Latex anaphylaxis causing heart block: role of ranitidine

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Purpose: Treatment with H_2 receptor antagonists may cause the heart to be more susceptible to atrioventricular conduction delay when exposed to an overwhelming insult by histamine released during an anaphylactic reaction. We present the case of a woman, pretreated with ranitidine, who developed 3:1 heart block secondary to latex anaphylaxis. We propose that H_2 antagonist premedication alone in patients susceptible to anaphylaxis increases their risk of heart block.

Clinical Features: A 38 yr old obese woman with cervical cancer presented for a radical hysterectomy. Systems review yielded a history of sleep apnea, orthopnea, gastroesophageal reflux, and sciatica. Medications included preoperative ranitidine, 150 mg. There was no history of atopy or allergy. Following general anesthesia induction, at the onset of the surgical procedure the patient developed a severe anaphylactic reaction which was heralded by the onset of 3:1 heart block, with decreases in SpO_2 , $P_{ET}CO_2$ and a decrease in systolic blood pressure to 45 mmHg. This was diagnosed as a possible latex reaction and treated using epinephrine boluses and infusion, fluids, 50 mg diphenhydramine, 50 mg ranitidine and 100 mg hydrocortisone. Following a 48 hr stay in the ICU the patient made an uneventful recovery. Allergy testing with intradermal latex injection and increased plasma tryptase levels confirmed a latex anaphylaxis.

Conclusion: The use of H_2 antagonists alone as a prophylaxis for gastroesophageal reflux may increase the risk of heart block in patients who develop anaphylaxis.

Objectif : Un traitement aux antagonistes des récepteurs d' H_2 peut entraîner une plus grande susceptibilité du cœur au retard de conduction atrioventriculaire lorsqu'exposé à une importante agression par la libération d'histamine pendant une réaction anaphylactique. Voici le cas d'une femme, prétraitée avec de la ranitidine, qui a développé un bloc cardiaque 3:1 secondaire à l'anaphylaxie au latex. Nous croyons que, chez les patients susceptibles d'anaphylaxie, la seule prémédication aux antagonistes de l' H_2 augmente le risque de bloc cardiaque.

Éléments cliniques : Une femme de 38 ans, obèse, atteinte d'un cancer du col de l'utérus, s'est présentée pour une hystérectomie radicale. L'anamnèse a révélé : apnée du sommeil, orthopnée, reflux gastro-œsophagien, sciatalgie, mais pas d'antécédents d'atopie ou d'allergie. La médication comprenait 150 mg de ranitidine préopératoire. Après l'induction de l'anesthésie générale, au début de l'intervention, la patiente a développé une réaction anaphylactique sévère annoncée par la survenue d'un bloc cardiaque 3:1 accompagné d'une baisse de SpO_2 , $P_{ET}CO_2$ et d'une chute de tension artérielle systolique à 45 mmHg. On a cru à une possible réaction au latex qu'on a traitée avec des bolus et des perfusions d'épinéphrine, des liquides, 50 mg de diphenhydramine, 50 mg de ranitidine et 100 mg d'hydrocortisone. La récupération s'est faite sans incident à la suite d'un séjour de 48 h à l'USI. Les tests allergologiques, au moyen d'une injection intradermique de latex et de l'accroissement des niveaux de tryptase plasmatique, ont confirmé une anaphylaxie au latex.

Conclusion : L'utilisation des seuls antagonistes d' H_2 comme prophylaxie du reflux gastro-œsophagien peut accroître le risque de bloc cardiaque dans les cas d'anaphylaxie.

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THE heart is a target organ in anaphylaxis¹ and the role of H₂ receptor antagonist therapy in the treatment of anaphylaxis has been debated for several years with no clear consensus on its use.² The myocardium contains both H₁ and H₂ histamine receptors which have differing roles in cardiac physiology. The H₁ receptors are involved in atrioventricular conduction delay and constriction of epicardial coronary vessels while H₂ receptor stimulation mediates an increase in heart rate and myocardial contractility, and coronary vasodilatation.³ Thus, it has been suggested the cardiac H₂ receptor stimulation may physiologically compensate and counteract the cardiodepressant actions of anaphylactic mediators and that therapy with H₂ receptor antagonists may be disadvantageous in the treatment of anaphylaxis.³ We present the case of a woman, pre-treated with ranitidine, who developed a 3:1 heart block secondary to latex anaphylaxis. We postulate that the use of ranitidine contributed to this heart block by allowing only the H₁ receptors to be activated. Preoperative use of both H₁ and H₂ antihistamines in patients at risk of anaphylaxis may help prevent the development of heart block.

Case report

A 38 yr old woman presented for a radical hysterectomy for cancer of the cervix. She was obese, had a history of sleep apnea, orthopnea, smoking, petit mal epilepsy, gastroesophageal reflux, and sciatica. Current medications included ranitidine, an oral contraceptive, methylphenydate HCl, furosemide, ethosuximide, morphine, perphenazine, misoprostol, domperidone and lorazepam. She denied any food or drug allergies or history of atopy. Previous surgical history included multiple uneventful operations for Cesarean sections, a cholecystectomy and multiple orthopedic procedures. All preoperative blood work and ECG were normal. The patient was prescribed a premedication of 150 mg ranitidine, 10 mg metoclopramide, and 30 ml of sodium citrate for her reflux symptoms. On arrival to the operating room following placement of an intravenous catheter, a lumbar epidural catheter was placed and the site confirmed using lidocaine with an epinephrine test dose. The patient was then anesthetised using a rapid sequence technique with cricoid pressure using thiopental and succinylcholine, and maintained with fentanyl, rocuronium, isoflurane, nitrous oxide, and oxygen. A central line, arterial line and latex Foley catheter were then placed and 3 mg morphine, 5 ml bupivacaine 0.125% / lidocaine 1% administered epidurally. During this period, all vital signs were stable. Surgery with the surgeons and scrub

