A Protocol for the Emergency Treatment of Alpha-2 Agonist Overdose using Atipamezole, a Selective Alpha-2 Antagonist

M Greenberg, A Rama, J R Zuba

Abstract

Highly concentrated alpha-2 agonists such as medetomidine commonly used in veterinary anesthesia, can potentially cause significant harm or death if accidentally exposed to a human. Current treatments for alpha-2 agonist overdose in humans are nonspecific and unreliable. Atipamezole, a drug which is not FDA approved for human use, is a potent alpha-2 specific antagonist, which could be used as lifesaving therapy to reverse the adverse effects of an accidental alpha-2 agonist overdose. To develop a resuscitation algorithm using atipamezole for alpha-2 agonist overdose, we performed a literature review of atipamezole use in humans from 1970 to the present. We compared this to the data from atipamezole use in non-human primates and other wild animals. The results show that when compared to animals, humans require approximately 10 times less alpha-2 agonists for deep sedation, but 10 times more atipamezole for adequate reversal. Using this evidence based information, a resuscitation protocol, which includes the potential use of atipamezole in the field for emergency overdose is presented. When intensive care treatment is not available, atipamezole should be made available for intravenous or intramuscular administration in humans for life-threatening alpha 2-agonist overdose. The use of atipamezole in this circumstance could be lifesaving.

INTRODUCTION:

Accidental overdose (OD) with an alpha-2 agonist (a2a), such as dexmedetomidine (DEX) medetomidine (MED), or clonidine can potentially be life-threatening.[1-5] When using MED for large animal immobilizations, accidental overdose due to MED availability in high concentration, is especially worrisome for veterinarians and their staff. Life- threatening accidents with veterinary a2a's have been described in the literature.[1,6] The current management of accidental OD of a2a is primarily supportive care including; activated charcoal, tracheal intubation, mechanical ventilation, and administration of fluids and inotropes. Nonspecific alpha-2 antagonists (a2ANT) such as tolazoline, and naloxone an opioid antagonist, have also been tried with limited but unpredictable success.[7]

When using highly concentrated a2a's for anesthetizing wildlife in the field, the potential for fatal accidents in humans is concerning because there is no antidote. With MED supplied in a concentration up to 40 mg/ml (Wildlife Pharmaceuticals, Inc, Windsor, CO 80550 USA), an accidental dose of one milliliter is potentially 200 times an intravenous dose known to cause cardiac arrest in humans.[8] Atipamezole (AT) is a selective a2ANT, which competitively inhibits alpha-2 adrenergic receptors. AT is routinely used in animals anesthetized with a2a for the rapid reversal of sedation and analgesia.[9] AT has been studied in both unanesthetized and DEX sedated humans, and has been shown to be both safe and effective.[10-12] Review of the literature reveals that, compared to animals (including primates[13-15]), humans appear to be 10 times more sensitive to DEX, and approximately 10 times less sensitive to AT.

Using a literature review of the use of AT in humans and personal experience with its use in animals, we provide a scientific basis for the use of AT to reverse the adverse effects associated with an accidental human a2a overdose. We also provide an algorithm and recommended dosage for using atipamezole as a potential antidote for life-threating human a2a OD in the field or emergency department.

MATERIALS AND METHODS:

We performed a PubMed search from 1970 to 2017 for all information related to AT use in humans. We then compared the experimental AT dosing information obtained in human subjects with its clinical use in non-human primates and other animals. Using this information, we present a dosing range for human use as well as an algorithm for the emergent management of a2a OD.

RESULTS:

Human Research

Human research of AT use in healthy non-sedated and DEX sedated volunteers has been conducted. In 1990, Karhuvaara et al. studied the effect of intravenous AT in healthy, unanesthetized male volunteers at doses of 10, 30 and 100 mg.[11] The authors found that subjects receiving a 100 mg AT intravenous (IV) infusion over 20 minutes had increased plasma norepinephrine (NE) concentrations by 484 +/- 269 %, and elevated systolic and diastolic blood pressure (mean increases 17 +/- 7 and 14 +/- 2 mm Hg, respectively). There were minimal side effects, but some subjects noticed increased awareness, nervousness, shivering and sweating. Pentillä et al. also studied AT in healthy, male human volunteers and found when given by slow IV infusion there was a slight but measurable vagolytic effect on the heart, which was manifested in a reduction in heart rate variability related to respiration.[16] In addition, two other studies investigated prolactin secretion, and EEG/neuropsychological effects of AT on human subjects.[17,18]

The most relevant data comes from two studies on healthy, male volunteers (weighing 64-88 kg) given AT to reverse DEX sedation. In one study by Scheinin et al., human volunteers were exposed to 2.5 mcg/kg intramuscular (IM) DEX and then given 3 different doses of IV AT, one hour after the injection[19]. The IV AT was given at doses of 15, 50, 150 mcg/kg over 2 minutes which corresponds to AT/DEX ratios of 6:1, 20:1, and 60:1. The results show that 150 mcg/kg AT (AT/DEX ratio 60:1) fully reversed the sedative and cardiovascular effects, and significantly increased plasma NE above pre and post DEX sedation levels. The lower AT doses were partially effective, but only the highest dose was able to reverse all effects of the DEX.

