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Case Report

Suspected Anaphylactic Reaction to Ketamine in 3 Yucatan Swine (*Sus scrofa*)

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This case series describes the clinical courses of 3 juvenile Yucatan miniature swine (*Sus scrofa*) that experienced a suspected anaphylactic reaction to ketamine hydrochloride during premedication for protocol-related surgery. All 3 swine rapidly developed diffuse erythema shortly after injection with ketamine-containing drug combinations. Clinical signs ranged from tachycardia and erythema alone to tachycardia and erythema followed by respiratory and cardiac arrest. Ketamine was considered the most likely cause of these reactions because it was the only agent in the premedication sedation combination that was used in all 3 swine. Subsequent intradermal skin testing confirmed this suspicion. With supportive care measures and standard medical interventions for anaphylaxis, all 3 animals recovered well and went on to be successful experimental subjects when an alternative anesthetic regimen that did not contain ketamine was used. To our knowledge, this report is the first description of a suspected adverse ketamine reaction of this type in swine despite the widespread use of the drug in this species. Ketamine anaphylaxis is rare in people, but the few cases described presented with symptoms similar to the clinical signs seen in the pigs in this report. In addition to highlighting a potential adverse drug reaction to ketamine in swine, this case series demonstrates the value of emergency preparedness for even the most routine of procedures.

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Anaphylactic drug reactions are a rare but potentially serious complication of anesthesia. In humans, estimates of anaphylaxis during anesthesia vary widely from one study to another, with frequencies ranging from 1 case in 2100[22] to 1 in 20,000, with a mortality rate of as high as 10%.[11] Although substances known to most commonly elicit an anaphylactic response include neuromuscular blockers and latex, virtually every anesthetic, with the exception of volatile inhalant agents, has been implicated in anaphylactic reactions.[4,11,12,22] Anaphylaxis occurs in anesthetized veterinary patients as well, but these episodes are less well documented than in humans. Evaluation of anaphylaxis in veterinary species is complicated by low sample sizes due to relative rarity of the condition, and definitive diagnoses are rarely made even in successfully managed cases.[6,25,32,36,42,44,45,56] An additional complicating factor for veterinary patients is that different species may react with varying severity to the same trigger.[2]

Although swine have been used as an experimental model for anaphylaxis,[49,51] review of the literature shows that naturally occurring anaphylaxis seems to be either rare or underreported in swine. The reports of anaphylaxis in swine that do exist document reactions to drugs, usually vaccines, given in the context of a meat production setting and not in animals undergoing anesthesia.[19,54] Ketamine is one of the most common anesthetics used in swine and is generally considered to be a safe drug with few side effects of concern.[15] In the following case series, we present 3 adverse events in anesthetized Yucatan minipigs that we attribute to ketamine anaphylaxis.

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Case Report

The 3 swine presented in the current report were apparently healthy, juvenile (age, 5 to 6 mo) Yucatan minipigs (Sinclair BioResources, Windham, ME). Prior to arrival, the pigs were vaccinated for *Haemophilus parasius* (Ingelvac HP1, Boehringer Ingelheim, St Joseph, MO), porcine circovirus (Circumvent PCV, Merck Animal Health, Madison, NJ), *Erysipelas rhusiopathiae* and *Mycoplasma hypneumoniae* (RespiSure-One/ER Bac Plus, Zoetis, Kalamazoo, MI). The source herd tested negative for brucellosis and pseudorabies and was free of tuberculosis. On arrival, the pigs underwent a routine quarantine and acclimation period, during which physical exam and fecal parasite analysis were performed. Physical examinations were within normal limits for each pig, and fecal exam for ova and parasites showed cysts of *Entamoeba* spp., which is considered a commensal organism of the pig gastrointestinal tract. After release from quarantine, each animal was enrolled in an IACUC-approved experimental protocol within the AAALAC-accredited program at the University of Pennsylvania. Pigs were given water without restriction and were fed standard minipig grower diet (5081, LabDiet, St Louis, MO) at rations appropriate to their weight and body condition. All pigs were socially housed with at least one conspecific and had olfactory and tactile contact with other pigs except for immediately postoperatively.

Clinical case 1 (animal A). In preparation for a protocol-related surgery in July 2016, a 7-mo-old female pig was sedated

with ketamine (20 mg/kg IM) and midazolam (0.5 mg/kg IM) and then supplemented with isoflurane through a facemask. Glycopyrrolate (0.1 mg/kg SC) and meloxicam (0.5 mg/kg SC) were administered approximately 5 min later, according to protocol. Initial physiologic monitoring included a heart rate of 90 bpm, respiratory rate of 16 breaths per minute, and SpO_2 of 100%. When the animal was repositioned for intubation, severe erythema was noted diffusely on the face and thorax. Spontaneous respirations then ceased, and the heart rate increased to 180 to 200 bpm. Isoflurane was discontinued, and the animal was immediately intubated to allow for assisted respiration with 100% oxygen. Midazolam was reversed with flumazenil (0.01 mg/kg IM). Dexamethasone (1.3 mg/kg IM) and diphenhydramine (2 mg/kg IM) were administered. Respirations were assisted for 25 min, until the pig again regained spontaneous breathing. A catheter was placed in the marginal ear vein, and isotonic crystalloid fluid replacement therapy was initiated at approximately 60 mL/kg administered over 1 h. Skin coloration and vital signs improved over a period of 120 min, and recovery from the anesthetic event was prolonged but smooth. Body temperature decreased to 96.8 °F, but returned to normal (101.4 °F) with heat support within 4 h. Omeprazole (1.2 mg/kg PO) was given for 3 d, given the potential for gastrointestinal upset due to poor perfusion during the event. The pig remained quiet but responsive with a slightly decreased appetite for 24 to 48 h after the event but was clinically normal within 72 h.

