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Successful management of suspected minoxidil toxicosis in a cat following accidental dermal exposure

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Abstract: Minoxidil was originally introduced as a potent vasodilator, but is now widely used as a topical treatment for human alopecia. A 4-year-old neutered male Norwegian Forest cat presented with a 2-day history of anorexia, lethargy, and dyspnoea. A physical examination revealed hypothermia, tachypnoea, hypotension, and bilateral pulmonary crackles. The radiographs revealed pulmonary oedema and pleural effusions. The hypotension and pleural effusions exacerbated despite the supportive therapy, and the underlying cause remained undetermined. A further medical inquiry revealed the cat had been exposed to a topical minoxidil solution 3 days before admission. Accordingly, minoxidil toxicosis was managed using both i.v. fluids and vasopressors. Dopamine and norepinephrine were infused for 3 days to normalise the patient's blood pressure and related clinical signs. The cat recovered fully and was discharged 6 days after the minoxidil exposure. This is the first report on the successful management of minoxidil toxicosis in a cat. To broaden our knowledge of minoxidil toxicosis in cats, we have also described the serial changes in the clinical findings of this cat over the treatment period. Furthermore, on the basis of the experience gained from this case, we suggest an optimised management plan for future cases of feline minoxidil toxicosis.

Keywords: dopamine; echocardiography; norepinephrine; radiography; ultrasonography

Minoxidil was originally prescribed as an oral medication for refractory hypertension. Interestingly, hypertrichosis was a commonly observed side effect of minoxidil (Mehta et al. 1975); hence, it became a treatment option for human alopecia (Messenger and Rundegren 2004). Currently, minoxidil is one of the most popular anti-alopecia medications, and topical formulations are available over-the-counter in many countries. Since the conventional dosage of topical minoxidil is insufficient to cause systemic adverse events in humans, topical minoxidil poisoning has not been well-described (Smorlesi et al. 2003; Scarinci et al. 2012). However, owing to its easy availability, systemic toxicosis associated with its ingestion has been reported in humans (Farrell and Epstein 1999). Moreover, household pets are at risk of minoxidil poisoning from dermal or oral exposure. To date, only a few cases of accidental exposure to a topical minoxidil solution have been documented in the veterinary literature (DeClementi et al. 2004; Jordan et al. 2018). Minoxidil toxicosis (MXT) induces severe hypotension, which, in turn, leads to cardiovascular damage and even death. These toxicological effects of minoxidil are well-described in experimental studies (Herman et al. 1979; Mesfin et al. 1989); however, no compelling research suggests an optimal treatment strategy for MXT. Only one previous report documented MXT in two household cats following dermal applications and offered a potential management plan

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(DeClementi et al. 2004). Unfortunately, both cats died immediately after admission despite supportive treatment (undescribed). Herein, we report the first case of the successful management of MXT in a cat following dermal exposure to a topical minoxidil solution. To broaden our knowledge of MXT in cats, we also describe the serial changes in the clinical findings of the patient over the treatment period. Furthermore, on the basis of the experience gained from this case, we suggest an optimised management plan for future cases of feline MXT.

Case description

A 4-year-old neutered male Norwegian Forest cat, weighing 4 kg, was presented with a 2-day history of anorexia, lethargy, and dyspnoea. A complete physical examination revealed hypothermia (rectal temperature, 35.0 °C; reference range: 38.0–39.5 °C), normocardia (160 bpm; reference range: 140–200 bpm), tachypnoea (respiratory rate, 108 bpm; reference range: 20–30 bpm), hypotension [Doppler-derived systolic arterial pressure (SAP), 80 mmHg; reference range: 90–168 mmHg], and bilateral pulmonary crackles (Tim 2014). The cat was responsive and euhydrated on a skin turgor test.

The results of a complete blood cell count (ProCyte Dx; IDEXX Laboratories, Westbrook, ME, USA) were unremarkable. A serum biochemical analysis (PT10V; Samsung, Suwon, Republic of Korea) revealed an elevated alanine aminotransferase activity (6.22 μkat/l; reference range: 0.22–1.85 μkat/l), blood glucose concentration (16.15 mmol/l; reference range: 4.11–8.44 mmol/l), amylase activity (24.4μkat/l; reference range: 8.5–23.8 μkat/l), and lipase activity (0.67 μkat/l; reference range: 0–0.53 μkat/l), but low total calcium (2.2 mmol/l; reference range: 2.22–3.14 mmol/l), hyponatraemia (138 mmol/l; reference range: 150–165 mmol/l), and hypochloraemia (111 mmol/l; reference range: 112–129 mmol/l). A feline pancreatic lipase SNAP test (IDEXX Laboratories, Westbrook, ME, USA) result was within the normal reference range. Radiographs revealed diffuse interstitial pulmonary oedema and bilateral pleural effusions (Figure 1A).