nurse wearing latex gloves then commenced and, within five minutes, the SpO₂ decreased from 97% to 95% and blood pressure decreased from 120 mmHg to 105 mmHg systolic. Heart rate remained stable between 90 and 100 bpm. Heart rate and blood pressure did not improve when the FiO₂ was increased from 33% to 50%, and 5 mg ephedrine and 100 µg phenylephrine *iv* were administered, and continued to decrease gradually. At this point, 10 min after the start of surgery, the surgeons proceeded to pack the upper abdomen gently to improve the surgical view. The patient suddenly developed 3:1 heart block, with decreases in SpO₂ to 89%, P_{ET}CO₂ to 20 mmHg, and systolic blood pressure to 65 mmHg. Airway pressures increased to 50 cm H₂O. The surgeons immediately removed the packs and the patient was given O₂ 100%, 1.6 mg atropine and Ringer's lactate *iv*. Despite this therapy, the systolic pressure decreased to 45 mmHg and heart rate to 30 bpm with 3:1 heart block. Cardiopulmonary resuscitation was started and epinephrine boluses given. The patient responded immediately to the epinephrine, developing fast atrial fibrillation at a rate of 160 beats/min. The SpO₂ increased to 94% and P_{ET}CO₂ to 34 mmHg, with an airway pressure of 40 cmH₂O, and systolic pressure of 200 mmHg. A working diagnosis of pulmonary embolus or anaphylaxis was made and it was decided to abandon the procedure.

During closure of the abdomen the patient again became unstable with decreasing SpO₂ and blood pressure, and slowing atrial fibrillation, with increasing airway pressure. The working diagnosis at this time became anaphylaxis perhaps due to latex, and so all latex was removed with the exception of the Foley catheter since access to the patient's perineum was not possible with an open abdomen. The patient was given 50 mg ranitidine, 50 mg diphenhydramine HCl and 100 mg hydrocortisone *iv* but required an epinephrine infusion to maintain a systolic blood pressure of 110 mmHg. Following surgery the drapes were removed revealing urticaria on the thighs. The Foley catheter was removed and the patient sent to the PAR receiving mechanical ventilation. Blood samples for tryptase levels were taken two hours after the initial reaction. Over the next 24 hr the patient was weaned off the epinephrine infusion but developed pulmonary edema requiring ventilation for a further 24 hr. Subsequent tests excluded a pulmonary embolism and allergy testing was performed. This involved intradermal injection of latex with control using the carrier fluid. The patient developed a severe reaction to the latex injection but not to the control. A tryptase level of 120 ng·ml⁻¹ (5.6 – 13.5 normal range) indicated an

anaphylactic reaction had occurred. Following a 48 hr stay in ICU, the patient then made an uneventful recovery. In retrospect she admitted on directed questioning to developing a rash when wearing rubber gloves. Subsequently she underwent a latex free general anesthetic for insertion of a radioactive implant without complication.

Discussion

There has been a recent epidemic of latex allergy^{4,5} and this case demonstrates the occurrence of heart block heralding the onset of latex induced anaphylaxis. We feel the development of 3:1 heart block may have been precipitated by preoperative treatment with the H₂ receptor antagonist ranitidine.

There is substantial evidence that the heart is a primary target organ in anaphylactic reactions with mediators including histamine, prostaglandins, thromboxanes, and leukotrienes being released.^{1,6} Sinus tachycardia, atrioventricular conduction block, increased ventricular automaticity and histamine release are characteristic features of cardiac anaphylaxis *in vivo* and *in vitro*.^{1,6} In the guinea pig, the onset of cardiac rhythm changes occurs approximately 20 sec after antigenic challenge, at the same time as the initial change in blood pressure, and immediately before the anaphylactic increase in bronchial resistance.¹ In man, anaphylactic reactions have been accompanied by electrocardiographic changes, including cardiac arrhythmias, heart block, and acute myocardial infarction and cardiac failure, which may occur without preceding respiratory distress which might otherwise be the cause of secondary cardiac symptoms.⁷

Histamine induces atrioventricular conduction delay and constriction of epicardial coronary vessels by stimulating H₁ receptors, and H₂ receptor stimulation mediates coronary vasodilatation and an increase in heart rate and myocardial contractility.³ Thus, as with this patient, the use of H₂ receptor antagonists prior to anaphylaxis may have predisposed the patient to the development of heart block by preventing the H₂ receptor system from physiologically counteracting the cardiodepressant actions of anaphylactic mediators. The use of H₂ receptor antagonists may also predispose to myocardial ischemia during cardiac anaphylaxis, although there was no evidence of ischemia in our patient. H₂ receptor blockade during cardiac anaphylaxis enhances coronary vasoconstriction,⁶ and blockade of H₂ receptors potentiates the constrictive effect of histamine on human atherosclerotic coronary arteries.⁸ Therefore, treatment with H₂ receptor antagonists during cardiac anaphylaxis in clinical practice could be detrimental, especially in patients with ischemic heart disease.

In summary, we report a case of latex anaphylaxis which was heralded by the onset of 3:1 heart block. We theorize that the use of the H₂ receptor antagonist ranitidine contributed to this heart block. Preoperative use of H₂ antihistamines alone in patients at risk of anaphylaxis may help contribute to the development of heart block if anaphylaxis occurs.

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