Clinical case 2 (animal B). Another pig, also a 7-mo-old female, was sedated 10 d later by using the same sedation protocol and for the same protocol-related surgery as case 1. Animal B was a littermate of animal A and arrived to the facility in the same cohort. Glycopyrrolate (0.1 mg/kg SC) and meloxicam (0.5 mg/kg SC) were administered; the pig was then intubated and maintained on 2.5% isoflurane. New bottles of ketamine, midazolam, and glycopyrrolate were used for this sedation event. The meloxicam originated from the same bottle as for animal A, but this bottle had been used for other animals without incident. Initial vital signs included a heart rate of 90 to 110 bpm, respiratory rate of 26 to 39 breaths per minute, and SpO_2 of 96% to 100%. The pig was transported to the operating suite and prepped and draped for aseptic surgery. Prior to the first incision, the heart rate increased to 180 to 200 bpm, and the skin on the head and trunk was noted to be diffusely erythematous. Isoflurane was discontinued, and the animal was maintained on 100% oxygen via endotracheal tube. Dexamethasone (0.5 mg/kg IM) was administered. Recovery was prolonged and lasted approximately 90 min, during which time the heart rate stabilized at 130 bpm. The temperature decreased to 98.3 °F during the event but returned to 99.5 °F within 2 h. As with the first pig, omeprazole (1.2 mg/kg PO) was given for 3 d. The pig remained quiet for approximately 6 h, after which point she was clinically normal.

At 2 to 3 wk after the initial event, both animals A and B were sedated to determine a safe sedation protocol to complete the experimental objectives and to perform intradermal skin testing to evaluate ketamine as a potential anaphylactic trigger. The pigs were sedated with midazolam (0.4 mg/kg IM), dexmedetomidine (0.04 mg/kg IM), and buprenorphine (0.015 mg/kg IM). After 30 min of stable sedation with no clinical signs of anaphylaxis, glycopyrrolate (0.01 mg/kg SC) was administered. The lack of an adverse reaction was again confirmed, and isoflurane was initiated and provided through a facemask for 45 min. In addition, 0.05 mL of 100 mg/mL ketamine was injected intradermally near the ear to test for an allergic skin reaction (Figure 1). Near the opposite ear, the same volume of saline

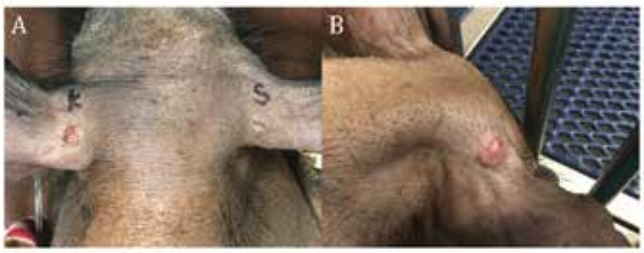

Figure 1. Intradermal skin testing in animal A (left image) and animal B (right image). In the left image, ketamine (left ear) and saline (right ear) were injected intradermally, and the boundaries of the initial injection were marked with a permanent marker. The image was taken 15 min after initial injection, showing localized wheal and flare at the site of ketamine injection and no reaction at the site of saline injection. The right image shows marked wheal and flare reaction at the site of intradermal ketamine testing after 1.5 h, with initial injection boundaries in black.

was injected as a negative control. Within 2 min, wheal and flare formation developed at the site of ketamine injection; no skin reaction was observed at the site of saline injection. At the end of the anesthesia trial, isoflurane was discontinued, and the pigs recovered from anesthesia. Throughout the procedure, heart rate remained below 160 bpm. Indirect blood pressure was measured by using a cuff placed just above the stifle. Mean arterial blood pressure remained between 68 and 82 mm Hg for pig A. For pig B, mean arterial blood pressure remained within the same range as for pig A until isoflurane was introduced, at which time mean arterial blood pressure decreased to 45 to 60 mm Hg, consistent with vasodilation secondary to inhalant anesthesia. Once isoflurane was discontinued, mean arterial blood pressure returned to 68 mm Hg prior to recovery. At the end of the procedure, both pigs received atipamezole at 0.4 mg/kg IM for anesthetic reversal and recovered smoothly. No skin erythema or tachycardia was noted during either procedure, and only one pig developed mild transient hypotension. A local wheal-and-flare skin reaction to intradermal ketamine injection persisted for over 5 d, showing a well-circumscribed circular lesion of pale skin. Both pigs later successfully and without anesthetic complications underwent protocol-prescribed surgery by using the altered anesthesia protocol but were premedicated with diphenhydramine IM as a precaution due to previous anaphylactic response: premedication diphenhydramine (1 mg/kg), sedation with midazolam (0.4 mg/kg), dexmedetomidine (0.04 mg/kg), and buprenorphine (0.015 mg/kg) IM, followed with inhaled isoflurane maintenance.

