pISSN 1598-298X / eISSN 2384-0749
J Vet Clin 37(3) : 145-148 (2020)
https://doi.org/10.17555/jvc.2020.06.37.3.145

Journal of Veterinary Clinics
www.ksvc.or.kr

Dobutamine-Induced Perioperative Anaphylaxis in a Dog

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(Received: May 05, 2020 / Accepted: May 26, 2020)

Abstract : A 9-years old spayed female Maltese was referred for the treatment of mass on the right 1st mammary gland and acute weight bearing lameness of right hindlimb. It was diagnosed as malignant mammary tumor and cranial cruciate ligament rupture of right stifle joint. Right upper regional mastectomy followed by cranial closing wedge osteotomy (CCWO) of the right tibia were planned for the present problems. Preanesthetic work-up did not show any remarkable abnormalities. Forty-five minutes after induction of anesthesia dobutamine was administered at a rate of 5 μg/kg/min by constant rate infusion due to gradual decrease of blood pressure below MAP 60 mmHg during surgical procedure. Despite of the increase of dobutamine infusion rate up to 20 μg/kg/min, blood pressure didn't recover. At the end of regional mastectomy generalized skin redness and eyelid edema were identified. Anesthesia was stopped and CCWO procedure was cancelled. To recover from the anaphylactic reactions dexamethasone and diphenhydramine were administered. After about one hour, the patient completely recovered from hypotension and anaphylactic reactions. After 4 weeks, intradermal skin test (IDST) was performed for all the drugs used during anesthesia. Only dobutamine showed positive reaction in IDST. Therefore, dobutamine was considered as the causative agent of anaphylaxis in this patient during the anesthesia. In case of perioperative anaphylactic reaction, postoperative investigation should be performed to identify causative agent and to provide safe recommendations for future anesthetic procedure.

Key words **:** anaphylaxis, dobutamine, intradermal skin test, anesthesia, dog.

Introduction

Perioperative anaphylaxis is a severe, life-threatening generalized or systemic hypersensitivity (10,12,13). It has been typically a result of drugs or substance used for anesthesia or surgery. In human literatures, perioperative anaphylaxis is rarely seen in 1/10,000-20,000 cases but has a high mortality rate of 3-10% (7,10,12,13). In veterinary medicine, it is difficult to know exact mortality due to limited number of published veterinary reports, but it is considered to be as high as in the case of human beings. The most common triggers of anaphylaxis in human anesthesia are neuromuscular blocking agents (NMBAs), latex, and antibiotics (10,15). Although limited reports in the veterinary literature preclude identifying common triggers, suspected triggers include antibiotics, opioids, radiocontrast media, NSAIDs, and intravenous anesthesia (6,14).

Clinical signs of anaphylaxis are classified into 4 stages (5). Grade 1 is cutaneous-mucous signs such as erythema, grade 2 is moderate multivisceral signs that is hypotension, or tachycardia, grade 3 is life-threatening mono- or multivisceral signs and if there is a cardiac arrest, it can be defined as grade 4. The diagnosis of anaphylaxis is based on the interval time between the drug administration and the clinical symptoms. To determine anaphylaxis and causative agent, the concentration of mast cells, histamine and tryptase is measured, or intradermal skin test is performed 4-6 weeks after anaphylaxis. It is essential in treatment of perioperative anaphylaxis to withdraw the suspected causative drug promptly, discontinue the anesthesia, and maintain a 100% oxygen supply (4,8). Subsequently, the surgical procedure should be abbreviated as much as possible and providing epinephrine in patients with grade 3 or 4 is necessary for better outcomes.

Early recognition of anaphylaxis and aggressive intervention would be led to successful outcome. But hypotension is common side effect of anesthetic drugs, and tachycardia exhibit from nociceptive response. Because of this reasons, Early diagnosis of anaphylaxis during surgical procedure is challenging and it is hard to get rapid treatment (17). Furthermore, if causative drugs for anaphylaxis is administered to resolve anesthetic side effect, this would make more confusing the diagnosis and treatment of anaphylaxis.

To the best of the author's knowledge, this is the first case report to describe the diagnosis and treatment of anaphylaxis caused by dobutamine, resulting in more severe hypotension.

Case

A 9-years old spayed female Maltese dog was referred for the treatment of mammary gland mass and acute weight-bearing lameness of right hind limb. The patient was diagnosed as malignant mammary gland tumor at the right first mammary gland and cranial cruciate ligament rupture on the right stifle joint. Right upper regional mastectomy followed by cranial closing wedge osteotomy (CCWO) of the right tibia were planned for the present problems.