After the initial examination, two boluses of furosemide (2 mg/kg, Lasix; Handok Inc., Seoul, Republic of Korea) were intravenously (i.v.) administered at 1-h intervals to relieve the pleural effusions. Given the absence of systemic inflammation, a constant rate infusion (CRI) of dobutamine (Dobutamine HCl; Myungmoon Pharm., Seoul, Republic of Korea) was initiated at 2 μg/kg/min to improve the fluid retention and hypotension. The rate was later increased to 5 μg/kg/min. The patient showed transient improvement in the respiratory rate to 48 bpm and SAP to 90 mmHg. Another physical examina-

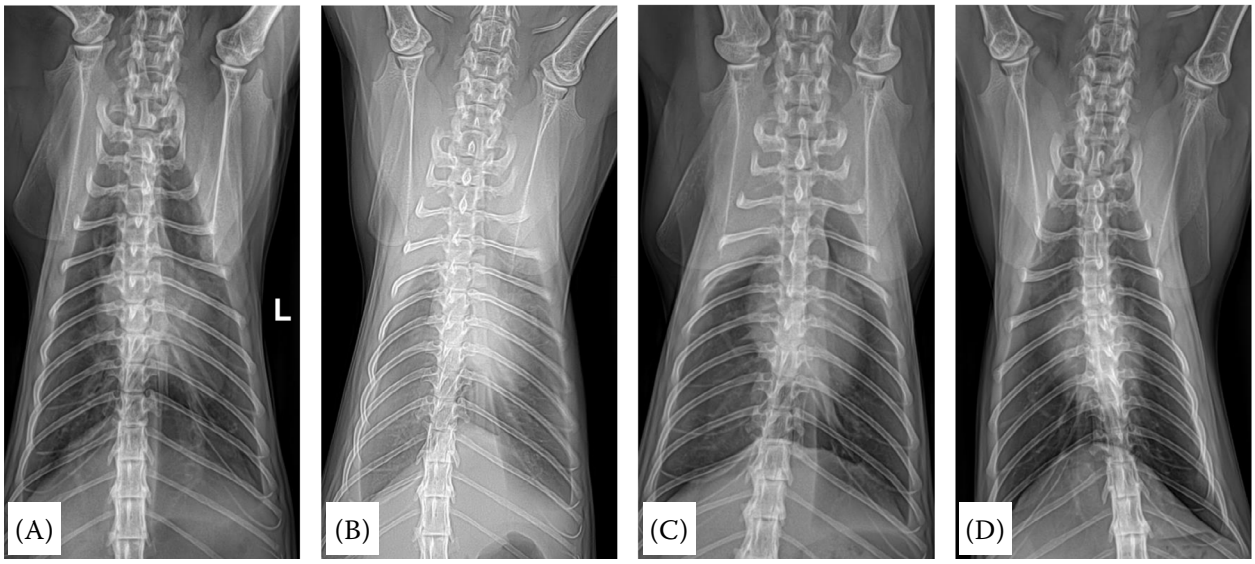

Figure 1. Serial chest radiographic images of the cat with minoxidil toxicosis
Chest radiography at admission (A) shows a diffuse interstitial pulmonary oedema and bilateral pleural effusions. The effusions worsen on hospital day 2 (B). After instituting appropriate vasopressor therapy, pleural effusions improve on hospital day 3 (C). Pleural effusions completely resolve on the follow-up evaluation at 7 days after discharge (D)
L = left

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Table 1. Echocardiographic variables of a cat with minoxidil toxicosis

Variable	Value	Reference values[1]
LA/Ao ratio	1.28	0.88–1.70
IVSd (cm)	0.55	0.30–0.60
IVSs (cm)	0.52	0.40–0.90
LVIDd (cm)	1.13	1.12–2.18
LVIDs (cm)	0.52[2]	0.64–1.68
LVPWd (cm)	0.61[2]	0.25–0.60
LVPWs (cm)	0.69	0.43–0.98
FS (%)	53.85	40.00–67.00
EF (%)	88.13	55.00–85.00