Clinical case 3 (animal C). In July 2017, a 6-mo-old male castrated pig was sedated for use on another experimental protocol by using ketamine (20 mg/kg IM; different bottle and lot number than for pigs A and B) and xylazine (2.2 mg/kg IM). Meloxicam (0.2 mg/kg SC) was administered, an auricular intravenous catheter was placed, endotracheal intubation was performed, and the pig was provided 2.5% isoflurane. Although the pig initially had normal vital signs (heart rate, 90 bpm; temperature, 100.1 °F; respiratory rate, 40 breaths per minute), approximately 20 min after premedication, he developed diffuse skin erythema and experienced simultaneous respiratory and cardiac arrest. Anesthesia was discontinued, atropine (0.04 mg/kg IV) was administered, chest compressions were initiated, and the pig was ventilated at 10 mL/kg tidal volume with 100% oxygen. When asystole continued despite several minutes of continued ventilatory support and cardiac compressions, epinephrine (0.01 mg/kg IV), an intravenous bolus of 20 mL/kg of a balanced

electrolyte solution, and diphenhydramine (2 mg/kg IV) were administered; spontaneous circulation ensued (heart rate, 130 bpm). The researchers elected to abort the surgical procedure and to allow the animal to recover from anesthesia.

The pig was recovered with continuous monitoring and support (heat support, fluid therapy, flow-by oxygen therapy as tolerated). Starting when spontaneous respirations resumed, he showed moderate tachypnea (70 breaths per minute) despite no increase in effort and an appropriate SPO_2 (98%); this tachypnea resolved over the course of his recovery with no intervention beyond supplementation with 100% oxygen. Prior to extubation, the pig vomited; after receiving maropitant citrate (1 mg/kg IV), he showed no further signs of nausea. The animal was extubated approximately 1 h after initial premedication. The diffuse erythema noted immediately prior to cardiopulmonary arrest resolved over the course of his recovery, although a 4- to 5-cm, firm, red wheal at his premedication injection site was noted during recovery. His temperature decreased throughout the time of the event and recovery (lowest temperature recorded 97.6 °F), and returned to normothermia with the addition of heat support. Approximately 5 h after extubation, vital signs stabilized to within the normal range (heart rate, 132 bpm; temperature, 100.8 °F; respiratory rate, 42 breaths per minute), and appetite returned.

Over the subsequent week, the red swelling at the pig's injection site diminished in size without treatment. Approximately 2 wk after initial presentation, the pig was successfully anesthetized for his protocol-prescribed surgery by using an alternative sedation regimen (dexmedetomidine, 10 µg/kg IM; midazolam, 0.3 mg/kg IM; hydromorphone, 0.1 mg/kg IM), with anesthesia maintenance by using isoflurane. No noteworthy anesthetic complications occurred.

Discussion

In the cases we described here, 3 pigs presented with classic signs of an anaphylactic reaction during anesthesia, including diffuse cutaneous erythema, tachycardia, and suspected hypotension. Two of the pigs developed respiratory arrest, and one of those pigs experienced cardiac arrest. Treatment varied according to each animal's clinical signs, but emergency treatment included standard interventions for anaphylactic reactions under anesthesia, including reversal and discontinuation of anesthetic drugs and administration of fluids, epinephrine, other resuscitative drugs, respiratory support, corticosteroids, and antihistamines.[2,27,47] Supportive measures during the recovery phase included gastroprotectants and antiemetics tailored to the needs of individual animals. All 3 pigs recovered well, with no persistent or recurrent clinical signs, and all 3 pigs were later successfully anesthetized for protocol-related survival surgeries by using alternative drug regimens.

Ketamine is an NMDA-antagonistic dissociative agent commonly used for sedation and anesthesia in veterinary patients. In addition to inducing anesthesia, ketamine provides analgesia and is thought to have some neuroprotective properties.[1,3] In pigs, ketamine typically is used for minor procedures of short duration and for initial immobilization prior to anesthesia by using other methods (inhalant or intravenous anesthesia). In this species, ketamine is most commonly used in combination with other agents, including midazolam, acepromazine, and xylazine,[5] and it was used in conjunction with other agents for each of the 3 pigs in this case. Although we cannot definitively rule out a drug reaction to one of the other agents as the cause of the clinical signs observed, other than isoflurane, ketamine was the only drug common to all 3 of these animals at the time of their adverse events (Table 1). Furthermore, each of these animals was successfully anesthetized with no ill effects at a later date by using other agents including midazolam and isoflurane. For these reasons and in combination with the positive intradermal skin test response in pigs A and B and the pronounced wheal at the induction drug injection site in pig C at the time of his anaphylactic event, we believe that all 3 of these cases represent anaphylactic reactions to ketamine.[20,23]