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Preanesthetic work-up showed no remarkable findings. In previous history of 3 anesthetic records of general anesthesia for cholecystectomy, bilateral ureterotomy, and CT examination, there were no specific events related to anaphylaxis.

Anesthesia was performed for regional mastectomy and CCWO. The following drugs were administered for general anesthesia; cefazolin (Cefazolin Inj; Chongkundang) 22 mg/kg IV for prophylaxis, hydromorphone (Dilid injection 1 mg; Hana) 0.1 mg/kg IV and midazolam (Midazolam Inj; Bukwang) 0.2 mg/kg IV for premedication, and propofol (Anepol Inj; Hana) 4 mg/kg IV for induction. After intubation, anesthesia was maintained with 2% isoflurane under pure oxygen. At 15 minutes after induction of anesthesia isoflurane was decreased to 1.5% and glycopyrrolate (Mobinul Inj; Myungmoon) 0.011 mg/kg was administered intravenously due to gradual decrease of heart rate to 80 beats/min. At the time of incision for right upper regional mastectomy heart rate and blood pressure was maintained within normal range. Five minutes after incision, blood pressure was decreased to MAP 43 mmHg. Isoflurane was decreased to 1.2% and dobutamine (Dobutamine HCl Inj; Myungmoon) 5 μg/kg/min was administered by constant rate infusion. The blood pressure increased initially and then decreased subsequently without any massive bleeding history during surgical procedure. One hour after initial administration of dobutamine, infusion rate was increased up to 20 μg/kg/min, but hypotension persisted. After completion of regional mastectomy generalized skin redness and eyelid edema were identified after removing surgical drapes. Perioperative anaphylaxis was suspected according to refractory hypotension and systemic cutaneous-mucous signs. Anesthetic procedure was stopped and CCWO was cancelled. Dexamethasone (Dexamethasone Inj; Jeil) 1 mg/kg and diphenhydramine (Diphenhydramine HCl Inj; Mylan) 1 mg/kg were administered intravenously to resolve anaphylactic reactions. Five minutes after administration of dexamethasone and diphenhydramine blood pressure was started to increase (Fig 1). After one hour, generalized redness and eyelid edema were resolved.

After 4 weeks, intradermal skin test (IDST) was performed about drugs used during anesthesia to identify causative agent of anaphylaxis. The dose of the agents for IDST were as follows (Table 1). Only dobutamine reacted positively in

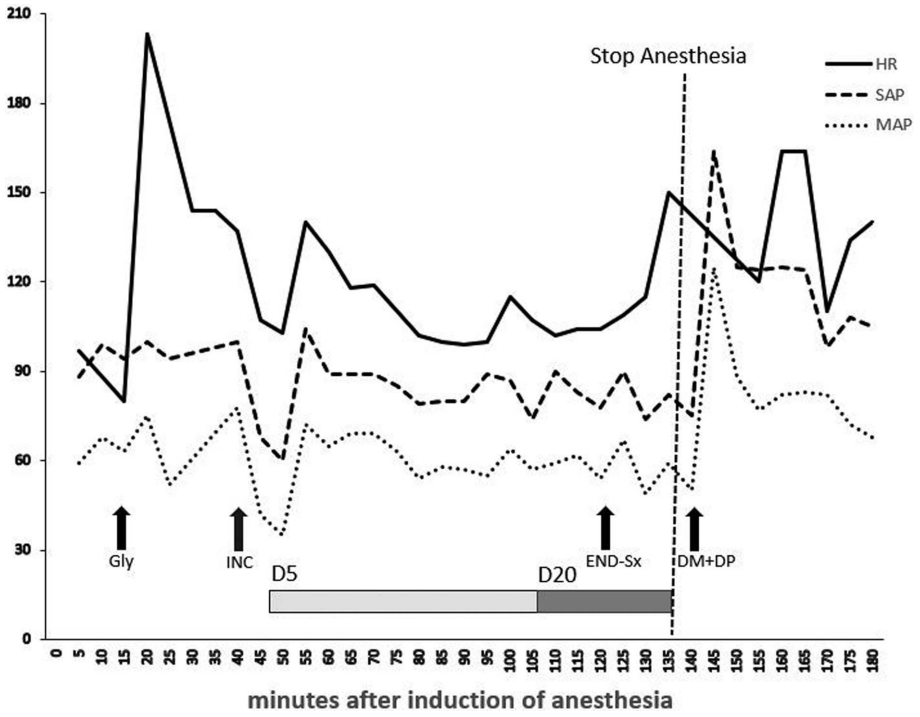

Fig 1. Changes in heart rate and blood pressure during surgery. HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; Gly, Glycopyrrolate 0.011 mg/kg IV; INC, Incision; END-Sx, End of surgery; D5, Dobutamine 5 μg/kg/min; D20, Dobutamine 20 μg/kg/min; DM, Dexamethasone 1 mg/kg IV; DH, Diphenhydramine 1 mg/kg IV.

