 28%, eosinophils 2% & monocytes 1%. Ultra sound of left joint shows minimal fluid in the joint space. Bacterial culture was done due to contamination of blood sample. Based on signs, symptoms and laboratory tests baby was diagnosed as 'septic arthritis'. At the time of admission baby was prescribed with;

1. Injection Vancomycin 70 mg iv tid in 30 cc normal saline over 30 min (30mg/kg/day)
2. Syrup combiflam 6ml (ibuprofen 100mg + paracetamol 195 mg) p.o tid

On the same day evening baby was shifted to children medical ward and was prescribed with;

3. Injection Vancomycin 90 mg iv tid in 30 cc normal saline over 30 min (40mg/kg/day)
4. Injection Amoxycillin & Clavulanate 350 mg iv bid (100mg/kg/day)
5. Syrup Paracetamol 4ml (each ml = 50 mg) *p.o* qid

On day 2, baby's condition was same as previous and injection amoxy-clav was substituted with injection Amikacin 105 mg iv od. On 6th day (20/02/2014) fever had subsided but septic arthritis condition was still persistant. On 10th day (24/02/2014) there was a complaint of fever & mild vomiting but on examination baby was afebrile and mild pallor was positive, so same medication continued with addition of syrup tonoferon (multivitamin, multimineral and folic acid) 2.5 ml po od. On 13th day (27/02/2014) condition of baby was improved as swelling was decreased in the joint, thus injection amikacin was stopped and rest were continued. On day 16th (02/03/2014) baby's fever had subsided so paracetamol was stopped and other medications were continued. On day 21st (07/03/201) there was a complaint of fever associated with chills and it was noted as Vancomycin infusion induced fever & chills. Situation was managed by addition of paracetamol syrup. On day 26th (12/03/2014) baby's condition was improved and ultra sono

graph report showed no significant fluid collection, joint lesion normal & resolved septic arthritis. Baby was in the hospital for 10 more days and was discharged on 22/03/2014 with complete resolution of septic arthritis. On discharge following medication was prescribed;

1. Syrup Linzolide 5ml *p.o* bid for 10 days
2. Syrup Paracetamol 4ml (each ml = 50 mg) *p.o* SOS

Physiotherapy was also advised along with medication.

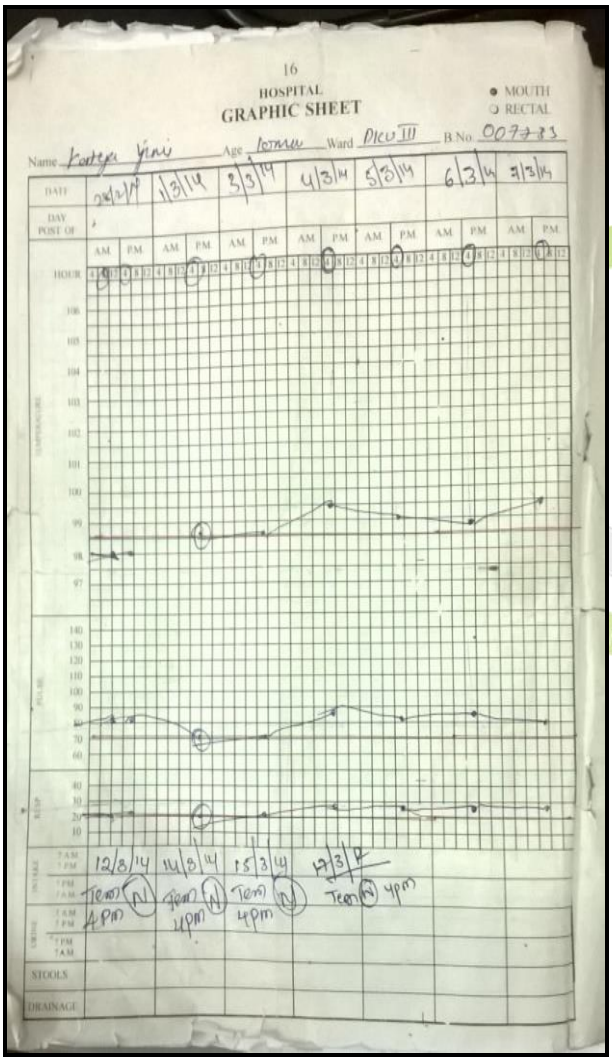

Figure 1: TPR (Temperature, pulse & respiration) chart showing increase in body temperature

Case 2

A 5 month old baby girl weighing about 7 kg was admitted in in-patient pediatric department on 19/03/2014 with chief complains of; gradual onset, progressive, pain & swelling of right knee since one week with fever (not associated with chills or rigors), unable to move the limb. On examination baby was conscious, coherent, active & febrile. Joint examination revealed swelling, redness, tenderness & immobility on right knee and other joints were normal. Cardiovascular sound, respiratory sound was normal at diagnosis. No past history trauma, bleeding disorder, seizure, shortness of breath or cough was there. Erythrocyte sedimentation rate value was 10 mm in 1st hour & 18 mm in 2nd hour. Ultra sound of the knee shows minimal fluid present in the joint. Based on signs, symptoms and physical examination; 'septic arthritis' was diagnosed provisionally. And were prescribed with;

1. Injection Pipericillin & Tazobactum 650 mg iv tid.
2. Injection Vancomycin 130 mg iv tid in 30 cc normal saline over 30 min.
3. Syrup Paracetamol 4ml (each ml = 50 mg) po qid

On the same day baby was referred to orthopedic department for recommendation and was confirmed with 'septic arthritis' and recommended to continue the same treatment. On next day fever reduced and other conditions remained same & so same treatment was continued.