Although studies and case reports show that pharmaceutical preservatives may cause allergic reactions,[37,55] there are no published reports of anaphylaxis due to benzethonium chloride associated with ketamine or with the preservative alone. The 2 bottles of ketamine were from different manufacturers, but both contained benzethonium chloride at 0.1 mg/mL. Benzethonium chloride is a common preservative in well-known pharmaceutical preparations and over-the-counter medicines.[17,30] A previous rodent study of chronic feeding of benzethonium found little or no toxic effects.[13] Most publications on benzethonium chloride address its use in cosmetics and report little to no toxicity.[31]

Anaphylactic reactions can be either nonallergic or allergic in origin, with allergic anaphylaxis being further subdivided into IgE- and nonIgE-dependent mechanisms (Figure 2).[23] It was once thought that allergic and nonallergic anaphylaxes could be distinguished clinically from one another because allergic anaphylaxis would require prior sensitization, whereas nonallergic anaphylaxis would not. However, the reality is not this simple, given that IgE receptor crossreactivity between structurally similar substances (for example, latex and various fruits; some neuromuscular blockers and ammonia-containing disinfectants) can result in sensitization to a drug before the patient's first exposure to that drug.[2,4] Regardless of the mechanism of anaphylaxis, the clinical picture is indistinguishable.[2,12,20] Anaphylaxis by either origin results in systemic release of inflammatory mediators by mast cells and basophils, and the resultant sequelae include vasodilation, skin erythema, bronchospasm, hypotension, and cardiovascular and respiratory collapse.[11,26]

Initial diagnosis of anaphylaxis typically relies on clinical signs.[12] Clinical signs may involve cutaneous (erythema and urticaria), cardiovascular (hypotension and tachycardia), respiratory (dyspnea, bronchospasm, wheezing), and gastrointestinal (nausea, vomiting, diarrhea) systems. Clinical presentations may vary in time frame, severity, and organ system involvement. Grading systems have been created to describe anaphylactic reactions and range from cutaneous signs only to complete cardiovascular collapse and death.[8,18,24]

Immediate clinical management for anaphylaxis is largely supportive and generally includes discontinuation of anesthesia when possible, administration of epinephrine and fluids, and respiratory support as indicated. In addition, antihistamines and corticosteroids are commonly used but are often considered secondary to the aforementioned stabilizing measures.[18,24,26] Close observation is necessary for at least 24 h to monitor for persistent or recurrent respiratory, hemodynamic, or gastrointestinal effects. Patients (human and animal) that have experienced an anaphylactic reaction while under anesthesia are commonly premedicated with antihistamines or corticosteroids before undergoing a subsequent anesthetic event, with the intent to reduce the likelihood of a repeat event; however although this practice is unlikely to cause harm, little evidence supports that it is effective.[2,4,18,24,27] The use of antihistamines is unlikely to prevent a severe reaction, but there is still a strong benefit to any reduction in severity of clinical signs during an anaphylactic response. Management of future anesthetic events in cases of known anaphylaxis are based on risk assessment

Table 1. Drugs administered prior to the presumed drug reaction in pigs A, B, and C

	A	B	C
Glycopyrrolate	X[a]	X[a]	
Isoflurane	X[a]	X[a]	X[a]
Ketamine	X	X	X
Meloxicam	X[a]	X[a]	X[a]
Midazolam	X[a]	X[a]	
Xylazine			X

All 3 pigs were later anesthetized by using dexmedetomidine, midazolam, an opioid, and isoflurane with no complications.
[a]Drugs that were used later in the same animal with no ill effects.

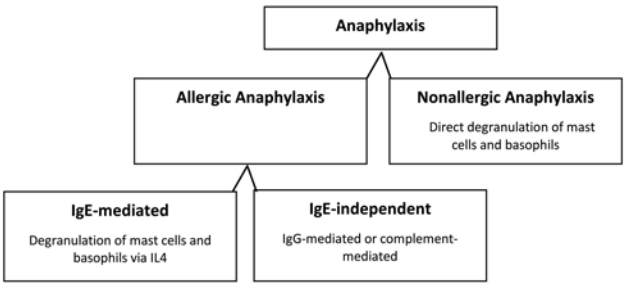

Figure 2. Overview of the categorization of anaphylactic reactions according to mechanism. Summarized from reference 23.

by the clinician and often are a matter of clinical preference. In animals A and B, the clinician chose to use antihistamine premedication to prevent or reduce the likelihood of recurrence, whereas the clinician for case C was comfortable with withholding antihistamines in future sedations. Alternatively, avoidance of the suspected offending drug altogether would be useful but, in the absence of a definitive diagnosis, may not be possible. In the pigs presented, further anesthetic drug choices excluded ketamine, and no additional anaphylactic events occurred.

