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Case Report

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Intravenous lipid emulsion and dexmedetomidine for treatment of feline permethrin intoxication: a report from 4 cases

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Abstract
Four cases of feline permethrin intoxication are described. The cause of intoxication is the application of canine permethrin spot-on product (Advantix®, Bayer) by the owners. Principal clinical guidelines recommends the use of anticonvulsant drugs to treat seizures or neurological symptoms after initial stabilization and dermal decontamination. The use of lipid emulsion had an increasing interest in the last decade for treatment of toxicosis caused by lipophylic drugs as reported in human and in veterinary medical practices. All cats presented in this study, were treated with intravenous lipid emulsion (ILE) at variable dosages, and dexmedetomidine was also administered by intravenous way. No adverse reaction such as thrombophlebitis, overload circulation or others was noticed during and after administration of ILE. Dexmedetomidine was proved to be helpful in tranquillizing the cats. All cats were discharged in good condition faster than other cases treated without their use.
Keywords: Cat, Dexmedetomidine, Intravenous lipid emulsion, Permethrin.

Introduction

Permethrin toxicity is one of the most common cat toxicities reported by the Animal Poison Control Center (ASPCA) (Merola and Dunayer, 2006). Permethrin toxicity is also the most common toxicity cases reported in cats in Italy (Richardson, 2000; Giuliano and Nebbia, 2004; Caloni *et al*., 2012, 2014). The majority of feline permethrin intoxications are believed to be due to owners applying canine products. Exposure can also occur after oral ingestion or direct contact with treated dogs (Richardson, 2000). Pyrethrins are naturally occurring esters of chrysantheic acid and pyrethric extracted from the flowers of *Chrisanthemum cinerariifolium*. Pyrethroids are synthetic analogues of pyrethrins. Permethrin is a class I pyrethroid insecticide which was first described in 1973 (Meyer, 1999).

They act on sodium ion channels and keep them open for a longer period of time. As a consequence they cause repetitive discharging of the cell and clinical signs of toxicity. Permethrins are metabolized by hepatic microsomial esterases and oxidases. This is followed by hydroxylation and conjugation into glucuronides or sulphates, which are mainly eliminated in urine. Although the reason why cats are particularly sensitive to permethrins is not fully understood, a species-related deficiency in glucoronyl transferase pathway has been postulated. Acting primarily on central nervous system (CNS), clinical signs are characterized by tremors, muscle fasciculations, twiching, hypersalivation, mydriasis, pyrexia and in severe cases, seizures and coma (Meyer, 1999). Intravenous lipid emulsion (ILE) is an emerging treatment for certain lipophilic drugs (O'Brien *et al*., 2010; Fernandez *et al*., 2011; Gwaltney-Brant and Meadows, 2012; Kaplan and Whelan, 2012; Kidwell *et al*., 2014). As permethrins are very lipophilic molecules (Sangester, 1997), ILE was supposed to be a potential treatment. Some cases about the use of ILE in permethrin intoxication in cats were reported (Haworth and Smart, 2012; Kuo and Odunayo, 2013; DeGroot, 2014). General guidelines for treatment of permethrin intoxication in cats suggest the use of anticonvulsant drugs to control seizures or muscle fasciculations, dermal decontamination with lukewarm water and the use of methocarbamol, as well as a centrally acting muscle relaxant to treat tremors (Schildt and Jutkowitz, 2009). Alpha$_2$ (α_2) agonists have been used in veterinary medicine since the mid-80'. The sedative effect of α_2 agonists is due to the inhibitory action on the major noradrenergic nucleus in the brainstem, *locus ceruleus*. Their muscle relaxant effect is well known in animals (Lemke, 2007) and their use revealed helpful, in these specific cases reported.

In this report we evaluated the association of ILE and dexmedetomidine (DXMDT) for the treatment of permethrin intoxication in 4 cats.