[1]Reference values (Boon 2011); [2]Echocardiographic variables show a slight decrease in LVIDs and increase in LVPWd, which is attributable to dehydration (pseudohypertrophy)
EF = ejection fraction; FS = fractional shortening; IVSd = interventricular septum in diastole; IVSs = interventricular septum in systole; LA/Ao = left atrium/aorta; LVIDd = left ventricular internal diameter in diastole; LVIDs = left ventricular internal diameter in systole; LVPWd = left ventricular posterior wall in diastole; LVPWs = left ventricular posterior wall in systole

tion performed 12 h after the treatment initiation revealed dehydration (6–8%), hypothermia (36.2 °C), tachycardia (210 bpm), and exacerbation of the hypotension (58 mmHg) and dyspnoea (72 bpm). The cat showed dullness and weight loss (3.7 kg). We suspected a distributive and hypovolaemic shock status due to the systemic hypotension in conjunction with the diuresis. No additional furosemide and dobutamine were administered. Fluid resuscitation was performed using lactated Ringer's solution (total volume, 15 ml/kg) over 15 min, followed by rehydration (5 ml/kg/h) over 12 h, but the cat remained hypotensive with an SAP of 70 mmHg.

Additional examinations were performed to determine the underlying cause. Repeat radiographs (Figure 1B) revealed the pleural effusion had advanced. A thoracocentesis analysis revealed a transudate with a total protein value of 24 g/l and total nucleated cell count of 149 cells/µl. The echocardiographic findings were unremarkable except for a slight increase in the left ventricular ejection fraction (Table 1). These findings were supported by the normal result of the plasma N-terminal probrain natriuretic peptide test (SNAP Feline proBNP Test; IDEXX Laboratories, Westbrook, ME, USA). The heartworm antigen test (SNAP Feline Heartworm Test; IDEXX Laboratories, Westbrook, ME, USA) result was also negative. The ultrasonography revealed peritoneal fluid (Figure 2A) and a diseased gastrointestinal tract with a generalised functional ileus and corrugated small intestine (Figure 2B). To exclude feline infectious peritonitis, a real-time polymerase chain reaction (PCR) test was performed on a pleural effusion sample (IDEXX Laboratories, Westbrook, ME, USA), but it yielded negative results.

Further consultation with the owner revealed that a drop of a topical 5% minoxidil solution had accidentally dropped on the upper neck area of the patient 3 days before admission. Accordingly, we diagnosed the cat with MXT and accompanying hypotension.

The hypotension was managed using both fluid infusion and vasopressors. After partial fluid resuscitation, a CRI of dopamine (Dopamine HCl; Huons, Gyeonggi, Republic of Korea) was started at 1 µg/kg/min. The rate was increased in 1-µg/kg/min increments by titrating at approximately 15-min intervals until a rate of 5 µg/kg/min was reached. Although the SAP increased, it remained below the target range of > 90 mmHg for 1 hour. The heart rate ranged from 160 bpm to 190 bpm. A CRI of norepinephrine (Norpin; Dalim Biotech, Seoul, Republic of Korea) was newly added at 0.05 µg/kg/min to increase the SAP to > 90 mmHg. The CRI of norepinephrine was increased in 0.05 µg/kg/min increments by titrating at approximately 15-min intervals on the basis of serial SAP measurements until a rate of 0.2 µg/kg/min was reached. We progressively stabilised the SAP to between 90 and 100 mmHg two hours after starting the norepinephrine CRI. The heart rate decreased to between 156 and 174 bpm. Thereafter, the cat was administered metoclopramide (0.2 mg/kg, i.v. q8 h, Mekool inj.; Jeil Pharm, Daegu, Republic of Korea) to manage the gastrointestinal hypomotility, and metronidazole (10 mg/kg, p.o. q12 h, Flasinyl; CJ Pharma Corp., Seoul, Republic of Korea) to relieve the inflammation of the small intestine (Willard 1993). The vigilance, hypothermia, and tachycardia improved over the following 24 hours. The respiratory rate gradually decreased, but the mild tachypnoea and pleural effusion (Figure 1C) persisted.