Confirmation of a diagnosis of anaphylaxis is challenging, no single diagnostic test provides a definitive diagnosis. Incidence of anaphylaxis is probably underreported, in large part due to the difficulty in making a definitive diagnosis.[26] Evaluation of serum histamine and tryptase, both of which are released from mast cells and basophils during degranulation, can be informative, but these assays must be performed during or shortly after the anaphylactic episode and frequently are not performed because clinicians are focused on patient stabilization during the hours after these events.[4] Furthermore, these data are best interpreted in conjunction with baseline levels of these substances, and those samples are often unavailable.[46] In humans, assays for IgE specific to suspected anaphylaxis triggers are available for various substances,[4,24] but these tests are not readily available for most anesthetic drugs and are only recently being developed for veterinary medicine.[41,42] Skin testing, either intradermal inoculation or 'skin prick' testing can be used to confirm anaphylactic triggers, although both false positives and false negatives are commonly reported.[18,24] To avoid false negatives, testing should be performed no sooner than 4 wk after the initial anaphylactic event, to give immune cells sufficient time to recover their contents after degranulation.[12,35] To prevent an additional sedation event, we performed skin testing during our anesthetic trial to find a safe regimen for the animals. Although this tested occurred just 2 to 3 wk after the initial event, the skin test still yielded a positive response. To avoid false positives due to local skin reaction, many authors recommend using diluted drug for skin testing,[18,33] although others do not make this recommendation.[4,33] In our pigs, skin testing used undiluted ketamine. Although we cannot rule out a local reaction to the undiluted drug as the cause of the positive skin reaction that we saw in animals A and B, we believe the positive skin reaction— together with the other clinical findings in these animals—supports our diagnosis of ketamine anaphylaxis.

Determining a definitive diagnosis of anaphylaxis is challenging. Identifying the cause of an anaphylactic reaction during a surgical event is fraught. Multiple drugs including anesthetics, antibiotics, analgesics, and topical antiseptics are used in the perioperative period for surgical preparation. Animals are exposed to various other products, such as latex gloves, adhesives, and catheter substances.[12,26,38] Further complicating diagnosis, some of the early clinical signs associated with anaphylaxis, such as hypotension and respiratory depression, are expected side effects of many anesthetic drugs.[4] Furthermore, the patient typically is draped, and the initial visual cues of anaphylaxis may be missed until the cardiorespiratory effects are observed during anesthetic monitoring. Some of the most common veterinary substances associated with anaphylaxis during anesthesia include neuromuscular blocking agents, antibiotics, and latex; however, there are reports of anaphylaxis to virtually all substances associated with anesthesia except for volatile inhalant anesthetics.[4,11,34] Anaphylactic reactions to ketamine are considered extremely rare,[11] although reports exist for both humans[7,9,21,33,39,40,43] and veterinary patients.[45]

Several parallels exist between the swine cases presented here and published reports of ketamine reactions in humans. First, the clinical signs were quite similar. All of the human cases referenced involve the rapid development of erythema, hives, or a rash after the administration of ketamine, and several cases also demonstrated respiratory compromise.[9,40] All 3 swine developed erythema and wheals in association with the ketamine injection site, and 2 of the 3 also experienced respiratory arrest. Second, most human cases of ketamine allergy have been in young women, and women are generally considered more likely than men to experience adverse drug reactions during anesthesia.[4,38] Two of the 3 cases we presented were young, intact female swine. Perhaps young female swine are more likely than males to experience adverse ketamine reactions, although additional investigation is required to confirm this hypothesis.

After the suspected anaphylactic events involving pigs A and B, we contacted the vendor to discuss whether this type of reaction had been seen at their facility or whether other customers were reporting similar events. The vendor responded that they had not received any similar reports from other institutions using their animals. The vendor did not routinely sedate animals with ketamine but did routinely use tiletamine, which is structurally related to ketamine. The vendor had not seen any allergic-type drug responses in their animals, nor are we familiar with any reports of tiletamine-associated anaphylaxis in veterinary patients.

Shared food allergies have been reported to occur between siblings,[14,16,29,53] but drug allergies are infrequently reported to have a genetic basis,[10,50,52] and there is no known predisposition of humans or animals with another allergic disease for having an anaphylactic reaction to injectable drugs.[2,4] Out of concern for a possible congenital component to the adverse reactions, we asked the vendor to compare the affected animals' lineages. Pigs A and B were littermates, sharing the same dam and sire, which could be suggestive of a genetic predisposition for an adverse reaction to ketamine in these cases. However, additional pigs from the same litter and shipment underwent the same initial anesthetic regimen as pigs A and B, and none of these littermates demonstrated similar adverse reactions. Pig C had no recent genetic relationship to pigs A and B despite coming from the same herd. Whether there is a heritable component to the reaction that we observed remains unclear at this time.