In another study by Karhuvaara et al., the subjects received a fixed IV dose of DEX, given over 5 minutes (0.67 mcg/kg) that resulted in profound sedation.[12] IV AT at three different doses (6.7 mcg/kg, 27 mcg/kg and 67 mcg/kg) or saline placebo was then infused over 5 minutes. Only AT doses of 27 mcg/kg and 67 mcg/kg effectively reversed the sedation and hypotension in the volunteers. This correlated with ratio ranges of AT:DEX at 40:1 to 100:1. An AT/DEX ratio of 10:1 was not effective in reversing the effects of DEX.[10]

Veterinary Practice

MED, DEX, xylazine, and detomidine are a2a's used extensively in veterinary anesthesia and sedation.[9] Highly concentrated medetomidine (HcMED), available for use in large animals is supplied as 20 mg/ml, 40 mg/ml and as part of the injectable anesthetic BAMä (butorphanol, azaperone, MED) (Wildlife Pharmaceuticals, Inc, Windsor, CO 80550 USA). Since these drugs can be remotely delivered intramuscularly by a single dart, they are especially useful for immobilization of zoo and wildlife species (Figure 1). In addition to the need for remote delivery, concentrated anesthetics are a necessity because animals appear to be less sensitive to a2a's than humans, requiring up to 160 mcg/kg MED for adequate anesthesia.[9] MED and DEX are routinely used in humans' closest relatives, the great apes: gorillas, chimpanzees and orangutans. a2ANT's are routinely used at the end of a veterinary anesthetic to reverse the a2a for rapid recovery. AT is dosed on a milligram-to-milligram ratio relative to the amount of the a2a used for anesthesia. This reversal ratio is consistent in the veterinary literature, at approximately 5 times the MED dose (Figure 1). [20-27] [1](Footnote [1] Small domestic and non-domestic veterinary species can be easily IM hand injected but in the large, non-compliant and dangerous patients commonly seen in zoo and wildlife practice, these drugs must be remotely delivered by a single dart. Therefore, concentrated anesthetic agents, such as HcMED, are a necessity due to limited volume of the dart and a need for much higher doses of a2a than are required in human anesthesia.

Figure 1

Table of medetomidine (MED) dose and atipamezole (AT) reversal ratio in different species

Species	Anesthetic Agents	MED Dose (mcg/kg)	AT/ MED Ratio	References
Human (*Homo sapiens*)	Dexmeditomidine	1-2	20-50	Karhuvaara S 1991, Schelnin M 1998
Gorilla (*Gorilla gorilla*)	Ketamine-MED Midazolam	40	5:1	Wenger S, 2013
Orangutan (*Pongo borneo*)	Telazole-MED	20	5:1	Fahlman A, 2006
Common Marmoset (*Callithrix jacchus*)	Ketamine-MED	50	5:1	Bakker J, 2013
Giant Panda (*Ailuropoda malanoleuca*)	Ketamine-MED	40	5:1	Reed F, 2013
Giraffe (*Giraffa cameloparalis*)	Ketamine-MED	10-50	4:1	Lamberski N, 2013
Polar Bears (*(Ursus maritimus*)	Telazole-MED	75-160	5:1	Cattet M, 1999
Dog (*Canis lupus familiaris*)	MED	30	5:1	Sinclair M, 2003
Cat (*Felis catus*)	Ketamine-MED	40-80	4:1	Verstegen J, 1989

Accidental Overdose

The availability of highly concentrated forms of common anesthetic agents and safe remote delivery systems has revolutionized zoo and wildlife medicine. As an example, veterinarians are able to provide safe and effective anesthesia of a 6,000 kg elephant with a single 3-ml dart delivered intramuscularly from distances up to 50 meters from the ground or by helicopter. The amount of a potent opioid and a2a in the dart (for example: 20 mg etorphine plus 30 mg MED for a large elephant) is extremely dangerous and would certainly be fatal, if a human was accidentally exposed. Human error and failure to follow established safety protocols when handling dangerous anesthetic agents is a compelling concern of every zoo and wildlife veterinarian. Catastrophic exposure scenarios are possible, and can occur at several points before, during and after the animal immobilization. During dart preparation, accidental skin prick with a needle, or spray into the eyes or oral mucosa from a pressurized syringe can result in absorption of the drug into the body. Intramuscular deposition of the drug from a dart puncture during handling can result in exposure to a large dose of anesthetic. Accidental discharge of a dart-loaded gun could hit a human bystander.