We decided to continue administering vasopressors and performed the palliative removal of the pleural effusion. After rehydration over 24 h, maintenance fluid therapy was continued to improve

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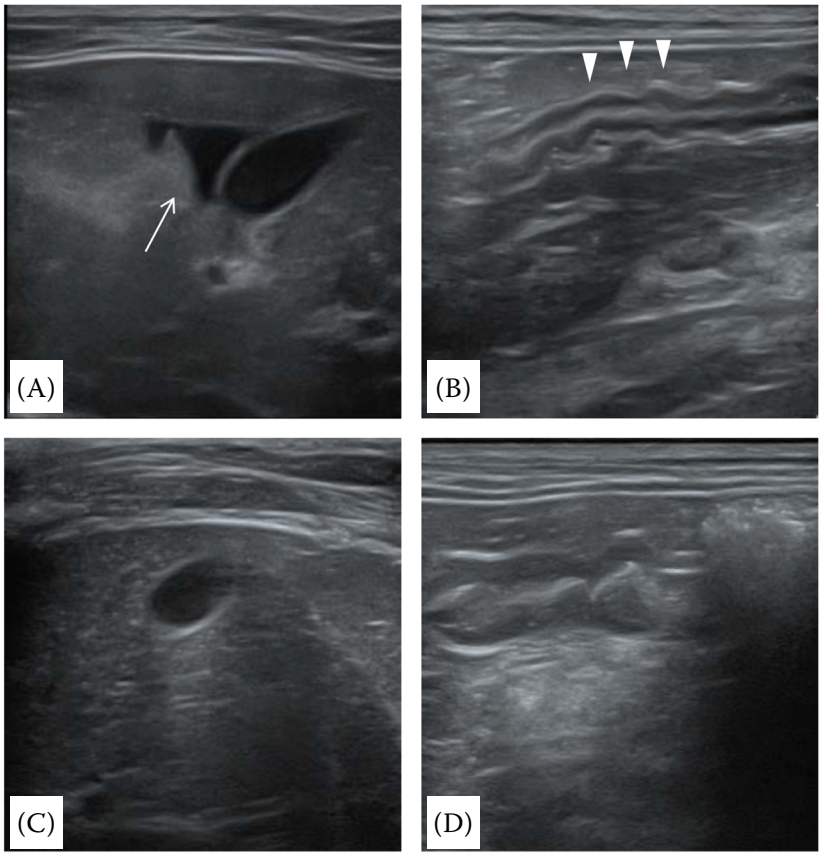

Figure 2. Abdominal ultrasonographic images at the initial assessment and follow-up examination
A small amount of anechoic free peritoneal fluid (arrow) is seen adjacent to the gall bladder (A). Corrugation of the small intestine (arrowheads) is seen on the longitudinal section of the proximal part of the duodenum (B). By 72 h after instituting appropriate vasopressor therapy, the peritoneal fluid (C) and corrugated small intestine (D) are no longer detected on the ultrasonography

the haemodynamics and urinary excretion of minoxidil. By 48 h after initiating the vasopressor treatment, the abnormalities noted on the physical examination had entirely normalised, including the blood pressure (110 mmHg) and respiratory rate (24 bpm), and the cat started feeding. The CRI of vasopressors was gradually tapered to the lowest effective dose required to maintain a normal SAP. All the treatments were discontinued approximately 72 h after initiating the vasopressor treatment, and the SAP remained stable between 110 and 120 mmHg without any intervention. No other abnormalities were found on a complete physical examination. A repeat blood examination revealed normalised biochemical parameters. The ascites and gastrointestinal lesions had also completely resolved (Figure 2C, D). The repeat echocardiography revealed normal findings. The cat returned to its normal condition and was discharged.

A follow-up examination performed 7 days after discharge revealed no clinical abnormalities, and the pleural effusion had completely resolved on the repeat chest radiographs (Figure 1D). The improvements were well-maintained at a 3-month follow-up.

DISCUSSION

The vasodilatory function of minoxidil is related to its ATP-sensitive potassium channel opening property (Meisheri et al. 1988). It stimulates the potassium channels in the arteriolar vascular smooth muscle cells, causing their relaxation and enhancing vascular permeability. Like other antihypertensive drugs, minoxidil produces sustained vascular relaxation and hypotension, leading to secondary reflex cardiac stimulation and vasodilatory oedema (Jett et al. 1988; Messerli 2002). Orally ingested minoxidil can induce a hypotensive effect lasting more than 24 h in both humans and dogs (Lowenthal and Affrime 1980; Mesfin et al. 1995). Despite the lack of pharmacokinetic evidence, studies suggested that cats were more likely to develop MXT than were other species owing to hepatic enzymatic differences in feline species (Oates 1996; DeClementi et al. 2004). The topical administration of minoxidil allows the slow and regulated absorption and is, hence, considered safe and effective. Topically applied minoxidil can also be absorbed into the systemic circulation (McEvoy 2000), but adverse effects have not been reported in humans and dogs.