Case 1

A 5-year-old, 2.5 Kg, spayed female, domestic European short hair cat, was presented for twitching and muscle tremors after the owner applied a topical permethrin flea product containing 1 gr/Lt imidacloprid and 500 g/Lt of permethrin in a 1 ml pipette (Advantix spot-on for 4-10 kg dogs. Bayer AG, Leverkusen, Germany) 2 hours

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prior to presentation, for a total toxic dose of permethrin of 200 mg/kg. At presentation the cat was tachypnoic (respiratory rate of 52 breaths per minute), heart rhythm was 128 beats per minute, oral membranes were pink and rectal temperature was 38.5°C (Table 1). The cat was depressed and indifferent and had convulsions after few minutes (Table 2). Cat was washed with a mild detergent and two endovenous catheters were placed at both cephalic veins. Micro-Hct and total protein were evaluated (Table 3). Ringer lactate solution infusion was started at 3 times the maintenance dose (6 ml/kg/h) for maintaining hydration and promote diuresis. Due to the severity of tremors, a single IV bolus of propofol (Proposure 10 mg/ml solution, Merial Italia, Milano- Italy) was given at 1 mg/kg. Then DXMDT (Dexdomitor 0.5 mg/ml solution for dogs and cats. Orion Corporation, Espoo, Finland) was administered IV at 1 µg/kg. After administration cat was quieter and tremors were reduced. Oxygen was given via face mask and it was well tolerated. ILE (Intralipid 20% IV Fat Emulsion, Fresenius Kabi, Canada) bolus was administered using the second venous access at 2 ml/kg in 3 minutes, followed by a constant rate infusion at 4 ml/kg/h for one hour. After the first hour the cat was reassessed and, because of persisting twitching, ILE infusion continued again for 2 hours. Two hours later facial twitching reduced, respiratory rhythm slowed to 40 bpm and rectal temperature reduced to 37.9 °C. As the cat was not able to stand up, still unresponsive to surrounding stimulus, with mild tremors, ILE infusion was still continued for another 2 hours at 2 ml/kg/h, for a total time of 5 hours (Table 4). After this time neurological symptoms improved and temperature, heart rate, mucous membranes were within normal limit. Little facial twitching was still present and the animal was ataxic. On day 2 the cat still presented facial twitching, presented mild ataxia no tremors were observed and the animal was alert and eating without any problems. In the afternoon of the same day the cat was discharged after 26 hours after presentation. During hospitalization the cat also received: amoxicilline and clavulanic acid (Synulox injectable suspension, 140 mg/ml amoxicilline+ 35 mg/ml clavulanic acid, Pfizer Italia Srl, Rome-Italy) at 12.5 mg/kg and ranitidine (Ranitidine 50 mg/5ml injectable solution, HEXAL S.p.a, Agrate Brianza (MB), Italy) at 2 mg/kg. Cat was discharged with antibiotic therapy (amoxicilline and clavulanic 12.5 mg/kg for a week). On follow-up for 10 months later, the owner had not noticed any abnormalities and the cat was well.

Case 2

A 14-year-old, 5 Kg female spayed European domestic short hair cat presented to Veterinary Teaching Hospital for lameness, muscle fasciculation, tremors and hypersalivation. A 25 ml pipette of Advantix, containing 250 mg of imidacloprid and 1250 mg of permethrin, was applied by the owner half an hour prior the presentation at clinical examination; for a toxic dose of 250 mg/kg. The cat was referred by colleagues that

Table 1. Vital signs of the four cats at the arrival in the emergency department.

Cats	*HR (bpm)*	*RR (Bpm)*	*MC*	*MRT (sec)*	*RT (°C)*
Cat 1	128	52	Pink	<2	38.5
Cat 2	140	48	Pale	<2	39.2
Cat 3	160	40	Pink	<2	<33
Cat 4	200	70	Pale	<2	37.7

bpm: Beats per minute; Bpm: Breaths per minute; sec: Seconds; °C: Celsius.

Table 2. Incidence of main neurological signs in four cats.

Neurological signs	*Cat affected*
Convulsions	C1, C3
Twitching	C1, C2, C4
Tremors	C1, C2 (still present after 24 h), C3
Salivation	C2, C3
Ataxia	C2, C3 (after 24 h)
Mydriasis	C4
Muscle fasciculations	C3, C4
Hypothermia	C3
Tachypnoea	C1, C2, C3, C4

C: Cat.

Table 3. Minimum emergency data base performed at arrival for treated cats.

