❖ PEER-REVIEWED

Breathe with ease when managing beta$_2$ agonist inhaler toxicoses in dogs

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Combine more than 14.6 million asthmatic people in the United States[1] with more than 61.5 million playful pet dogs,[2] and it's a sure bet that some curious Fidos will bite into their owners' life-saving inhalers.

Many metered dose inhalers contain selective beta$_2$ agonist medications that provide fast relief of bronchoconstriction in people. Examples of beta$_2$ agonists include albuterol (also known as salbutamol), metaproterenol, pirbuterol, isoetharine, terbutaline, and bitolterol.[3] Trade names include Ventolin HFA (albuterol sulfate HFA inhalation aerosol—GlaxoSmithKline), Combivent (ipratropium bromide and albuterol sulfate—Boehringer Ingelheim), and Alupent (metaproterenol sulfate USP—Boehringer Ingelheim).[4]

These relatively short-acting pharmaceuticals are delivered by chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellants,[5] which are critical to the intoxication of dogs that bite into the pressurized canister. An accidental exposure delivers not the indicated metered dose but potentially the entire inhaler's contents instantaneously. If appropriate veterinary care is provided, the acute toxicosis caused by these synthetic sympathomimetic amines is rarely fatal in otherwise healthy dogs (ASPCA APCC Database: Unpublished data, November 2001–May 2007).

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MECHANISM OF ACTION

At therapeutic dosages, selective beta$_2$ agonists target beta$_2$ receptors on bronchial smooth muscle, resulting in bronchodilation via cyclic adenosine monophosphate produced as a result of the activation of adenylate cyclase. A similar relaxation effect is seen with uterine, gastrointestinal, and vascular smooth muscle. Beta$_2$ receptors are also present in skeletal muscle, the liver, and the heart. At therapeutic doses, beta$_2$ agonists have minimal beta$_1$ effects.[6] Additionally, serum potassium concentrations may decrease transiently as a result of intracellular translocation due to stimulation of Na^+,K^+-ATPase.[7]

TOXICOSIS

Toxic dose

Extrapolating from the nebulization dose in dogs,[6] an appropriate dose of albuterol for a 60-lb (27.2-kg) dog is 2.5 mg (equivalent to 91.9 µg/kg) four times a day. According to GlaxoSmithKline, a full Ventolin HFA 90-µg metered dose inhaler weighing 18 g contains 28.8 mg of albuterol sulfate.[8] Thus, a 60-lb dog that punctures a full canister can be acutely exposed to about 10 times the therapeutic dose through inhalation, ingestion, or a combination of these two routes.

Beta$_1$, beta$_2$, and catecholamine effects

The selective beta$_2$ agonists lose their selectivity with overdosages, resulting in undesirable beta$_1$ (cardiac) effects in addition to excessive beta$_2$ activity.[3] Direct activation of beta$_1$ receptors results in positive inotropic and chronotropic effects on the heart (ASPCA APCC Database: Unpublished data, November 2001–May 2007). A secondary catecholamine surge also contributes to the development of tachycardia and possible hypertension (ASPCA APCC Data-

base: Unpublished data, November 2001–May 2007).[9] Excessive peripheral vasodilation mediated by beta$_2$ receptor activity typically predominates, however, resulting in a hypotensive state, potentiating the tachycardia via reflex mechanisms. Premature ventricular contractions and other arrhythmias (intermittent or sustained ventricular tachycardia, atrioventricular block, extreme sinus tachycardia, R on T phenomenon) may occur.[5] The CFCs dichlorodifluoromethane and trichloromonofluoromethane can also contribute to cardiotoxicity at high doses[5] by sensitizing the myocardium.[9] Additional evidence of the potential damage to the myocardium includes the development of cardiac fibrosis with or without mineralization of papillary muscles in dogs experimentally exposed to aerosolized albuterol daily for two weeks (dose range 16 to 64 µg/L).[10] Rarely, rupture of the chordae tendineae and subsequent pulmonary edema may be seen.[9]

Tremors are caused by overstimulation of skeletal muscle beta$_2$ receptors.[9] Seizures are uncommon but possible (ASPCA APCC Database: Unpublished data, November 2001–May 2007). Behavioral changes such as anxiety, restlessness, and apprehension may occur in response to the acute sympathetic stimulation (ASPCA APCC Database: Unpublished data, November 2001–May 2007). In the absence of pulmonary edema, changes in respiratory rate and character are also likely a result of increased sympathetic tone. Weakness and lethargy have been reported, particularly later in the course of the toxicosis when initial signs were untreated (ASPCA APCC Database: Unpublished data, November 2001–May 2007).

