Perioperative use of vancomycin for prophylaxis of infection for neurosurgery in penicillin-allergic patients is common. Hemodynamic responses to rapid infusion can be catastrophic. The authors report a case of such occurrence in a patient who had radial arterial and pulmonary artery catheters in place, and discuss the significance of the hemodynamic parameters.

Vancomycin is a potent antibiotic with excellent activity against staphylococcus. It has use in the operating room for infection prophylaxis in a number of circumstances. It has specific application in neurosurgery for antibiotic prophylaxis when ventricular shunts of all types are placed. It is also a leading secondary drug for prophylaxis when patients are penicillin- and cephalosporin-allergic. In numerous reports over the last 25 years, intravenous infusion of vancomycin has been associated with a variety of reactions including urticaria, chills, nausea, hypotension, ototoxicity, nephrotoxicity and cardiac arrest.

The authors here report a case in which a vancomycin reaction occurred in a patient who had a thermodilution pulmonary artery catheter in place. The hemodynamic data are presented along with the treatment rendered, and physiological mechanisms for the changes are discussed.

Report of a case

A 56-year-old, 59 kg man was scheduled for aorto-femoral bypass for claudication secondary to bilateral occlusive iliac disease. His past medical history included hypertension treated with hydrochlorothiazide, non-insulin dependent diabetes mellitus treated with chlorpropamide, and tobacco abuse. He had known allergies to penicillin and the cephalosporins, which presented as urticaria. On the morning of surgery, he was admitted to the surgical intensive care unit for placement of a radial arterial catheter and pulmonary artery catheter.

The surgical team selected vancomycin for surgical antibiotic prophylaxis. An order was written for one gram of vancomycin in 250 cc saline to be brought with the patient to the intensive care unit. This was infused slowly during transfer and invasive monitor placement. The invasive monitors were placed without difficulty. Room air blood gas analysis was pH 7.46, pCO₂ 36 mmHg, pO₂ 79 mmHg, saturation 94%. Hemoglobin was 14.1 gm/dl with a hematocrit of 41%. Electrolytes and clotting studies were within normal limits. Hemodynamic parameters were mean arterial pressure (MAP) 80 mmHg, central venous pressure (CVP) 10 mmHg, pulmonary capillary wedge pressure (PCWP) 8 mmHg, cardiac output (CO) 4.96 liters/minute, and systemic vascular resistance (SVR) 1129 dynes-sec/cm² (-5).

The surgical team was unaware that the first
dose of vancomycin had been administered. They prepared and began infusion of another dose of one gram vancomycin in 250 cc saline. The anesthesia team was not alerted and believed this to be the original dose.

The patient was transported to the operating room. Monitors were established, and prior to induction, hemodynamic parameters were pulse 80 beats/minute, MAP 85 mmHg, CVP 14 mmHg, PCWP 12 mmHg, CO 4.88, SVR 1164. Anesthesia was induced with thiopental and intubation facilitated with 20 µg/kg fentanyl and pancuronium bromide. Nitrous oxide, oxygen and isoflurane were used for initial maintenance. The vancomycin infusion was noted to be completed. Twenty minutes after the completion of the vancomycin infusion, hypotension was noted. Pulse was 100 beats/minute, MAP 60 mmHg, CVP 22 mmHg, PCWP 12 mmHg, CO 4.94 and SVR 627. The isoflurane (never more than 0.5%) and nitrous oxide were discontinued. Blood pressure was supported with head-down positioning and rapid crystalloid infusion.

A phenylephrine infusion was prepared (40 µg/ml) and incrementally increased to support blood pressure until it was running at maximal rate by minidripper. At this point, pulse was 110 beats/minute, MAP 70 mmHg, CVP 29 mmHg, PCWP 38 mmHg, CO 10, and SVR 328. Dopamine infusion was instituted when MAP fell to 50 mmHg. Surgery was cancelled. With phenylephrine running continuously and dopamine at 10 µg/kg/minute, MAP was 60 mmHg, CVP 29 mmHg, PCWP 33 mmHg, CO 12, and SVR 204. As MAP neared 80 mmHg, dopamine was decreased gradually to off prior to transfer to the ICU. Phenylephrine infusion was decreased gradually to 50µg/minute and maintained for transfer.