Parameters	*C1**	*C2*	*C3*	*C4*	*References values*
Hct (%)	37	33.8	17.8	28.3	37.0-55
TP (g/dL)	6.5	6.4	8	7	5.8-7.8
Alb (g/dL)	"n/a"	2.7	2.6	"n/a"	2.6-4.1
Glucose (mg/dl)	"n/a"	291	118	94	80-125
Alt (U/I)	"n/a"	41	46	68	20-70
Crea (mg/dl)	"n/a"	1.5	1.3	1.4	0.6-1.5
PH	"n/a"	7.28	7.39	7.32	7.28-7.41
Na+ (mEq/L)	"n/a"	148	148	158	146-156
K+ (mEq/L)	"n/a"	4.7	2.5	3.9	3.9-5.5
Cl− (mEq/L)	"n/a"	116	113	121	109-123
Hco3− (mEq/L)	"n/a"	19	20.4	20	22-27
Lac (mmol/L)	"n/a"	1.1	0.5	1.8	0.5-2.5
Presence of lipemia	No	No	Yes	Yes	

*Not performed due to financial limits. Hct: Haematocrit; TP: Total Protein; Alb: Albumine; Alt: Alanine Amino Transferase; Crea: Creatinine; Lac: Lactate; "n/a": not available; C: Cat.

Table 4. Dosages and time of administration of ILE (Intralipid 20%) and DXMDT (dexmedetomidine).

Cats	*ILE Bolus (ml/kg)*	*Time ILE bolus (min)*	*Rate of ILE CRI*	*Time CRI ILE (h)*	*DXMDT*	*DXMDT CRI*	*Other drugs*	*Days of hospitalization*	*Adverse effects observed*
1	2	3	4 ml/kg/h for 3 h, 2 ml/kg/h for 2 h	5	1 µg/kg IV	No	Propofol 1 mg/kg IV	1	None
2	1	5	5 ml/kg/h For 3 h, 2 ml/kg/h for 6	9	10 µg/kg IM	No	Diazepam 1 mg/kg ER Phenobarbital 2 mg/kg IM	1	None
3	2	5	4 ml/kg/h	6	1 µg/kg IV	1 µg/kg/h for 6 h	Midazolam 0.3 mg/kg IV	4	Lipemia +
4	2	5	2 ml/kg/h	4	10 µg/kg IM	No	Diazepam* Phenobarbital 2 mg/kg IM	1	Lipemia +

*Dosage unknown.

received the animal after one hour from intoxication and administered diazepam at 1 mg/kg by endorectal way. At our examination, the cat was indifferent and presented severe tremors (Table 2). Vital signs are reported in Table 1. We proceeded at dermal decontamination with dishwashing liquid. Emergency data base was performed (Table 3). DXMDT at 10 µg/kg was administered by intramuscular way. After administration, tremors were considerably reduced and oxygen via face mask was given. Two endovenous catheters in cephalic veins were placed. Ringer lactate solution was commenced at 25 ml/h. ILE bolus was administered at a dosage of 1 ml/kg in 5 min. Then constant rate infusion at dosage of 5 ml/kg/h was started. Cat was monitored hourly. Tremors and fasciculations were still present after 2 hours from the beginning of the infusion and cat had seizures. Phenobarbital (Luminale®: Luminale 200 mg/ml solution, Bracco S.p,a, Milano, Italy) at 2 mg/kg I/M was administered. After 3 hours twitching and tremors reduced and the ILE infusion was reduced at 2 ml/kg/h. After 6 hours neurological signs improved and CRI of ILE was stopped (Table 4) and gross lipemia was detected via mHct Tubes (Table 3). The cat was alert but ataxic and only very fine tremors of the ears were still discernible on close inspection. During hospitalization cat also received: ranitidine at 2 mg/kg IV. On day 2 the cat was successfully discharged and no additional doses of anticonvulsant drug were used. On follow-up for 12 months later, the owner had not noticed any abnormalities and the cat was well.