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However, the cases of two cats reported previously (DeClementi et al. 2004) and the current case confirmed that even mild dermal exposure to minoxidil could cause severe systemic disease. All three cats were hospitalised approximately 3 days after dermal exposure to topical minoxidil when their clinical signs became evident. During the peak phase of the symptoms, the cats showed similar clinical signs, such as hypothermia, dyspnoea, and hypotension, and the diagnoses of pulmonary oedema and pleural effusion were confirmed. Both cats in the previous case series died a few hours (10 and 15 h) after hospitalisation despite supportive care. In contrast, the present cat responded relatively well to the aggressive supportive therapy, and the interval between diagnosis and discharge was approximately 3 days. Therefore, we surmised that the topically applied minoxidil is slowly absorbed systemically and exerts a persistent adverse effect in cats. The duration of a single-dose effect of a topical minoxidil solution may be at least 3 days after exposure. However, the exact pharmacokinetic properties remain elusive in cats.

The cardiotoxicity of minoxidil is due to its haemodynamic effects rather than direct cardiotoxicity (Mesfin et al. 1995). Canine experimental studies on minoxidil cardiotoxicity documented many changes in the pathological findings and echocardiographic parameters (Mesfin et al. 1989; Hanton et al. 2004). Various cardiac lesions due to MXT are related to vasodilation-induced ischemic injury and cardiac stimulation-induced myocardial hyperperfusion and hypoxia. Only post-mortem histopathological changes in the heart, including myocardial ischemia, myocardial interstitial oedema, myodegeneration, and myocarditis, have been documented in two cats (DeClementi et al. 2004). Although the possibility of the echocardiography being affected by the drug used or hydration status could not be excluded, we described the echocardiographic findings of a cat with MXT. The slight increase in left ventricular ejection fraction was considered a reflex increase in cardiac contraction due to a reduction in the systemic vascular tone. This minimal echocardiographic change suggested that the early cardiac changes did not progress and could not be detected on the echocardiography. However, an increase in cardiac contractility in cats can be sustained and exacerbated because of the long-term effect of minoxidil, which can eventually induce cardiac problems such as ischemic myocardial injury and hypertrophic cardiomyopathy. Therefore, early intervention might effectively prevent further cardiac adverse events from MXT. However, the echocardiographic assessment may not properly represent the cardiac changes in cats with MXT; hence, further data are needed on minoxidil cardiotoxicity in cats.

Therapy for MXT should focus on clinical sign-based supportive care, as targeted antidotes are unavailable. Significant absorption of minoxidil (molecular weight of 209.251 g/mol; log*P* of 1.33; volume of distribution of 2–3 l/kg; no protein bound; solubility in water < 1) into the systemic circulation necessitates specific treatment methods, including haemodialysis and i.v. lipid emulsion injection (McEvoy 2000; Jordan et al. 2018), but no objective data are available. Supportive care mainly includes effusion management for short-term relief from respiratory failure and blood pressure support to counteract the vasodilatory effect of minoxidil.

In the present case, we tried to minimise the respiratory burden via oxygen supplementation, furosemide therapy, and thoracentesis. Due to the patient's symptoms (euhydration, pulmonary oedema, pleural effusion, and hypotension), furosemide and dobutamine were initially used. However, these treatments could not correct the vasodilatory oedema and only temporarily improved the respiratory signs. In addition, furosemide eventually caused body fluid loss, which resulted in an exacerbated hypotensive status. We thus recommend conservative furosemide therapy in cats in the unstable phase of MXT and close monitoring of the fluid status after fluid removal.