CLINICAL FINDINGS REPORTED TO THE ASPCA APCC

The ASPCA Animal Poison Control Center (APCC) has consulted on 414 public cases of dogs accidentally exposed to beta$_2$ agonist inhalers from November 2001 through May 2007 (*Table 1*) (ASPCA APCC Database: Unpublished data, November 2001–May 2007). These data represent accidental situations in which the exposure was witnessed or evidence substantiated drug exposure (a punctured canister).

Of the 414 cases, none of the patients was reported to have died, but death is possible, particularly if underlying cardiac disease is present, veterinary attention is not sought, or the exposure is potentiated by the concurrent use of drugs such as tricyclic antidepressants (*e.g.* clomipramine, imipramine, amitriptyline), monoamine oxidase inhibitors (*e.g.* selegiline), or digoxin.[6] Tricyclic antidepressants

TABLE 1

Clinical Findings in Dogs Accidentally Exposed to Inhalers Containing Beta$_2$ Agonist Drugs*

Clinical Findings	Number of Patients	Percentage of Total Patients (total of 414)
Cardiac Stimulation		
Tachycardia	293	70.8
Premature ventricular contractions	19	4.6
	312	**75.4**
Decreased Energy Level		
Lethargy	96	23.2
Weakness	22	5.3
Depression	9	2.2
Listlessness	5	1.2
	132	**31.9**
Respiratory Stimulation		
Tachypnea	55	13.3
Panting	29	7
Dyspnea	6	1.4
Labored breathing	4	1
Shallow breathing	3	0.7
	97	**23.4**
CNS Stimulation		
Agitation	42	10.1
Hyperactivity	25	6
Restlessness	19	4.6
Pacing	5	1.2
Anxiety	5	1.2
Aggression	3	0.7
Apprehension	2	0.5
Hiding	2	0.5
	103	**24.8**
Other		
Vomiting	79	19.1
Trembling/tremors	54	13
Hypokalemia	28	6.8
	161	**38.9**

*Reported to the ASPCA APCC November 2001 through May 2007.

can cause dysrhythmias even when given therapeutically. Monoamine oxidases are responsible for catecholamine degradation; inhibiting them allows for greater secondary catecholamine effects.

The most common clinical findings seen with beta$_2$ agonist inhaler toxicoses can be grouped into general categories:

- Cardiac stimulation (tachycardia, premature ventricular contractions)
- Decreased energy level (lethargy, weakness)
- Respiratory stimulation (tachypnea, panting)
- Behavioral changes associated with central nervous system stimulation (aggression, agitation)
- Vomiting and trembling or tremors.

Hypokalemia was documented in just 3% of cases. Twenty patients (3%) were reported to have no clinical signs at the time of consultation with the ASPCA APCC. This lack of clinical signs could be attributable to a low level of drug present in the canister or a lack of follow-up as a result of successfully managing subsequent clinical signs.

CLINICAL PATHOLOGY

Hypokalemia as a result of an intracellular shift can be severe in an acute toxicosis with albuterol and related drugs. Life-threatening arrhythmias and profound muscle weakness are possible sequelae of severe hypokalemia.[6] Among the 414 inhaler toxicosis cases, the lowest reported potassium concentration was 1.76 mEq/L (reference range = 3.8 to 5.1 mEq/L[6]) (ASPCA APCC Database: Unpublished data, November 2001–May 2007). Because the total body potassium is not depleted with this toxicosis, it is critical to monitor serum potassium for a rebound hyperkalemia as the effect of the beta$_2$ agonist wanes and the potassium redistributes to the blood.

Hypophosphatemia is a rare finding (ASPCA APCC Database: Unpublished data, November 2001–May 2007) that likely represents intracellular translocation. It may be due to the beta$_2$ agonist action itself or to secondary responses including increased catecholamine and insulin release or respiratory alkalosis.[7,11] Hypophosphatemia can potentiate cardiac arrhythmias and predispose the patient to hemolysis because of loss of red blood cell membrane integrity.[11] Most cases of hypophosphatemia spontaneously resolve once the underlying cause is removed. In severe cases (serum phosphorus concentrations < 1 mg/dl; reference range = 2.5 to 6.2 mg/dl[6]), intravenous supplementation with sodium or potassium phosphate may be necessary.[11]

Hyperglycemia and hypomagnesemia have also been associated with beta$_2$ agonist toxicosis but rarely need to be specifically addressed.[9]

Sinus tachycardia exceeding 180 to 200 beats/min, sustained ventricular tachycardia, or severe hypokalemia requires treatment.

TREATMENT

Because peak plasma concentrations are achieved as quickly as five minutes after inhalation,[6] decontamination by inducing emesis or by administering activated charcoal or a sorbitol cathartic is not recommended for patients exposed to beta$_2$ agonist inhalers.