Xylazine is another commonly used a2a in veterinary anesthesia.[9] It is less potent than MED and has been involved with numerous life-threatening exposures in humans. Intramuscular xylazine (100 mg/ml) exposures through accidental darts have resulted in bradycardia, hypotension, dizziness, and unconsciousness.[1] HcMED exposure has not been reported, but would be expected to be much more serious. The 40mg/ml concentration of MED used in zoo and wildlife anesthesia is equivalent to 200 times the highest concentration of DEX (0.1mg/ml) used in human practice. Furthermore, similar to what has been described in zoo and wildlife anesthesia using ultra potent opioids (UPO), if HcMED comes in contact with skin or mucous membranes, it could be absorbed causing adverse effects.[1] However, unlike the two most popular UPO's carfentanil (Wildnil) and etorphine (M99), which have naloxone as a reversal agent, there currently is no FDA approved antagonist for HcMED. Institutions that manage large animals using HcMED, have the potential for fatal accidental exposure incidents and many are seeking an emergency accidental a2a exposure protocol.[1,6]

Calculation of Atipamezole Dose Needed for Emergency Use in Humans

Determination of a potential human AT reversal dose for use in emergencies requires an estimate of how much AT would be both safe and effective using the known data from the human studies (Figure 2). As a reasonable comparison, MED and AT reversal doses commonly used in an example of non-human primate anesthesia are provided in Figure 3. Given an a2a OD scenario where the victim is in cardiac arrest, the dose of AT should be potent enough for cardiovascular rescue, with the lowest risk of toxicity. In the human AT trials, AT/DEX ratios of 60:1 up to 100:1 were found to be effective in reversing the cardiovascular and sedative effects of DEX.[12,19] AT was also shown to be relatively safe when given by IV infusion up to 100 mg, in unanesthetized subjects as described above.[10,11] In contrast, when used in non-human primates and other animals, effective doses of AT are commonly provided in dose ratios of AT/DEX of 10:1 (Figure 3). [2](Footnote 2)

The human trial data reveal that compared to animals including primates, humans require approximately 10 times less a2a such as DEX for deep sedation, and 10 times more AT for adequate reversal. It is also known that 100 mg AT is safe even in unanesthetized humans.

Figure 2

Review of human atipamezole studies (DEX: dexmedetomidine, AT: atipamezole, NE: norepinephrine) Karhuvaara S '90[11], Karhuvaara S '91[12], Scheinin H [19]

Human Atipamezole Studies: Review

KARHUVAARA 1990

-Single doses (10, 30, and 100 mg) of atipamezole were given to healthy volunteers.

-Minimal side effects: some increased alertness, nervousness, cold, sweating , shivering and tremors.

-100 mg increased NE levels, 30 mg had little effect, and 10 mg had no effect

KARHUVAARA 1991

Given to reverse 0.67 mcg/kg DEX   27 mcg/kg, 67 mcg/kg (40:1 and 100:1)

AT at 40:1 and 100:1 reversed sedation, increased NE levels, increased blood pressure. 10:1 had no effect

SCHEININ 1998

AT given to reverse 2.5 mcg/kg IM DEX.

15,50, 150 mcg/kg given 1 hr after dex 6:1, 20:1, and 60:1

150 mcg/kg 60:1 ratio reversed sedation, and increased Blood pressure

Figure 3

Sample anesthetic protocol for a Western Lowland Gorilla (Gorilla gorilla) using concentrated medetomidine with atipamezole reversal . Verstegen J,[26]


Sample Case :
Immobilization with Medetomidine + Ketamine

200 kg Western Lowland Gorilla *(Gorilla gorilla)*

Induction:

(30mcg/kg medetomidine + 5 mg/kg ketamine) x 200 kg animal = 6mg medetomidine +500mg ketamine
Induction: time to sternal recumbency: 6 minutes

Reversal

30 mg atipamezole (5:1 AT/ MED)
Emergence: time to sitting following typical 90 minute anesthetic for dental or health exam : 3-5 minutes

