Adverse reactions of α_2-adrenoceptor agonists in cats reported in 2003-2013 in Finland

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Running title:

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Abstract

Objective To describe suspected adverse drug reactions in cats associated with the use of α_2-adrenoceptor agonists.

Study design Retrospective study.

Animals A total of 90 cats.

Methods Data were collected from the reports on adverse reactions to veterinary medicines sent to the Finnish Medicines Agency during 2003-2013. All reports of suspected adverse reactions associated with the use of α_2-adrenoceptor agonists in cats were included. Probable pulmonary oedema was diagnosed based on *post mortem* or radiological examination, or presence of frothy or excess fluid from the nostrils or trachea. If only dyspnoea and crackles on auscultation were reported, possible pulmonary oedema was presumed.

Results Pulmonary oedema was suspected in 61 cases. Of these cats 37 were categorised as probable and 24 as possible pulmonary oedema. The first clinical signs had been noted between 1 minute and 2 days (median 15 minutes) after the α_2-adrenoceptor agonist administration. Many cats likely had no intravenous overhydration when the first clinical signs were detected, as either they presumably had no intravenous cannula or the signs appeared before, during or immediately after cannulation. Of the 61 cats, 43 survived, 14 died and for 4 the outcome was not clearly stated.

Conclusions and clinical relevance Pulmonary oedema is a perilous condition that may appear within minutes of an intramuscular administration of sedative or anaesthetic agents in cats. The symptoms were not caused by intravenous

overhydration, at least in cats that probably had no venous cannula when the first clinical signs were detected.

Introduction

The α_2-adrenoceptor agonists are widely used in clinical settings for feline sedation and premedication, and in many developed countries xylazine, medetomidine and dexmedetomidine have marketing authorisations for this use. These α_2-agonists are usually administered by intramuscular (IM) route and combined with other drugs such as opioids and ketamine (Allen et al. 1986; Verstegen et al. 1989; Selmi et al. 2003; Ko et al. 2011). In healthy cats, the use of α_2-adrenoceptor agonists alone and combined with other sedative and anaesthetic drugs has been considered to be efficient and safe (Verstegen et al. 1989; Granholm et al. 2006; McSweeney et al. 2012). However, the summary of product characteristics (SPC) of the products containing medetomidine or dexmedetomidine on the Finnish market states that in rare cases pulmonary oedema may occur.

Overall, the risk of anaesthetic- and sedation-related mortality is higher in cats than in dogs (Brodbelt et al. 2008, 2010). Poor health status, old age, endotracheal intubation and fluid therapy have been associated with the increased risk (Brodbelt et al. 2007). Van Der Linde-Sipman et al. (1992) described the necropsy findings of cats that had died after injectable anaesthesia, but they did not differentiate the clinical signs or *post mortem* findings associated with separate anaesthetic protocols. Only a single report about an adverse reaction associated with the use of α_2-adrenoceptor agonists in cats in clinical settings can be found in the literature (Raptopoulos et al. 1993).

Before a drug is granted marketing authorisation for European Union (EU) markets, its safety is studied by the pharmaceutical company involved and assessed by

competent EU authorities. Once the authorisation has been granted, the safety of the drug is monitored by the authorities on the basis of adverse reaction reports received from veterinarians and users and periodic safety reports from marketing authorisation holders. If necessary, changes may be made to the SPC or the package information leaflet on the basis of new data. Also the use of the medicine may be restricted or, in extreme cases, the marketing authorisation can be cancelled.

The objective of this study was to describe suspected adverse drug reactions in cats associated with the use of α_2-adrenoceptor agonists in clinical settings. The discussion is focused on the signs and potential aetiologies of feline anaesthesia-related pulmonary oedema, as it seemed to be the most common adverse reaction reported in this material.

Materials and methods

Data were collected from the Finnish Medicines Agency (Fimea) register of adverse reactions to veterinary medicinal products. During 2003-2013 Fimea received 2771 reports of suspected adverse reactions to veterinary medicines of which 464 (16.7%) concerned cats. All the 89 reports of suspected adverse reactions associated with the use of α_2-adrenoceptor agonists in cats (19.2%) were investigated further. One of the reports described the reactions of two cats, thus the total number of cats was 90.

We recorded the doses of the drugs and their routes of administration. The onset of signs after administration of α_2-adrenoceptor agonists was entered if the exact time was given in the report. If their onset was only described in relation to the phase of the

procedure, we estimated it: during cannulation – 10 minutes; during administration of propofol – 15 minutes; at the end of castration – 30 minutes; at the end of ovariohysterectomy – 40 minutes; after extubation – 10 minutes after the end of surgery. These estimations were partly based on reports where both the exact time and the corresponding phase of the procedure were given. Furthermore, we tried to infer whether the cat had been intubated and whether it had had an intravenous cannula when the first signs were detected.

We judged a probable pulmonary oedema based on clinical signs, i.e. presence of frothy or excess fluid from the nostrils or trachea, or on *post mortem* report or radiological diagnosis. We presumed a possible pulmonary oedema when the crackles on auscultation were reported to respond to administration of furosemide, or when both acute dyspnoea and crackles on auscultation were reported. In addition, we recorded a possible pulmonary oedema when the reporting veterinarian had given the diagnosis without any pathological or radiological confirmation and without describing any clinical signs.