Fluid therapy and monitoring

Many patients can be managed with supportive care such as intravenous fluids, but severe exposures may require more aggressive therapy. Heart rate, rhythm, and blood pressure need to be closely monitored. If catecholamine-induced hypertension predominates, cautious fluid administration is warranted. Continuous electrocardiography is recommended.[12] Sinus tachycardia exceeding 180 to 200 beats/min, other life-threatening arrhythmias

TABLE 2

Dosage Guidelines for Pharmaceuticals Useful in Beta$_2$ Agonist Intoxicated Dogs*

Pharmaceutical	Dosage
Propranolol	0.02 mg/kg IV slowly (maximum of 1 mg/kg)
Metoprolol	0.2–0.4 mg/kg b.i.d. orally
Diazepam	0.2–0.6 mg/kg IV (to effect)
Lidocaine	2–4 mg/kg slow IV bolus to effect

*Source: Plumb DC. *Veterinary drug handbook*. 5th ed. Stockholm, Wis: PharmaVet Inc, 2005;238,461,522,637.

such as sustained ventricular tachycardia, or severe hypokalemia requires treatment.[5]

Meticulous monitoring of serum potassium throughout the toxicosis period is warranted; check it every two hours unless there is a clinical indication to check it sooner (*e.g.* change in heart rate or rhythm indicating potassium aberrations, bradycardia due to hyperkalemia).

Beta antagonists, diazepam, and lidocaine

A nonselective beta antagonist such as propranolol can be given to reverse both $beta_1$ and $beta_2$ effects. Because the norepinephrine release associated with beta agonists is primarily mediated by $beta_2$ activity,[13] propranolol is a good choice to minimize secondary catecholamine effects such as behavioral aberrations. Diazepam may also be used to alleviate anxiety, hyperactivity, muscle tremors, and rare seizures. Metoprolol, a selective $beta_1$ antagonist, is an alternative to propranolol to normalize the heart rate.[5] Ventricular tachycardia may be treated with either propranolol or lidocaine.[6] *Table 2* provides dosage guidelines for drugs useful in $beta_2$ agonist intoxicated patients.

Potassium

Monitor the serum potassium concentration closely, and provide supplemental potassium according to the severity of hypokalemia (*Table 3*).[12] Keep in mind, however, that a rebound hyperkalemia can ensue after aggressive potassium supplementation because of extracellular translocation of potassium as the toxicosis abates. Patients treated with propranolol may also have an increase in serum potassium because of propranolol's direct effects.[6]

Duration of signs

The endpoint of therapy is resolution of the abnormal clinical findings. We can estimate the duration of signs based on exposure evidence and metabolism and excretion data extrapolated from human exposure. The plasma half-life in people for inhaled albuterol is about 3.8 hours (1.7- to 7.1-hour range in a separate study).[14] Albuterol is metabolized in the liver to the relatively inactive albuterol 4'-O-sulfate. Excretion of the parent drug and metabolites occurs rapidly, predominantly through the kidneys,[14] but about 10% is excreted in the feces.[9] Most dogs with mild signs recover within 12 hours of exposure with appropriate supportive care, but signs can persist for 24 to 48 hours with large overdoses.

TABLE 3

Guidelines for Intravenous Potassium Supplementation Based on Serum Potassium Concentrations*

Serum Potassium (mEq/L)	Potassium Chloride (mEq/L) to Add to 1 L of Fluids	Maximum Rate (ml/lb/hr) (maximum of 0.5 mEq/kg/hr)
3.6–5	20	12
3.1–3.5	30	8
2.6–3	40	5.5
2.1–2.5	60	4
< 2	80	3

*Source: Macintire DK. Metabolic derangements in critical patients, in *Proceedings*. Am Coll Vet Intern Med, 2003.

SUMMARY

The immediate delivery of massive amounts of $beta_2$ agonists from inhalers punctured by dogs warrants prompt veterinary attention. Clinical signs reported in such exposures are fairly predictable; lethargy, tachypnea, agitation, and trembling are among the most common. Tachycardia is the most consistent clinical finding. Be aware of the potential for this type of toxicosis and recognize it as a possible cause when signs consistent with $beta_2$ agonist overdose are encountered. With appropriate monitoring of vital signs and electrolytes, supportive care, and administration of pharmaceuticals to mitigate the adverse effects, toxicoses due to albuterol and other $beta_2$ agonists can be managed successfully. However, when existing cardiac disease is present or the toxicosis is compounded by the concurrent use of tricyclic antidepressants, monoamine oxidase inhibitors, or digoxin, complications such as cardiac decompensation or sudden death may occur. ❖

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