Figure 4

Alpha-2 agonist overdose resuscitation pathway [28, 45]
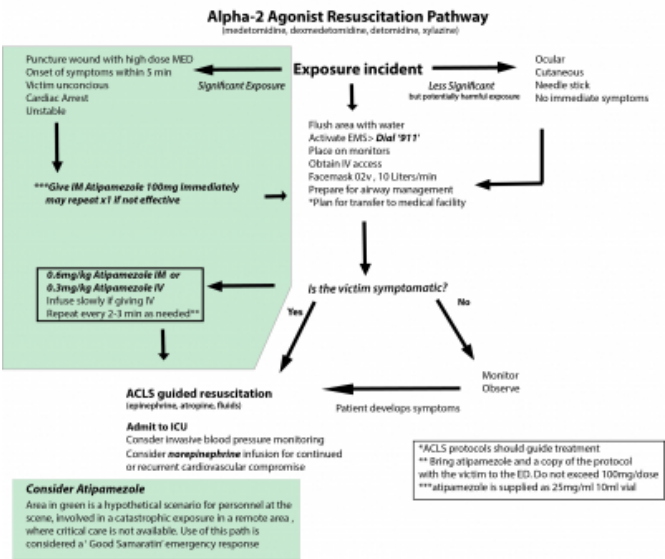
Alpha-2 agonist overdose resuscitation pathway

From the information reviewed above we have a devised a simple and practical algorithm for using AT in a human a2a OD emergency when other treatments are not available or are ineffective (Figure 4)[45]. For a significant a2a exposure where medical aid is not available, the rescuers should consider immediately giving 100 mg AT intramuscularly [3](Footnote 3). The absorption of AT when given by IM injection into a human should mimic that of a slow infusion, given its pharmacodynamics effect seen in animals.[9] AT is supplied by one manufacturer (Wildlife Pharmaceuticals, Inc, Windsor, CO 80550 USA) in 25mg/ml 10 ml vials, so a dose of 100mg would be 4 ml. The choice of injection site is not critical, but the drug is rapidly absorbed when injected deep in a large muscle such as the gluteus, quadriceps or deltoids.[29] Humans are relatively insensitive to AT compared to animals, so a single 100mg dose may not be adequate. Therefore, if the patient shows no response and remains in critical condition after the first AT dose, the rescue team should consider a second 100 mg IM dose. Individual doses of AT should not exceed 100mg, due to lack of human data. It is common practice in zoo and wildlife anesthesia to prepare reversal agents prior to the induction agents to ensure their availability for the procedure in case of an animal emergency (JRZ personal communication). Furthermore, in the event of significant accidental human exposure, these prepared reversal agents might be considered for rescue administration in a critically ill patient, if there is no other reasonable alternative. It is

important to note that although fatalities are rare in the human DEX OD experience, these incidents occur at hospitals where intensive care treatment including airway management, intravenous fluids and vasopressor infusions will be available. These therapies will not be available in the field.

In significant a2a OD as described above, the rescue team should follow the guidelines in Figure 4 and have the victim transported to a qualified medical center as soon as possible. If the patient arrives to the ED in cardiac arrest, the physicians should follow the standard ACLS protocol, which may include atropine, epinephrine or external pacing depending on the patients' cardiac rhythm.[28] Once the patient has been resuscitated, one should consider an infusion of norepinephrine to stabilize bradycardia and hypotension, as a2a pharmacologic effect is mediated through the NE and the adrenergic system.[28] Ongoing care should be managed in an intensive care unit, with invasive blood pressure monitoring.

If the victim is initially asymptomatic and the exposure was thought to be less serious, we have devised a per-kilogram dose of AT to be used after the initial resuscitation. This supplemental AT can be given when the patient develops symptoms, or for continued resuscitation of the initially 100 mg IM treated significant exposure victim when standard therapy fails. One should consider administering 0.3 mg/kg IV or 0.6mg/kg IM q 3-5 min, which is 24/48 mg of atipamezole for an 80 kg, adult human. The AT dose can be given in repeated doses, (not to exceed 100mg/dose), if needed, titrated to clinical effect. Given the research data that humans are relatively insensitive to AT, several extra doses may be required to reverse the clinical effects. The milligram per kilogram method of AT treatment may be more useful and safer than the ratio method of AT to a2a because of inherent inaccuracies with determining the exact dose received by the patient from an accidental exposure. If the overdose occurs in the hospital or emergency department, from a medication error or patient susceptibility, one should consider using a per-kilogram dose of AT for a patient in cardiac arrest, or who does not respond to standard medical therapy.