Case 3

A 2-years old, 3 Kg male intact European domestic short hair cat was referred to the Veterinary Teaching Hospital for muscle fasciculations and tremors. The morning before the owner applied a permethrin spot on product containing 1 gr/Lt imidacloprid and 500 g/Lt of permethrin in a 1 ml pipette (Adantix spot-on for 4-10 kg dogs. Bayer AG, Leverkusen, Germany), for a toxic dose of permethrin of 167 mg/kg. The cat had convulsions and was taken to the nearest Veterinary Centre. The cat was treated by colleagues with diazepam (Valium 10 mg/5 ml solution, ROCHE Italia S.p.a., Milano- Italy) IV (dosage was not reported) in bolus and propofol (Proposure 10 mg/ml solution, Merial Italia, Milano- Italy) at 1 mg/kg IV every 3 hours in the afternoon. The animal continued to have muscle tremors and didn't ameliorate and was referred in the evening to our hospital after 21 hours from permethrin administration. At clinical presentation, the cat was unresponsive and presented with a severe hypothermia (in the first hour non detectable, < 33 °C - Table 1), with muscle fasciculations and severe tremors (Table 2). We proceeded to give oxygen via face mask at 5 Lt/min and we started to warm the cat. Emergency data was then collected (Table 3). Ringer lactate at 18 ml/h was administered and infusion rate was then adjusted hourly on the base of evaluation of perfusions parameters (Heart rate, pressure, quality of pulse, mucosal colour and refilling time). Midazolam (Midazolam 5 mg/ml solution, Roche S.p,a, Milano, Italy) bolus at 0.3 mg/kg IV was administered. A second venous catheter was placed in the other cephalic vein. A bolus of ILE at 2 ml/kg IV in 5 min followed by a CRI of 4 ml/kg/h was administered using the second vascular access. After 3 hours, the cat had still muscle fasciculations and tremors and temperature rise up to 37.8 °C. DXMDT (Dexdomitor 0.5 mg/ml solution for dogs and cats. Orion Corporation, Espoo, Finland) at 1 µg/kg IV followed by a CRI at 0.5 µg/kg/h was started. After 3 hours tremors ceased and ILE was discontinued. Only mild muscle fasciculations were still present and CRI of DXMDT was continued until the next morning (5 hours - Table 4). During infusion cat was monitored continuously by electrocardiogram. On day 2, the cat didn't show a normal gag response

and was ataxic. The evening of the day 2 the cat was able to eat, but was dysphagic and still ataxic. On day 4 the cat was discharged without complication with a hepatoprotective therapy. During hospitalization ranitidine at 2 mg/kg IV and amoxicilline and clavulanic acid (Synulox injectable suspension, 140 mg/ml amoxicilline+ 35 mg/ml clavulanic acid, Pfizer Italia Srl, Rome-Italy) at 12.5 mg/kg s/c was administered. On follow-up for 3 months later, the owner had not noticed any abnormalities.

Case 4

A 6-years-old, 3.5 Kg female spayed European domestic short hair cat was referred to Veterinary Teaching Hospital for twitching and muscle fasciculations. The owner divided the same pipette containing 250 mg of imidacloprid and 1250 mg of permethrin (ADVANTIX spot-on for 10-25 kg dogs. Bayer AG, Leverkusen, Germany) for a toxic dose of 119 mg/kg, to the coat of his three cats, but only this cat presented neurological symptoms. The cat was referred to our hospital after an initial evaluation by other colleagues that administered diazepam by endorectal way and DXMDT at 10 µg/Kg IM. At arrival, the cat was indifferent, had tremors and muscle fasciculations and showed a Horner syndrome. The cat was tachypnoic and tachycardic (Tables 1 and 2). Ringer lactate solution was commenced at 20 ml/kg/h and oxygen was administered via face mask. The cat was decontaminated with a lukewarm water bath and mild hand washing detergent. A second cephalic IV catheter was then placed and sample was collected for emergency data base (Table 3). A bolus of ILE (7 ml, 2 ml/kg) was then administered IV for over 5 minutes followed by a constant rate infusion at rate of 2 ml/kg/h. The cat was revalued hourly and after 3 hours tremors increased again and phenobarbital at 2 mg/kg I/M was then administered. ILE was discontinued after 4 hours due to the improvement of tremors and fasciculations (Table 4). On day 2, the cat was alert and the examination of intracranial nerves was good, normal gag response was present and the cat was ambulatory. The cat was eating without problem and was discharged the same day with a hepatoprotective therapy (Epato pasta DNR, Cremona, Italy) and amoxicillin and clavulanic acid (Synulox injectable suspension, 140 mg/ml amoxicillin+ 35 mg/ml clavulanic acid, Pfizer Italia Srl, Rome-Italy) at 12.5 mg/kg for a week. During hospitalization the cat received ranitidine at 2 mg/kg IV and acetyl cysteine (Acetilcysteine 300mg/3ml solution, HEXAL S.p.a, Agrate Brianza (MB), Italy) at 70 mg/kg IV. On follow-up for 3 months later, the owner had not noticed any abnormalities.