Conclusion

To our knowledge, this case series contains the first reports of suspected anaphylaxis from ketamine in swine. While often used in combination with other anesthetic agents, ketamine is used very commonly in swine and is frequently touted as a safe and effective drug for use even in animals with cardiovascular compromise.[5,28,48] Even though these 3 cases arose in relative temporal proximity to one another, such adverse reactions appear to be rare. Our institution acquires approximately 50 Yucatan swine per year, many are exposed to ketamine, and many are anesthetized multiple times for a given protocol, and to-date we have observed similar reactions in only these 3 animals. We have not noticed a similar phenomenon in Yorkshire-cross swine, a much more commonly used breed at our institution. Nonetheless, we encourage veterinary staff working with Yucatan swine to keep this report in mind when selecting an anesthetic regimen. Using ketamine-free protocols may be beneficial in some cases.

Perhaps the most important lesson to learn from this report is that emergency readiness is crucial whenever an animal undergoes anesthesia. Despite our facility's frequent use of these sedation combinations in this breed of swine, 2 of the 3 swine presented in this case report experienced respiratory arrest, and one required cardiopulmonary resuscitation. But for the presence of trained veterinary technical staff and institutional standard operating procedures that ensured the availability of emergency drugs, the clinical outcomes might have been different. The reactions we saw were unexpected and serious but appear to have been completely reversible, and each animal recovered fully, enrolled in a surgical study with an alternative anesthetic protocol, and reached its planned study endpoint.

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References

1. **Allen CA, Ivester JR, Jr.** 2018. Low-dose ketamine for postoperative pain management. J Perianesth Nurs **33:**389–398. https://doi.org/10.1016/j.jopan.2016.12.009.
2. **Armitage–Chan E.** 2010. Anaphylaxis and anaesthesia. Vet Anaesth Analg **37:**306–310. https://doi.org/10.1111/j.1467-2995.2010.00551.x.
3. **Bell JD.** 2017. In vogue: ketamine for neuroprotection in acute neurologic injury. Anesth Analg **124:**1237–1243. https://doi.org/10.1213/ANE.0000000000001856.
4. **Bevanda DG, Čačić M, Mihaljević S, Bevanda M, Bogut A, Karin M.** 2017. Allergic reactions and anesthesia. Psychiatr Danub **29 Suppl 4:**778–786.
5. **Boschert K, Flecknell PA, Fosse RT, Framstad T, Ganter M, Sjøstrand U, Stevens J, Thurman J.** 1996. Ketamine and its use in the pig. Recommendations of the consensus meeting on ketamine anaesthesia in pigs, Bergen 1994. Ketamine consensus working group. Lab Anim **30:**209–219. https://doi.org/10.1258/002367796780684863.
6. **Bosmans T, Melis S, De Rooster H, Van Goethem B, Defauw P, Van Soens I, Polis I.** 2014. Anaphylaxis after intravenous administration of amoxicillin/clavulanic acid in two dogs under general anesthesia. Vlaams Diergeneeskd Tijdschr **83:**14–19.
7. **Boynes SG, Lemak AL, Skradski DM, Cuddy MA.** 2006. An allergic reaction following intramuscular administration of ketamine and midazolam. J Clin Pediatr Dent **31:**77–79. https://doi.org/10.17796/jcpd.31.2.6q619k3664634250.
8. **Brown SG.** 2004. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol **114:**371–376. https://doi.org/10.1016/j.jaci.2004.04.029.
9. **Bylund W, Delahanty L, Cooper M.** 2017. The case of ketamine allergy. Clin Pract Cases Emerg Med **1:**323–325. https://doi.org/10.5811/cpcem.2017.7.34405.
10. **Demoly P, Viola M, Gomes E, Romano A.** 2007. Epidemiology and causes of drug hypersensitivity, p 2–17. In: Pichler WJB, editor. Drug hypersensitivity. Basel (Switzerland): Karger. https://doi.org/10.1159/000104184
11. **Dippenaar JM, Naidoo S.** 2015. Allergic reactions and anaphylaxis during anaesthesia: review article. Curr Allergy Clin Immunol **28:**18–22.
12. **Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ.** 2007. Anaphylaxis during anaesthesia: diagnostic approach. Allergy **62:**471–487. https://doi.org/10.1111/j.1398-9995.2007.01347.x.
13. **Expert Panel of the American College of Toxicology.** 1985. 3 final report on the safety assessment of benzethonium chloride and methylbenzethonium chloride. J Am Coll Toxicol **4:**65–106. https://doi.org/10.3109/10915818509078687.
14. **Finkelman FD.** 2010. Peanut allergy and anaphylaxis. Curr Opin Immunol **22:**783–788. https://doi.org/10.1016/j.coi.2010.10.005.
15. **Flecknell P, Lofgren JLS, Dyson MC, Marini RR, Michael Swindle M, Wilson RP.** 2015. Preanesthesia, anesthesia, analgesia, and euthanasia, p 1135–1200. Chapter 24. In: Fox JG, Anderson LC, Otto GM, Pritchett-Corning KR, Whary MT, editors. Laboratory animal medicine, 3rd ed. Boston (MA): Academic Press.
16. **Fong A, Schuyler AJ, Platts-Mills TAE, Becker A.** 2015. Rapid onset anaphylaxis to red meat in three siblings from Uganda. J Allergy Clin Immunol **135 Suppl:** AB206. https://doi.org/10.1016/j.jaci.2014.12.1607.
17. **Gaber M, Abu Shawish HM, Khedr AM, Abed-Almonem KI.** 2012. Determination of benzalkonium chloride preservative in pharmaceutical formulation of eye and ear drops using new potentiometric sensors. Mater Sci Eng C Mater Biol Appl **32:**2299–2305. https://doi.org/10.1016/j.msec.2012.06.018.
18. **Hepner DL, Castells MC.** 2003. Anaphylaxis during the perioperative period. Anesth Analg **97:**1381–1395. https://doi.org/10.1213/01.ANE.0000082993.84883.7D.
19. **Izs ÓF.** 1950. [Anaphylaxis in hogs.] Casopis Ceskoslovenskych Veterinaru **5:**200–201.[Article in Undetermined Language].
20. **Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC.** 2004. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol **113:**832–836. https://doi.org/10.1016/j.jaci.2003.12.591.