Table 1. Nonirritating test concentrations for intradermal skin test (IDST)

Generic name	Undiluted concentration (mg/ml)	Dilution	Maximum concentration (mg/ml)
Cefazoline	200	1/100	2.0
Dobutamine	50	1/100	0.5
Hydromorphone	1	1/100	0.01
Midazolam	1	1/10	0.1
Propofol	10	1/10	0.1
Glycopyrrolate	0.2	1/10	0.02

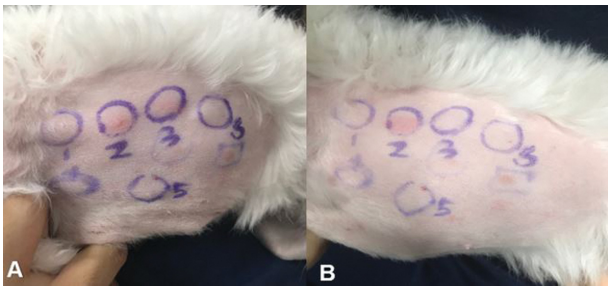

Fig 2. Intradermal skin test (IDST). Immediately (A) and 15 minutes (B) after intradermal injection. 1, cefazoline; 2, dobutamine; 3, hydromorphone; 4, midazolam; 5, propofol; 6, glycopyrrolate; □, normal saline.

the IDST after 15 minutes (Fig 2). Therefore, dobutamine was considered to be the causative agent of anaphylaxis in this patient.

Discussion

This report is for all cases of redness and periorbital edema caused by anaphylaxis of dobutamine administered during surgery, and was successfully treated with dexamethasone, diphenhydramine, and fluid therapy, and diagnosis was made through IDST. In the case reported herein, it was considered as a grade 2 anaphylaxis because the patient exhibited hypotension and cutaneous signs such as generalized redness and periorbital edema (5). But, early recognition of anaphylactic reaction was failed, and anaphylaxis was suspected due to cutaneous signs while removing the surgical drapes 105 minutes after injecting dobutamine. If anesthetist observed more precisely eye and the inotropic efficacy of dobutamine, early detection of anaphylactic reaction could be made. Anaphylaxis was successfully managed with dexamethasone, diphenhydramine, fluid therapy and oxygen supply (4,8). However, the causative agent should be identified due to pre-planned 2nd surgery, CCWO, to provide safe anesthetic regimen for future surgery.

Among anesthetic records of general anesthesia for cholecystectomy, bilateral ureterotomy, and CT examination, the patient had received dobutamine once 15 months ago as inotropic agent at the previous history of general anesthesia, and there were no signs of anaphylaxis during that course of anesthesia. It is thought that the anaphylaxis was due to the response of dobutamine after previous exposure (1).

IDST is considered as the gold standard for the detection of IgE-mediated reactions. It could identify the culprit agent, prove the pathophysiologic mechanism and suggest a safe alternative anesthetic regimen (2,3,11). In veterinary literature, perioperative anaphylaxis was provisionally diagnosed with interval between clinical signs and drug administration (12). In this case, dobutamine was found to be the causative drug by postoperative IDST.

Anaphylactoid reaction due to sodium bisulfite, preservative of dobutamine, used in the vehicles of drugs was reported in human medicine (16). The dobutamine used in this case contained sodium pyrosulfite as a preservative. Further study is needed whether the anaphylaxis was caused by dobutamine itself or sodium pyrosulfite.

Conclusion

Dobutamine-induced anaphylaxis is rare in veterinary procedure, but it can occur due to prior exposure. However, anaphylaxis can be recognized early by precise patient monitoring and can be managed by proper treatment. Also, postoperative IDST should be considered after perioperative anaphylaxis to identify causative agent or drug and to provide proper future anesthetic regimen avoiding the causative drug.

Acknowledgements

This work was supported by research fund of Chungnam National University.

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