Discussion

Permethrin toxicosis is a commonly reported poisoning in small animals in United States, UK, Australia and Italy (Merola and Dunayer, 2006; Caloni *et al*., 2012, 2014). Most frequently, cats are intoxicated by owners by applying canine spot on products (Dymond and Swift, 2008). Cats are more likely than dogs to develop pyrethroid toxicosis. This is due to the feline liver being inefficient at glucuronide conjugation. Glucuronide conjugation is needed to metabolize permethrin. The low concentration products approved for cats contain 0.05-0.1% of permethrin and do not seem to cause the signs that the concentrated (45-65% permethrin) canine spot-on do (MacDonald, 1995). Based on the public database of the American Society for the Prevention of Cruelty to Animals and ASPCA, 'spot on' product that contain permethrin which are labelled for use on dogs only, can result in serious toxicosis when applied on cats. Based on these cases, the application of product containing 100 mg/kg permethrin (1 ml of 45% permethrin applied dermally on a 4-5 kg cat) can result in a life-threatening toxicosis. The minimum toxic dose is still unknown, but it would be expected to be lower. Cats should be considered more sensitive to permethrin compared with dogs, rats, or human; permethrin products formulated for dogs can contain up to 65% of permethrin, those formulated for cats less than 0.2%. All the cats that were presented for treatment received on average of 184 mg/kg. However there is no reported correlation between the amount of permethrin applied and the severity of clinical signs induced (Boland and Angles, 2010). No real antidote or antagonist is available and treatment recommendations include intravenous fluid support to maintain electrolyte balance and hydration and to promote diuresis, dermal decontamination with a mild detergent and luke warm water to prevent further absorption (Whittem, 1995; Dymond and Swift, 2008). Every cat received a mean of 3 time maintenance of crystalloids, given intravenously as a bolus, followed by a reassessment of perfusion parameters (heart rate, quality of pulse, mucosal membrane colour). This is according to recent guidelines for emergency management of fluid therapy in the critical ill (Hopper *et al*., 2012) by which the use of 'shock dose' (60 ml/kg for cat and 90 ml/kg for dog) is abandoned. In emergency setting it is preferable to give a bolus intravenously in 15 or 20 minutes and then reassess the cat, giving some 'end points' for heart rate, mucosal membranes colour and refilling time in order to ameliorate tissue perfusion, diuresis, maintain systemic pressure and tissue oxygenation.

Intravenous fluids are also recommended to protect the kidney tubules from myoglobin breakdown products in cats with active seizures and tremors (Dymond and Swift, 2008; Linnett, 2008).

Seizure control can be achieved with diazepam, midazolam, barbiturates, propofol or inhalation anesthesia (Martin and Campbell, 2000; Linnett, 2008; Boland and Angles, 2010). Methocarbamol is also reported to reduce tremors and muscle fasciculations

(Meyer, 1999; Linnett, 2008).

In the last decade an increasing amount of evidence supports the use of ILE to reverse or attenuate the clinical manifestations of many lipophilic toxins (Rosenblatt *et al*., 2006). Permethrins are very lipophilic compounds, with a lipid solubility (log P) of 6.5 (Sangester, 1997) and ILE would be expected to be an efficacious treatment. The mechanism of action is still unknown, but several theories have been proposed. One of the mechanisms is based on the possibility that a serum lipid partition creates a concentration gradient that facilitates the passage of toxicants from the interstitial tissue, decreasing their availability in target tissues as demonstrated in bupivacaine intoxication (Weinberg *et al*., 1998). Many case series regarding the use of ILE in feline permethrin intoxication have been reported (Haworth and Smart, 2012). Dosage of intravenous boluses or continuous infusion of lipids have not been assessed in animals for treatment of drug toxicity. In rats, the LD_{50} for rapid high volume lipid infusion was estimated to be 67 ml/kg (Johnson, 2011). In our study the amount of ILE administered was 18 ml/kg for cat 1 (45 ml); 28 ml/kg for cat 2 (140 ml); 26.3 ml/kg for cat 3 (79 ml); 10 ml/kg for cat 4 (35 ml). The LD_{50} reported in the study for rats, far exceeds from dosages we used and was obtained by experimental studies and for high rapid volume of infusion.