21. **Karayan J, Lacoste L, Breuil K.** 1990. [Allergie à la ketamine]. Ann Fr Anesth Reanim **9:**396–397. https://doi.org/10.1016/S0750-7658(05)80256-4. [Article in French].
22. **Karila C, Brunet-Langot D, Labbez F, Jacqmarcq O, Ponvert C, Paupe J, Scheinmann P, de Blic J.** 2005. Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center. Allergy **60:**828–834. https://doi.org/10.1111/j.1398-9995.2005.00787.x.
23. **Khan BQ, Kemp SF.** 2011. Pathophysiology of anaphylaxis. Curr Opin Allergy Clin Immunol **11:**319–325. https://doi.org/10.1097/ACI.0b013e3283481ab6.
24. **Kroigaard M, Garvey LH, Gillberg L, Johansson SG, Mosbech H, Florvaag E, Harboe T, Eriksson LI, Dahlgren G, Seeman-Lodding H, Takala R, Wattwil M, Hirlekar G, Dahlen B, Guttormsen AB.** 2007. Scandinavian clinical practice guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. Acta Anaesthesiol Scand **51:**655–670. https://doi.org/10.1111/j.1399-6576.2007.01313.x.
25. **Kushner LI, Trim CM.** 1994. Suspected thiopental-induced anaphylaxis in a dog. J Am Anim Hosp Assoc **30:**451–456.
26. **Lagopoulos V, Gigi E.** 2011. Anaphylactic and anaphylactoid reactions during the perioperative period. Hippokratia **15:**138–140.
27. **Liccardi G, Lobefalo G, Di Florio E, Di Iorio C, Occhiochiuso L, Romano L, Savoia G, Massa RM, D'Amato G; Cardarelli Hospital Radiocontraast Medica and Anesthetic-Induced Anaphylaxis Prevention Working Group.** 2008. Strategies for the prevention of asthmatic, anaphylactic and anaphylactoid reactions during the administration of anesthetics and/or contrast media. J Investig Allergol Clin Immunol **18:**1–11.
28. **Linkenhoker JR, Burkholder TH, Linton CGG, Walden A, Abusakran-Monday KA, Rosero AP, Foltz CJ.** 2010. Effective and safe anesthesia for Yorkshire and Yucatan Swine with and without cardiovascular injury and intervention. J Am Assoc Lab Anim Sci **49:**344–351.
29. **Liu X, Zhang S, Tsai HJ, Hong X, Wang B, Fang Y, Liu X, Pongracic JA, Wang X**. 2009. Genetic and environmental contributions to allergen sensitization in a Chinese twin study. Clin Exp Allergy **39:**991–998. https://doi.org/10.1111/j.1365-2222.2009.03228.x
30. **Madsen T, Boyd H, Nylén D, Pedersen A, Petersen GI, Simonsen F.** 2001. Environmental and health assessment of substances in household detergents and cosmetic detergent products. Copenhagen: Danish Environmental Protection Agency.
31. **Marple B, Roland P, Benninger M.** 2004. Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. Otolaryngol Head Neck Surg **130:**131–141. https://doi.org/10.1016/j.otohns.2003.07.005.PubMed
32. **Mason TA.** 1976. Anaphylactic response to thiopentone in a dog. Vet Rec **98:**136. https://doi.org/10.1136/vr.98.7.136.
33. **Mathieu A, Goudsouzian N, Snider MT.** 1975. Reaction to ketamine: anaphylactoid or anaphylactic? Br J Anaesth **47:**624–627. https://doi.org/10.1093/bja/47.5.624.
34. **Mertes PM, Laxenaire MC, Alla F.** 2003. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology **99:**536–545. https://doi.org/10.1097/00000542-200309000-00007.
35. **Mertes PM, Laxenaire MC, Lienhart A, Aberer W, Ring J, Pichler WJ, Demoly P, Working Group for the SFAR; ENDA; EAACI Interest Group on Drug Hypersensitivity.** 2005. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. J Investig Allergol Clin Immunol **15:**91–101.
36. **Meyer EK.** 1997. Rare, idiosyncratic reaction to acepromazine in dogs. J Am Vet Med Assoc **210:**1114–1115.
37. **Mezger E, Wendler O, Mayr S, Bozzato A.** 2012. Anaphylactic reaction following administration of nose drops containing benzalkonium chloride. Head Face Med **8:**1–3. https://doi.org/10.1186/1746-160X-8-29.