Shortly after arrival in the ICU, one hour and forty-five minutes after the second vancomycin infusion was completed, MAP was 100 mmHg, CVP 15 mmHg, PCWP 10 mmHg, CO 5.85 and SVR 1162 with no vasoactive substance being administered. One hour later the PCWP had dropped to 6 mmHg. Initially the patient was left with mechanical ventilation and mild sedation. He was weaned quickly from ventilator support and was extubated uneventfully four hours after departure from the operating room. He was placed on a rule-out myocardial infarction protocol. There were no acute changes on his ECG from preoperative results and his cardiac enzymes were within normal limits.

Discussion

Vancomycin has been in clinical use for 25 years. It has been used extensively for prophylaxis in neurosurgery and penicillin-allergic patients. There is no scarcity of reports of reactions to its intravenous use, particularly if the infusion rate is rapid. Mayhew reported the death of a child given a rapid infusion of vancomycin via central venous access. The first presentation was hypotension, followed rapidly by atropine resistant bradycardia and cardiac arrest.

Odio reports the milder presentation of maculopapular rash on the trunk and upper extremities, followed rapidly by hypotension if the infusion is not slowed or terminated. The onset of the rash and hypotension can be sudden or up to 20-30 minutes after the infusion is begun, lasting for 70-90 minutes in the worst cases, even after infusion is terminated. One case presented 50 minutes after the start of a continuous steady infusion. The incidence was up to 35% of adverse reactions in this series. No rash was noted in the patient discussed here.

The etiology of vancomycin-induced hypotension has been discussed many times. Newfield attributes the events to histamine release. In the absence of prior exposure, direct mast cell degranulation, without immune-mediation, fits the anaphylactoid reaction pattern. Cohen was able to demonstrate direct vasodilation in isolated hindlimbs with each injection of vancomycin, in a dose-related fashion, independent of histamine release. Rapid infusion accentuated the fall in vascular resistance in this model. Others attribute the clinical peripheral vasodilation to histamine release.

Direct myocardial depression, or synergism with myocardial depressant actions of inhalation agents, is also a proposed mechanism. Cohen was able to demonstrate a dose-dependent diminished contractility in isolated heart preparations. This was also accented by the "bolus" effect. Regan and Safer attribute the membrane active properties of these antibiotics to cation binding, particularly potassium, or calcium.

This patient appeared to have a marked vasodilative response to peak vancomycin levels. Despite alpha range dopamine, and huge amounts of phenylephrine, his systemic vascular resistance was dramatically decreased. Whether the increase in cardiac output is a physiologic response to low SVR with normal contractility, or whether myocardial depression was masked by the inotropic support from dopamine cannot be determined. It cannot be determined which mechanism led to the precipitous, refractory decrease in this patient's sys-
temic vascular resistance. Isoflurane was used briefly in this procedure, but never more than 0.5%. Despite isoflurane's tendency to decrease SVR, it was discontinued so early in this event, that it is unlikely to have been the major contributor to this protracted reaction. Waters\(^6\) has also reported this refractory vasodilation that is unresponsive to alpha agonists. If histamine is the mediator, then alpha agonism may accentuate the mediator release by decreasing intra-cellular cyclic adenosine monophosphate (C-AMP). Perhaps epinephrine would have been more effective by its known action, increasing intra-cellular C-AMP.

It would appear prudent to administer vancomycin intravenously to perioperative patients only when strongly indicated, in dilute solutions (0.25\%-0.5\%)\(^5\), infused slowly over 45-60 minutes\(^5\)&\(^6\) and preferably, well before the induction of anesthesia. When not possible, increased vigilance is necessary to detect signs of reaction, and preparations must be made to deal with possible marked hemodynamic instability.

REFERENCES


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