When the patient is brought to a medical facility, a member of the veterinary rescue team should accompany the patient, to provide essential information about the incident, and bring enough AT with the victim for potential use in the ED or ICU, as human hospitals will not have access to this drug. A copy of the protocol in Figure 4 would be helpful for the physicians caring for such a patient. It would also be helpful for veterinary teams working with HcMED to proactively meet with the local ED physicians or poison control center and review this protocol as an overall plan for management of a2a OD.

[1] Footnote 1: MED is a combination of both levo and dextrorotary isomers where DEX contains only the dextrorotary isomer, which is the active form that induces sedation. DEX is twice as potent MED on a milligram per milligram basis. A 10:1 mg: mg ratio of AT to DEX, would be equal to 5:1 mg ratio of AT to MED. Thus, DEX requires twice as much AT to achieve the same reversal effect as when MED is used as the a2a.

[2] Footnote 2: When using MED on primates a 5:1 AT/MED ratio is standard practice. Since DEX is 2x more potent than MED, this would correlate to a 10:1 AT/DEX ratio had DEX been used instead of MED.

[3] Footnote 3: Definition of Significant a2a exposure; accidental dart injection with any HcMED, exposure to any a2a, and the victim experiences symptoms within the first 5 min, any exposure with bradycardia and hypotension: patient is unstable, cardiac arrest develops during the event. Ocular, cutaneous hypodermic needle prick without injection are not considered significant.

DISCUSSION:

Alpha-2 agonist toxicity and overdose has been reported in the perioperative setting, emergency rooms, and critical care units.[30-39] It has also been documented following accidental exposure to xylazine, detomidine, alone or in combination with other anesthetic agents.[1] In one case of high dose xylazine overdose, the patient lost consciousness and experienced asystolic cardiac arrest.[40] After the initial resuscitation from cardiac arrest the patient continued to experience severe bradycardia. The patient recovered after 2 days of intensive care, which included mechanical ventilation, vasopressors and IV fluids. Due to the lack of an FDA approved antidote, accidental a2a exposure and fatal overdose is an overwhelming human health and safety concern for institutions and veterinary practitioners working with these agents. A survey of other previously unreported cases showed that even a very small exposure can result in symptoms.[1] With the concentration of MED being available

at 20 and 40 mg/ml, a typical anesthetic dose in a dart for a megavertebrate might have as much as 80 mg of MED. That is equivalent to 40,000 mcg of DEX. Without treatment, much smaller doses would likely result in fatal cardiac arrest.

Overdose with clonidine in human children and adults has been described in the literature and involves a wide range of symptoms including depressed sensorium, bradycardia, hypotension, hypothermia, recurrent seizures, atrioventricular conduction defects, arrhythmias, and rarely apnea.[30-32] A review of the case series and reports in the literature also highlight adverse effects with use of DEX[33-38]. These effects range from prolonged sedation to profound hemodynamic instability. Hypotension and bradycardia progressing to cardiac arrest has been described.

The current treatment of a2a OD is supportive and non-specific. Reported emergency therapy for accidental clonidine and DEX overdoses include basic airway management and hemodynamic support with fluid and inotropes. Naloxone and atropine have been used with limited success.[3,4,7] Yohimbine, which has high affinity for alpha 2 receptors and moderate affinity for alpha 1 receptors, has been investigated as a treatment for clonidine overdose.[31] It is widely used in animals and is effective at reversing the anesthetic effects of a2a. However, hypertension, tachycardia, and arrhythmias have been reported with its use.[31] In addition, yohimbine is not available for intravenous use in humans, thus would not be helpful in an accidental a2a OD. However, a veterinary preparation for IV/IM use is available. In an emergency a2a OD, parenteral yohimbine, like AT would likely be successful in reversing cardiac arrest. Tolazoline, a non-specific alpha-1 and alpha-2 blocker, available for parenteral use in humans has been used to reverse refractory hypotension associated with clonidine.[39] However compared to yohimbine and AT, tolazoline has the least affinity for all types of alpha-2 receptors and does not reliably reverse alpha-2 caused hypotension.[41]

Since during most large animal immobilizations, a combination of anesthetic agents are used, additional antagonists will be required for resuscitation of an accidentally darted human. UPOs, even in minute quantities, will cause respiratory depression and loss of consciousness, requiring naloxone to resuscitate the patient. When using BAM, even with reversal of the a2a and the opioid component of the mixture, the victim may still not immediately regain consciousness due to the non-reversible azaperone component. One should also expect the possibility of a more rapid and profound sedation and cardiovascular depressive effect when using a combined agent. Knowledge of the dart contents is critically important to the receiving emergency physicians. Having a member of the veterinary team accompany the patient to provide details will be critical to a successful outcome.