On 4th day baby developed intermittent fever with chills and rigors, this was managed by addition of paracetamol. On 8th day arthritis condition was decreased but baby developed hospital acquired pneumonia. Amoxicillin & clavulanic acid was added with existing Vancomycin and paracetamol treatment. Oxygen inhalation & NaCl nasal drop were also added to support the condition. Baby got complete cure on 16th day and was discharged on 17th day (04/04/2014) with following discharge medication;

1. Syrup Linzolide 3.5ml po bid (100mg/ml)
2. Syrup Chlorpheniramine maleate (2mg/ml) & Phenylephrine (5mg/ml) 5 drops po tid.

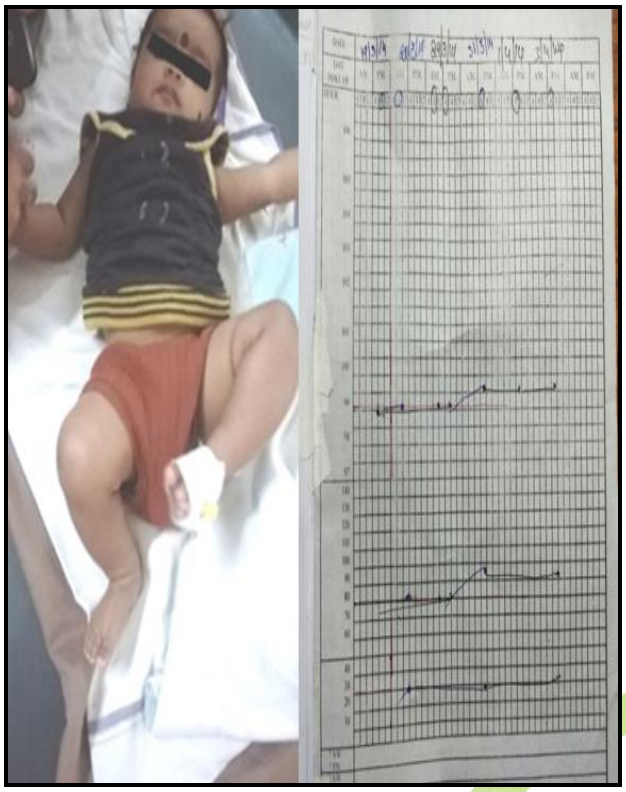

Figure 2: Swollen knee joint and increase in body temperature in TPR (Temperature, pulse & respiration) chart

DISCUSSION

Adverse reactions to antibiotics are a frequent incidence in hospitalized patients[16]. The onset may occur within a few minutes and usually resolves over several hours. Some rare adverse effects may develop even after several days of treatment. In these case reports both the children were admitted due to septic arthritis and were prescribed with Vancomycin. In both the cases a rare adverse effect, fever & chills was developed after several days of drug administration. Diagnosis of drug fever should be made on the basis of a strong clinical belief, excluding other causes, and resolution of the fever following discontinuation of the offending agent. This translates into a clinical ‘‘pearl’’ misleading the physician from detecting adverse effect as the patient often appears better than the physician would suspect after seeing the fever curve[17]. In both the cases ‘drug induced fever & chills’ was confirmed based on increase in temperature noted in temperature chart. The presence of rash or eosinophilia also favors this diagnosis. The most sensible approach to treating drug fever is to discontinue the offending agent, if appropriate. Determining the appropriate agent can be a challenge, and there is no standard approach. Depending on the severity of the accompanying reaction, it may be appropriate to stop all suspected drugs, those added recently or all nonessential drugs. The resolution of fever generally occurs within 48–72 hours, although it may persist for days to weeks if other manifestations of hypersensitivity accompany the fever, such as a maculopapular rash, or if the elimination rate of the agent is low[18-21]. Though Vancomycin induced fever & chills is a rare adverse effect and can be well managed with administration of paracetamol (acetaminophen) without causing any further complications. Careful and constant monitoring by clinical pharmacist should be implemented. There are only few articles related to this condition and its management. Hence, it is essential that such adverse effects must be reported properly. In summary, each intravenous dose of Vancomycin should be administered over at least a 60 min interval to minimize the infusion-related adverse effects. 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[22]. In clinical situations where prolonged infusion times are often inevitable, as in the intensive care unit or an operative setting, especially ambulatory orthopedic or emergency procedures, pretreatment with antihistamines combined with an H2 receptor blocker can offer protection against this infusion related reaction with Vancomycin[23].

CONCLUSION

The heterogeneity seen with cases of drug fever makes conclusions to be drawn difficult. The variety of reports in the literature points to a wide variety of drugs that are the cause for inducing fever. When drug fever is suspected, clinicians are often faced with weighing the risks and benefits of discontinuing suspected agents. The drug with the highest directory of

suspicion for causing the fever should be omitted if possible. The management of each episode of suspected drug fever must be individualized for the patient's situation, taking into account the severity of illness that the suspected drug is treating, co morbid conditions, and other factors. A diagnosis of presumed drug fever should also not divert the clinician from pursing other diagnostic probabilities for fever, particularly in acutely ill patients. Clinical Pharmacists and other Clinicians must remain attentive, as there is a possibility that the curative agent itself can cause the fever rather than the regularly suspected reason.

ACKNOWLEDGEMENT

We sincerely convey our regards to the pediatricians of Department of Pediatrics, Gandhi Hospital, Secunderabad for their constant support, help and suggestion during the period of both of these cases. We would like to convey our gratitude to all other medical, paramedical and supporting staffs of the department whose constant support has made the work easy for us and we were able to collect and correlated each and every point appropriately.

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