38. **Michalska-Krzanowska G.** 2012. Anaphylactic reactions during anaesthesia and the perioperative period. Anaesthesiol Intensive Ther **44:**104–111.
39. **Nguyen TT, Baker B, Ferguson JD.** 2017. Allergic reaction to ketamine as monotherapy for procedural sedation. J Emerg Med **52:**562–564. https://doi.org/10.1016/j.jemermed.2016.09.020.
40. **Nwasor EO, Mshelbwala PM.** 2010. An unusual reaction to ketamine in a child. Annals of Nigerian medicine 28–30. https://doi.org/10.4103/0331-3131.73880.
41. **Okayama T, Matsuno Y, Yasuda N, Tsukui T, Suzuta Y, Koyanagi M, Sakaguchi M, Ishii Y, Olivry T, Masuda K.** 2011. Establishment of a quantitative ELISA for the measurement of allergen-specific IgE in dogs using anti-IgE antibody cross-reactive to mouse and dog IgE. Vet Immunol Immunopathol **139:**99–106. https://doi.org/10.1016/j.vetimm.2010.09.002.
42. **Onuma M, Terada M, Ono S, Murakami A, Ishida T, Sano T**. 2017. Incidence of anaphylactic reactions after propofol administration in dogs. J Vet Med Sci **79:**1446–1452. https://doi.org/10.1292/jvms.16-0550.
43. **Ozcan J, Nicholls K, Jones K**. 2016. Immunoglobulin e-mediated hypersensitivity reaction to ketamine. Pain Pract **16:**E94–E98. https://doi.org/10.1111/papr.12466.
44. **Pollard RE, Pascoe PJ.** 2008. Severe reaction to intravenous administration of an ionic iodinated contrast agent in two anesthetized dogs. J Am Vet Med Assoc **233:**274–278. https://doi.org/10.2460/javma.233.2.274.
45. **Raptopoulos D, Papazoglou L, Galatos A.** 1993. Suspected adverse reaction to xylazine-ketamine anesthesia in a cat. Feline practice **21:**27–30.
46. **Schwartz LB.** 2006. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin North Am **26:**451–463. https://doi.org/10.1016/j.iac.2006.05.010.
47. **Shmuel DL, Cortes Y.** 2013. Anaphylaxis in dogs and cats. J Vet Emerg Crit Care (San Antonio) **23:**377–394. https://doi.org/10.1111/vec.12066.
48. **Swindle MM, Smith AC.** 2015. Swine in the laboratory: surgery, anesthesia, imaging, and experimental techniques, 3rd ed. Boca Raton (FL): CRC press. https://doi.org/10.1201/b19430
49. **Szebeni J, Baranyi L, Sávay S, Bodó M, Milosevits J, Alving CR, Bünger R.** 2006. Complement activation-related cardiac anaphylaxis in pigs: role of C5a anaphylatoxin and adenosine in liposome-induced abnormalities in ECG and heart function. Am J Physiol Heart Circ Physiol **290:**H1050–H1058. https://doi.org/10.1152/ajpheart.00622.2005.
50. **Teich N.** 2011. Infliximab anaphylaxis in siblings. Inflamm Bowel Dis **17:**E108. https://doi.org/10.1002/ibd.21778.
51. **Teige J** Jr, **Nordstoga K.** 1977. Experimental anaphylaxis in pigs. The influence of the vitamin E content in the feed. Acta Vet Scand **18:**210–220.
52. **Thong BY, Tan TC.** 2011. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol **71:**684–700. https://doi.org/10.1111/j.1365-2125.2010.03774.x.
53. **Tsai HJ, Kumar R, Pongracic J, Liu X, Story R, Yu Y, Caruso D, Costello J, Schroeder A, Fang Y, Demirtas H, Meyer KE, O'Gorman MRG, Wang X**. 2009. Familial aggregation of food allergy and sensitization to food allergens: a family-based study. Clin Exp Allergy **39:**101–109. https://doi.org/10.1111/j.1365-2222.2008.03111.x. PubMed
54. **Turnquist SE, Bouchard G, Fischer JR.** 1993. Naturally occurring systemic anaphylactic and anaphylactoid reactions in four groups of pigs injected with commercially available bacterins. J Vet Diagn Invest **5:**103–105. https://doi.org/10.1177/104063879300500124.
55. **Vally H, Misso NLA.** 2012. Adverse reactions to the sulphite additives. Gastroenterol Hepatol Bed Bench **5:**16–23.
56. **Waechter RA.** 1982. Unusual reaction to acepromazine maleate in the dog. J Am Vet Med Assoc **180:**73–74.