We should consider that a larger volume of ILE was used in cat 2, in which clinical symptoms were more severe. Previous recommendation reported a dose of 1.5 ml/kg as a bolus of ILE followed by a continuous infusion of 0.25 ml/kg/min (15 ml/kg/h) for 30-60 min. (Fernandez *et al*., 2011). As appended in previous studies (Brückner and Scwedes, 2012; Kuo and Odunayo, 2013) it is not reported the use of the same dosage and rate of infusion of ILE for all the cats treated. Authors used different doses and rate of CRI for ILE. In our cases, especially for the rate of infusion, this could be related to a different adjustment of dosage in relation to the improvement of neurological clinical symptoms (reduction of tremors, twitching). We have to also consider that we collected the data retrospectively, and this could in part explain why for example cat 2, received a bolus of 1 ml/kg instead of 2 ml/kg as the others cats, considering however a range of 1-2 ml/kg as initial bolus. Different dosages have been used based on human recommendations or on the veterinary guidelines of parenteral nutrition. In agreement with Brückner and Scwedes (2012), we opted for a bolus of 2 ml/kg (except for cat 2) followed by a mean rate of CRI of 4.25 ml/kg/h in all the treated cats. In the present case series a slow rate of infusion (2-5 ml/kg/h) for a longer time (max 9 hours for cat 2) seemed to be more effective in controlling muscle fasciculations, without risks of repeated venous line handling, reported in other case reports (Kuo and Odunayo, 2013). To reduce this complication to minimum we placed a dedicated intravenous catheter (20 gauge), in all the treated cats. Despite Brückner and Scwedes (2012), we placed a peripheral catheter as the osmolarity of the lipid emulsion was compatible with the size of the catheter (Intralipid 20%, Deerfield (Il): Baxter Healthcare Corporation; 2000). None of the cats showed any phlebitis, infection or cutaneous hyperaemia at the site of infusion. In a critical case, the shock status, with a consequent reduction of perfusion and tissue oxygenation, the presence of an oxidative stress, could result in a reduction of the efficiency of immune system. There are many reports in human medicine and experimental studies made on rats and dogs that argue about the possibility that ILE promotes lymphocyte and neutrophil death that may enhance the susceptibility of the patients to infections (Waitzberg *et al*., 2002; Cury-Boaventura *et al*., 2006; Kang and Yang, 2008). For these reasons we retain that the use of antibiotics in these cases could reduce or could help to reduce and prevent an eventual infection. However, the guidelines for peripheral parenteral nutrition in companion animals (Chandler *et al*., 2000) suggested the possibility for using a peripheral venous access with a maximum of 600 mOsm/Lt of the solution administered and the osmolarity of the ILE we used (Lipofundin®) is of 280 mOsm/Lt.

At present, the maximum daily dosage of intravenous lipids in veterinary patients is still unknown. Previous authors suggested to check for gross lipemia via micro-Hct tubes, before administrating additional doses (Johnson, 2011). In our study we evaluated the degree of lipemia by serum observation, and only two cases showed a lipemic serum. However, no other side effects (hypersensivity, pulmonary oedema, thrombophlebitis) were noticed. Anyway the ideal dose and frequency for ILE administration has not been determined and warrants further study. Because of the low number of cases, it is difficult to say if the total volume of ILE varied in relation of anticonvulsant drugs or DXMDT. In all the treated cats, we tried to reduce at minimum the use of anticonvulsant drugs because authors preferred to use as soon as possible ILE as a part of the decontamination protocol. Comparing with retrospectives studies (Dymond and Swift, 2008; Boland and Angles, 2010) our four cats recovered faster, with a mean treatment time of 6 hours. A retrospective study (Boland and Angles, 2010) describes feline permethrin intoxication in 42 cases. In common of this report, we have the lack of availability of methocarbamol, but the main difference is the reduction of time of recovery and hospitalization in our study. In the Boland and Angles (2010) study, despite the use of anticonvulsant drugs such as midazolam used in CRI or propofol, they reported a mean of duration of tremors of 35 h with a median of duration of midazolam CRI of 38.5 h. They

also needed to intubate 12 cats because of respiratory depression caused by propofol used in CRI (for a median time of 23 h). They recorded the hospitalisation time for 34 cats and it was 3 days in average.