Our observations show that the therapy should focus on maintaining a normal vascular tone, since most of the side effects are due to the vasodilatory effect of minoxidil. Blood pressure support is achieved by carefully administering vasopressors. Because we were initially unsure if the cat was exposed to minoxidil, the furosemide and dobutamine therapies were started assuming a decrease in the cardiac performance (low output heart failure). This treatment likely improved the third-space fluid loss transiently by improving the cardiac circulation, but did not affect the vasodilatory effect of MXT. Dopamine infusion was initiated after confirming the diagnosis. A medium dosage of dopamine infusion had a favourable effect on the blood pressure, but the heart rate was not

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stabilised. The infusion was titrated at a maximum rate of 5 μg/kg/min and was not increased further to prevent the concomitant cardiac-stimulating effect of dopamine (Pascoe et al. 2006). A norepinephrine infusion, which exerts a more potent α1-adrenergic effect than dopaminedoes (Edward 2013), was then added to offset the strong vasodilation from minoxidil. Although norepinephrine also has a modest β1-adrenergic activity (Steve 2014), it successfully managed the hypotension and stabilised the tachycardia. Accordingly, we suggest that α1-adrenergic activation should be maximised to combat the hypotensive crisis in MXT. Furthermore, since α-adrenoceptor-mediated increases in systemic vascular resistance can mitigate reflex cardiac stimulation induced by sympathetic activity, a certain degree of β-adrenergic agonist activity would not adversely affect the patient outcome. Additionally, pure α-agonists without β activity, such as phenylephrine or midodrine, may be promising alternatives for managing MXT in cats.

Besides causing cardiac damage, minoxidil-induced systemic vasodilation may affect organs vulnerable to circulatory compromise. The present cat showed some changes in the blood chemistry values at the initial evaluation, and these were best explained by hepatic and pancreatic hypoperfusion or hypoxic injury from systemic hypotension. Previous studies on MXT did not report gastrointestinal adverse effects. One dog showed immediate vomiting only after oral exposure to minoxidil (Jordan et al. 2018). The present cat showed obvious ascites, gastrointestinal corrugation, and a functional ileus, which improved with recovery. The gastrointestinal effects may be explained by a systemic vasodilation-induced bowel-wall ischemia (Moon et al. 2003). Therefore, vascular tone-related organ damage should be suspected and managed in cats with MXT.

Owing to the lack of distinctive features and information about topical MXT, we did not suspect the cat was exposed to minoxidil at the initial presentation. The diagnosis was finally made via a consultation-based approach about one day later. Thus, we could not immediately wash the exposed surface of the patient to prevent further absorption of minoxidil.

Accordingly, we recommend that MXT should be suspected in cats with sustained idiopathic systemic hypotension. Furthermore, in such cats, exposed skin areas should be detected first via a thorough physical examination and suspicious areas should be cleaned immediately with an appropriate detergent (liquid dishwashing detergent). An Elizabethan collar should also be used to prevent additional oral exposure.

The major limitations of this report are that we did not document any serial electrocardiographic (ECG) recordings and serum minoxidil concentrations. In humans and dogs, ECG recordings have been advocated because of the potential ECG changes (tachycardia) in MXT (Poff and Rose 1992; Jordan et al. 2018).

Moreover, ECG abnormalities in cats with MXT are unknown. Tachycardia was identified in the present case, but it was milder than that in dogs (Mesfin et al. 1996; Hanton et al. 2004; Jordan et al. 2018). The tachycardia likely did not significantly affect the disease course in this cat. We thus predicted a difference between cats and dogs in the reflex cardiac response to minoxidil, but an exact explanation is warranted.

We report the first feline case of the successful clinical management of MXT following dermal exposure to a topical minoxidil solution. Even a small dose of topical minoxidil is slowly absorbed systemically and can exert significant and prolonged adverse vasodilatory events in cats.

Given the widespread use of minoxidil, MXT should be suspected in cats with non-definable and sustained hypotension and pleural effusions. Minoxidil-induced systemic vasodilation may also affect organs vulnerable to circulatory compromise. Therapy should focus on maintaining a normal vascular tone and promoting the excretion of minoxidil.

Vasopressors with a strong α1-adrenergic activity may effectively combat the life-threatening hypotensive crisis in MXT. Affected cats may need a few days of in-hospital treatment for full recovery. In summary, management of MXT following dermal exposure should start from bathing a patient with a liquid dishwashing detergent to prevent further absorption of minoxidil. If the pleural effusion causes the respiratory symptoms, a thoracocentesis would be a good option for relieving the patients. Overt hypotension should be managed using both i.v. fluid infusion and one or more vasopressors with potent α1-adrenergic effects (e.g., dopamine, norepinephrine, phenylephrine, midodrine) until complete elimination of the drug effects.

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Conflict of interest

The authors declare no conflict of interest.

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