While the above recommendations are currently directed at the specific case of accidental exposure to potent veterinary a2a, use of AT would be equally useful in cases of symptomatic DEX, or clonidine overdose, which occur at the hospital. The use of AT with the dosing schedule described in Figure 4, would be useful for the ED, OR and ICU in major medical centers, as the use of DEX increases and overdoses become more common. Although not currently available at human medical facilities or licensed by the FDA, having the pharmacy stock AT for compassionate use with the protocol in Figure 4 could be lifesaving in extreme overdose situations. We recommend more research into the use of AT in humans, as a potential antidote in clonidine and DEX poisonings.

Even with a detailed examination of the human AT data, using this drug clinically in humans represents many unknowns. In the one study where AT was used on humans during surgery, the dosages were low.[42] Since an accidental exposure dose of a2a may be massive, the ultimate dose of AT to reverse the clinical effects may also be very large. Due to the lack of clinical data, it is not known if the dose of AT recommended in Figure 4 would be effective. However, there may be instances in which quick decisions must be made to resuscitate a person exposed to high doses of MED or DEX and its use should be considered. Using an a2ANT where the a2a plasma levels are extremely high may be problematic. DEX has been shown to cause transient hypertension, either from a1 or a2b binding.[43,44] While AT is highly alpha-2 receptor specific, it is possible that the unopposed a1/a2b agonist activity of MED, even though very weak, may be clinically relevant at very high doses. This could lead to unwanted hypertension. In these cases invasive blood pressure monitoring will be essential to allow rapid treatment of hemodynamic derangements. Infusions of antihypertensive agents, such as nitroprusside, or nicardipine may be used to acutely lower blood pressure. Theoretically, beta-blockers should be avoided to prevent unopposed alpha blocking effects of MED. The half-life of AT in humans is

approximately 2 hours, which correlates with the half-life of DEX.[12] However with large MED exposures, it is possible that the a2a effect may out last the AT with recurrence of symptoms, highlighting the need for repeat doses of AT and monitoring in intensive care. Clearly the most significant limitation to the current review is the lack of clinical research data in massive doses of MED and other a2a and their effects on humans. We would encourage further research on animals on the effects on veterinary doses of a2a and the dose effect of AT on reversing the clinical effects. Also, since AT is not FDA approved for use in humans, its use even in life threatening situations has medical-legal and ethical implications. We hope that in the future, further research will be done in humans or as an animal exemption to define the use of AT for FDA approval perhaps as an orphan drug for use in emergency situations.

CONCLUSION:

The current management of accidental overdose of a2a's with a specific antagonist is lacking. Currently used antidote agents including naloxone, tolazoline, are nonspecific and can have unpredictable outcomes. Accidental HcMED in a setting where there is no immediate intensive care available would be life-threatening. An emergency protocol for the resuscitation of an overdose of a2a's with a specific receptor antagonist is needed for remote field accidents. While clinical experience of using atipamezole in humans is limited, its use in non-human primates and other veterinary species is extensive and proven to be highly effective. Using the existing data from the human trials we have a created a pathway for emergency resuscitation of an a2a OD using AT. We recommend having atipamezole available at major medical centers for compassionate human use, while more studies are performed.