In our study, we didn't need to intubate the cats, with all those complications deriving from that procedure (general anesthesia, possibility of aspiration pneumonia, the need of change the monitoring etc.); all our cats were discharged the day after, except for one cat that was discharged at day 4, due to the owner's availability; although he was clinically stable and ready to go home 24 hours after presentation.

In feline permethrin intoxication, hematology and biochemistry panels are usually without abnormal finding (Talcott, 2009; Boland and Angles, 2010) except for stress-related responses such as hyperglycemia (as we found in cat 2) and neutrophilia (Bottcher *et al*., 2006; Linnett, 2008). Bottcher *et al*. (2006) also reported an increase in hematocrit and blood urea nitrogen. Long lasting seizure activity causes myoglobinuria which may lead to acute kidney injury (Dymond and Swift, 2008; Linnett, 2008). In our cases we find two cats (3 and 4) that showed low values of hematocrit at the entrance in emergency room and the other two with values in the ranges. This could be related to the fact that cats 3 and 4 were brought to us from other institutions and they received intravenous fluids before presentation to our hospital. Cat 3 was referred after 21 hours from intoxication; we can also hypothesize that it could be related to the oxidative stress or administration of propofol in CRI which can cause anemia with Heinz bodies in cats. In our cases, the rest of values were within normal range. We observed a moderate hypokaliemia for cat 3 (2.5 mEq/Lt). Among the causes reported of hypokaliemia (renal potassium wasting, diuretics drugs, severe diarrhea) it's reported that an increased level of catecholamines could determine a disorder of internal balance (redistribution) that results in a decrease of the cation (Riordan and Schaer, 2009). In addition to that, cat 3 had a very severe salivation.

At present there are no practical diagnostic tests available to confirm permethrin intoxication. Many others toxic agents and also medical conditions like trauma, hypocalcemia, hypoglicemia, hepatic encephalopathy and encephalitis should be ruled out (Whittem, 1995; Linnett, 2008; Boland and Angles, 2010).

As mentioned above, methocarbamol is a drug classically used to treat tremors in feline permethrin intoxication. The use methocarbamol, alone or in addition to anticonvulsant drugs is available intravenously or orally. Methocarbamol is a centrally acting muscle relaxant. At time of our study, in Italy and other European countries this drug was not available. As a consequence we opted for the use of anticonvulsants as diazepam, midazolam or propofol. Benzodiazepines produce most of their pharmacological effects by modulating gamma-aminobutyric acid (GABA)-mediated neurotransmission (Tanelian *et al*., 1993); two main types of GABA receptors are involved in neuronal transmission: $GABA_A$ and $GABA_B$. The benzodiazepines-binding site is located in $GABA_A$ receptor complex and its activation increases chloride conductance and generates slow inhibitory postsynaptic potentials. This is one of the mechanism that promotes muscle relaxant and sedative effects. Permethrin act as antagonist of the GABA receptor by reducing the GABA-stimulated chloride ion flux. This anti-inhibitory action could lead to hyperexcitability and contribute to or exacerbate some clinical signs (Whittem, 1995). For these reasons, in accordance with previous studies, we decided to use these drugs.

According to Löscher *et al*. (2002), methocarbamol is not recommended in cats due to possible side effects. In a case series of Dymond and Swift (2008), rectal or oral use of methocarbamol was reported; there was no difference in the duration of treatment of methocarbamol-treated cats compared with those receiving only diazepam or propofol. The only noticed difference was the fact that cats treated with methocarbamol did not require any further treatment with diazepam or propofol (Dymond and Swift, 2008).

According to the Authors' knowledge this is the first case series in which ILE has been associated with an α_2 agonist drug. $Alpha_2$ agonists are well studied, known and used in veterinary medicine since the mid-80's. Sedative effect of α_2 agonists is due to the inhibitory action on the major noradrenergic nucleus in the brainstem, *locus ceruleus*. Their muscle relaxant effect is well known in animals (Lemke, 2007) and its neuroprotective and cardioprotective effects have been also documented, as well as their positive effects on cerebral blood flow in human neuroanesthesia (Farag *et al*., 2011).

DXMDT is the pharmacologically active isomer of medetomidine, with several advantages, such as reversibility, lower possibility of interaction with other drugs used and lower hepatic metabolism (Kuusela *et al*., 2000). Variable dosages are suggested in literature for its use. The dosages we used, were in agreement with most reports (Anash *et al*., 2000) and derived by Authors' clinical experience and confidence. When DXMDT is administered intramuscularly, higher dosage is recommended; in accordance with previous studies we opted for using large dose by intramuscular way in order to obtain a good sedation and muscle relaxant effect (cats 2 and 4: administered by colleagues: 10 microgram/kg vs 1 microgram/kg IV for cats 1 and 3). After the administration of single bolus, cats became calmer and tremors were reduced. This resulted in a reduction of stress and facilitated

the possibility to manipulate the animals, to give them oxygen or others medicaments. It is known that in permethrin intoxication a quiet environment, silence and darkness are recommended. DXMDT revealed helpful for the management of the animals, reducing the restrain and the stress; cats are less scared and more collaborative. In addition to that, DXMDT allows to asses neurological function (examination of intracranial nerves, spinal reflexes) due to its reversibility, even stimulating the animal. In one cat we used a constant rate infusion of DXMDT to achieve a longer effect of sedation and tranquilization. To our knowledge there are no reports in literature about the use of DXMDT CRI as adjunctive therapy in feline permethrin intoxication and only few reports about the use of continuous infusion of this drug in the cat (Anash *et al*., 2000). However, further investigations are needed to evaluate the efficacy of DXMDT in the feline patient.

All drugs we used, such as benzodiazepines (diazepam, midazolam), propofol and DXMDT are lipophilic. The lipophilicity of a substance may be measured by the partition coefficient (P), which is a ratio of the distribution of a substance between 2 liquids that are incapable of mixing, such as water and octanol (Sangester, 1997). The logarithm of P is reported to describe lipophilicity, the higher the Log P value, the more lipophilic a drug become. Drugs are determined to be lipophilic if their log P>1.0.

One can suppose that the use of ILE may affect the availability of other lipophilic drugs administered, such as mentioned above and also in the case of use of methocarbamol. If we consider the Log P for DXMDT (Log P 2.8) midazolam (Log P 3.3), phenobarbital (Log P 1.47) diazepam (Log P 2.82) and propofol (Log P 3.8), given that permethrin is even more lipophilic with a Log P of 6.5 (Sangester, 1997), it would be expected that ILE be efficacious for the treatment of feline permethrin toxicosis and theoretically should have minimal effects on the use of that drug or methocarbamol (Log P 0.55). The cases described illustrate no appreciable negative effects using ILE in conjunction with DXMDT. The clinical effect we observed after its administration (sedation, muscle relaxation) it's not far different from that we observed when we used the drug as a sedative in anesthesia section without ILE. We can assume that it could probably depend from the lipophilicity of the substance, but also from the dosage one uses. We don't know if the prospect of increasing the dose of lipophilic drugs such as dexmedetomine may need to be considered when used in conjunction with ILE, even if the Log P respect to the permethrin one is quite lower. DXMDT produce an excellent sedation and promote a neurological status similar to physiological sleep (Serafim *et al*., 2015). This effect in addition to the muscle relaxant effect, promotes the reduction of tremors and the reduction of cerebral oxygen consumption and metabolism by reducing cerebral blood flow (Zornow *et al*., 1993).

ILE seemed to be well tolerated and no adverse effects were noticed. A shorter time of hospitalization and reduced cost of recovery were reported. Although we tried to use standardized dosages and protocols for all cases, the use of ILE is not recommended as a single treatment, without any further seizure control or supportive care. In the present study, DXMDT appeared to be useful as a sedative and muscle relaxant for affected cats, particularly in the early phases of treatment. We hypothesize that DXMDT could be considered as a replacement in those cases in which other medicaments considered 'elective' for treatment of permethrin intoxication, such as methocarbamol, are not available.

A prospective and controlled clinical trial should be performed in order to validate the use of DXMDT as a part of the emergency protocol for feline permethrin intoxication.

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Conflict of interest

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