Conflicts of interest: none

References

1. Haymerle A, Fahlman A, Walzer C. Human exposures to immobilizing agents: results of an online survey. Vet Rec. 20120;167(9):327-32.
2. Anderson RJ, Hart GR, Crumpler CP, Lerman MJ. Clonidine overdose: report of six cases and review of the literature. Ann Emerg Med. 1981;10(2):107-12.
3. Nath S, Singh S, Pawar S. Dexmedetomidine overdosage: An unusual presentation . Indian J Anaesth. 2013 May-Jun; 57(3): 289–291.
4. Wiley JF, Wiley CC, Torrey SB, Henretig FM. Clonidine poisoning in young children. J Pediatr. 1990;116(4):654-8.
5. Jorden VS, Pousman RM, Sanford MM, Thorborg PA, Hutchens MP. Dexmedetomidine overdose in the perioperative setting. Ann Pharmacother. 2004;38(5):803-7.
6. Kreeger, T. J., and J. M. Arnemo. 2012. Handbook of Wildlife Chemical Immobilization. Fourth Edition. Eds. Kreeger, T. J., and J. M. Arnemo. Laramie, Wyoming.
7. https://www.uptodate.com/contents/clonidine-and-related-imidazoline-poisoning. Kevin C Osterhoudt, MD, MS. May 29, 2017
8. Bharati S, Pal A, Biswas C, Biswas R. Incidence of cardiac arrest increases with the indiscriminate use of dexmedetomidine: a case series and review of published case reports. Acta Anaesthesiol Taiwan. 2011;49(4):165-7.
9. Lysa P. Posner and Patrick Burns. 2013. Sedative Agents: Tranquilizers, Alpha-2 Agonists, and Related Agents. In: Veterinary Pharmacology and Therapeutics, Ninth Edition. Eds. Jim E. Riviere, and Mark G. Papich. Pp 337-380.
10. Karhuvaara,S.,Kallio,A.,Scheinin,M.,Koulu,M.,Scheinin,H.&Viikari,J. Tolerability and effects of atipamezole, a novel alpha2-adrenoceptor antagonist in healthy male volunteers. An open dose-finding study.Curr.Ther.Res. 1989; 45,633-642
11. Karhuvaara S, Kallio A, Scheinin M, Anttila M, Salonen JS, Scheinin H. Pharmacological effects and pharmacokinetics of atipamezole, a novel alpha 2-adrenoceptor antagonist--a randomized, double-blind cross-over study in healthy male volunteers. Br J Clin Pharmacol. 1990;30(1):97-106.
12. Karhuvaara S, Kallio A, Salonen M, Tuominen J, Scheinin M. Rapid reversal of alpha 2-adrenoceptor agonist effects by atipamezole in human volunteers. Br J Clin Pharmacol. 1991;31(2):160-5.
13. Wenger S, Hoby S, Wyss F, Adami C, Wenker C. 2013. Anaesthesia with medetomidine, midazolam and ketamine in six gorillas after premedication with oral zuclopenthixol dihydrochloride. Vet Anaesth Analg. 40(2):176-80.
14. Adami, C., C. Wenker, S. Hoby, and A. Bergadano. 2012. Evaluation of effectiveness, safety and reliability of intramuscular medetomidine-ketamine for captive great apes. Vet Rec.171(8):196.
15. Cerveny, S., and J. Sleeman. 2014. Great Ape Anesthesia. In: Zoo Animal and Wildlife Immobilization and Anesthesia, 2nd Edition. Eds. Gary West, Darryl Heard, and Nigel Caulkett. Pp. 573-584.
16. Penttilä J, Kaila T, Helminen A, et al. Effects of atipamezole--a selective alpha-adrenoceptor antagonist--on cardiac parasympathetic regulation in human subjects. Auton Autacoid Pharmacol. 2004;24(3):69-75.
17. Karhuvaara S, Kallio A, Koulu M, Scheinin H, Scheinin M. No involvement of alpha 2-adrenoceptors in the regulation of basal prolactin secretion in healthy men. Psychoneuroendocrinology. 1990;15(2):125-9.
18. Mervaala E, Alhainen K, Helkala EL, et al. Electrophysiological and neuropsychological effects of a central alpha 2-antagonist atipamezole in healthy volunteers. Behav Brain Res. 1993;55(1):85-91.
19. Scheinin H, Aantaa R, Anttila M, Hakola P, Helminen A, Karhuvaara S. Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific alpha2-adrenoceptor antagonist atipamezole: a pharmacodynamic and kinetic study in healthy volunteers. Anesthesiology. 1998;89(3):574-84.
20. Wenger S, Hoby S, Wyss F, Adami C, Wenker C. Anaesthesia with medetomidine, midazolam and ketamine in

six gorillas after premedication with oral zuclopenthixol dihydrochloride. Vet Anaesth Analg. 2013;40(2):176-80.

21. Fahlman A, Bosi EJ, Nyman G. Reversible anesthesia of Southeast Asian primates with medetomidine, zolazepam, and tiletamine. J Zoo Wildl Med. 2006;37(4):558-61.

22. Bakker J, Uilenreef JJ, Pelt ER, Brok HP, Remarque EJ, Langermans JA. Comparison of three different sedative-anaesthetic protocols (ketamine, ketamine-medetomidine and alphaxalone) in common marmosets (Callithrix jacchus). BMC Vet Res. 2013;9:113.

23. Reed F, Gregson R, Girling S, Pizzi R, Clutton RE. Anaesthesia of a captive, male giant panda (Ailuropoda melanoleuca). Vet Anaesth Analg. 2013;40(1):103-4.

24. Lamberski N / Newell, A. / Radcliffe, R. W. Thirty immobilizations of captive Giraffe (Giraffa camelopardalis) using a combination of medetomidine and ketamine. American Association of Zoo Veterinarians; health and conservation of captive and free-ranging wildlife; 121-123, 2006

25. Cattet MR, Caulkett NA, Polischuk SC, Ramsay MA. Reversible immobilization of free-ranging polar bears with medetomidine-zolazepam-tiletamine and atipamezole. J Wildl Dis. 1997;33(3):611-7.

26. Sinclair MD. A review of the physiological effects of alpha2-agonists related to the clinical use of medetomidine in small animal practice. Can Vet J. 2003;44(11):885-97.

27. Verstegen J, Fargetton X, Zanker S, Donnay I, Ectors F. Antagonistic activities of atipamezole, 4-aminopyridine and yohimbine against medetomidine/ketamine-induced anaesthesia in cats. Vet Rec. 1991;128(3):57-60.

28. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(18 Suppl 2):S444-64.

29. Plumb DC. Plumb's Veterinary Drug Handbook. John Wiley & Sons; 2015.

30. Anderson RJ, Hart GR, Crumpler CP, Lerman MJ. Clonidine overdose: report of six cases and review of the literature. Ann Emerg Med. 1981;10(2):107-12.

31. Roberge RJ, Mcguire SP, Krenzelok EP. Yohimbine as an antidote for clonidine overdose. Am J Emerg Med. 1996;14(7):678-80.

32. Wiley JF, Wiley CC, Torrey SB, Henretig FM. Clonidine poisoning in young children. J Pediatr. 1990;116(4):654-8.

33. Bharati S, Pal A, Biswas C, Biswas R. Incidence of cardiac arrest increases with the indiscriminate use of dexmedetomidine: a case series and review of published case reports. Acta Anaesthesiol Taiwan. 2011;49(4):165-7.

34. Nagasaka Y, Machino A, Fujikake K, Kawamoto E, Wakamatsu M. [Cardiac arrest induced by dexmedetomidine]. Masui. 2009;58(8):987-9.

35. Zhang X, Schmidt U, Wain JC, Bigatello L. Bradycardia leading to asystole during dexmedetomidine infusion in an 18 year-old double-lung transplant recipient. J Clin Anesth. 2010;22(1):45-9.

36. Ingersoll-weng E, Manecke GR, Thistlethwaite PA. Dexmedetomidine and cardiac arrest. Anesthesiology. 2004;100(3):738-9.

37. Shah AN, Koneru J, Nicoara A, Goldfeder LB, Thomas K, Ehlert FA. Dexmedetomidine related cardiac arrest in a patient with permanent pacemaker; a cautionary tale. Pacing Clin Electrophysiol. 2007;30(9):1158-60.

38. Sichrovsky TC, Mittal S, Steinberg JS. Dexmedetomidine sedation leading to refractory cardiogenic shock. Anesth Analg. 2008;106(6):1784-6.

39. Schieber RA, Kaufman ND. Use of tolazoline in massive clonidine poisoning. Am J Dis Child. 1981;135(1):77-8.

40. Hoffmann U, Meister CM, Golle K, Zschiesche M. Severe intoxication with the veterinary tranquilizer xylazine in humans. J Anal Toxicol. 2001;25(4):245-9.

41. Schwartz DD, Clark TP. Selectivity of atipamezole, yohimbine and tolazoline for alpha-2 adrenergic receptor subtypes: implications for clinical reversal of alpha-2 adrenergic receptor mediated sedation in sheep. J Vet Pharmacol Ther. 1998;21(5):342-7.

42. Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Comparison of dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. J Clin Anesth. 1993;5(3):194-203.

43. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. Eur J Pharmacol. 1988;150(1-2)

44. Soria C, Greenberg M, Brzenski A. Paradoxical Hypertension Following Administration Of Dexmedetomidine During Embolization Of A Congenital Arteriovenous Malformation In A 15-Month-Old Male. The Internet Journal of Anesthesiology. 2016 Volume 35 Number 1

45. Greenberg M, Rama A, Zuba J. Atipamezole as an Emergency Treatment for Overdose from Highly Concentrated Alpha-2 Agonists Used in Zoo and Wildlife Anesthesia. AM J Emergency MED. 2017, in press.

Author Information

Mark Greenberg, MD

Department of Anesthesiology, University of California, San Diego, UCSD Medical Center

San Diego, CA, USA

Asheen Rama, MD

Department of Anesthesiology, University of California, San Diego, UCSD Medical Center

San Diego, CA, USA

Jeffery R Zuba, DVM

Department of Veterinary Services, San Diego Zoo Safari Park, San Diego Zoo Global

San Diego, CA, USA