The data were analysed by using IBM SPSS Statistics 22 software. The difference between groups for age was analysed with *t*-test and for onset of clinical signs with Mann-Whitney U-test. The presence of symptoms was compared between dead and survived cats with Fisher's exact test. Significance was set at $p < 0.05$.

Results

The 89 reports contained information on 90 cats with suspected adverse reactions associated with the use of α_2-adrenoceptor agonists. The population consisted of 10 breeds, most of them being domestic shorthaired cats (n = 53; the breeds of nine cats were not specified). Forty-eight cats were female, 37 male and the sex of five cats was not given. The age of the cats was 5.1 ± 4.2 years (mean ± SD), ranging from 5 months to 16 years (for five cats not reported), and their weight was 4.0 ± 1.1 kg (for 29 cats not reported). The most common indications for sedation or anaesthesia (when given) were dental care (n = 21), castration (n = 8) and ovariohysterectomy (n = 7). For most of the cats, no preceding diseases were reported, but one of the cats was sedated due to urinary tract obstruction, two for enema, one for abscess and one for anorexia and vomiting.

Two of the cats had received xylazine as the α_2-adrenoceptor agonist, the others had been administered medetomidine (n = 58) or dexmedetomidine (n = 30). In most cats (n = 80), the IM route was reported to have been used for administration of the α_2-adrenoceptor agonist. One cat was reported to have received the α_2-agonist intravenously (IV), two subcutaneously and one both IM and IV. In six reports, the route of administration was not specified. The recommended doses stated in the SPC had been exceeded in none of the cats where the dose of the drugs per body weight had been reported or could be calculated.

According to the reports, 37 cats were deduced to have had a probable and 24 cats a possible pulmonary oedema. The symptoms of 28 cats were stated to likely not be associated with pulmonary oedema (Table 1). In addition, for one cat the presence of pulmonary oedema could not be evaluated due to scanty information in the report. All

the cats with suspected (probable or possible) pulmonary oedema had received either medetomidine or dexmedetomidine as the symptoms of the two cats having been administered xylazine (excitation in one cat and vomiting and seizures in the other one) were not suggestive to pulmonary oedema.

Two of the 61 cats with suspected pulmonary oedema had evidently received no other sedative, anaesthetic or analgesic drug than the α_2-adrenoceptor agonist at the time when the first signs were noted. The sedative, anaesthetic or analgesic drugs reported to have been administered to the cats in addition to the α_2-adrenoceptor agonist, and evidently before the first signs of the suspected pulmonary oedema, were ketamine (n = 19), opioids (butorphanol or buprenorphine; n = 38), propofol (n = 8), midazolam (n = 2) and non-steroidal anti-inflammatory drugs (carprofen or meloxicam; n = 5). In five reports, the use of other drugs was not clearly stated. In addition, administration of antimicrobials (betalactam antibiotics) was mentioned in seven reports. In many reports, the exact timing of the administration of the other drugs related to the α_2-adrenoceptor agonist was not specified.

The first clinical signs of pulmonary oedema, such as dyspnoea or frothy sputum, were estimated to have appeared between 1 minute and 2 days (median 15 minutes) after the administration of the α_2-adrenoceptor agonist (Table 1). Only one cat was reported to have received IV fluids before the clinical signs of suspected pulmonary oedema were detected. That cat was treated for anaesthetic hypotension, after which it presented dyspnoea and cyanosis and had pronounced respiratory sounds in auscultation; pulmonary oedema was confirmed with chest radiography. Nine other cats were deduced to have had an intravenous cannula before onset of the signs of

suspected pulmonary oedema, as they had earlier been administered intravenous drugs such as propofol. On the other hand, in 28 cats with suspected pulmonary oedema, the clinical signs were first noted before, during or immediately after placing the intravenous cannula, or there had likely not been enough time to place the cannula before onset of signs, as they were perceived within 10 minutes after intramuscular administration of the first drugs. The reports of 23 cats did not contain the required information to evaluate the presence of an intravenous cannula or the timing of its placement and thus their opportunity to have received intravenous fluids before the onset of the signs.

The reported interventions after noting the clinical signs of suspected pulmonary oedema are presented in Table 2. Most of the cats with suspected pulmonary oedema survived (Table 3). The deaths were presumably spontaneous and occurred rather soon after the first clinical signs were noted. Nevertheless, one cat died five hours after the procedure during which time it had had respiratory problems, and two cats were reported to have been euthanized due to poor prognosis; all of these cats were categorized as suspected pulmonary oedema. Five of the survived cats had later been examined with echocardiography, and no abnormalities were detected. The frequencies of some clinical symptoms reported in the cats with suspected pulmonary oedema are cross-tabulated with the outcomes in Table 3.

The *post mortem* findings of ten cats were described in the reports. For six cats, the diagnosis of pulmonary oedema was confirmed. For three of these cats, no other pathological findings were described, whereas in one anaphylaxis was suspected, another one had eosinophilic inflammation in the lungs and the third one had blood in

the pericardium, but the heart was reported to have no alterations. The cat with suspected anaphylaxis had been sedated with medetomidine and butorphanol, and the signs were first noted 10 minutes after the intramuscular injection. One cat reported to have had crackles on auscultation and bloody fluid from the lungs, but no specific *post mortem* findings was finally categorised as a possible pulmonary oedema. The necropsy findings reported for three other cats did not suggest pulmonary oedema: one was diagnosed as acute interstitial pneumonia, one had a chronic subclinical pneumonitis and findings suggesting cardiac arrest caused by respiratory arrest and one had findings typical of acute cardiac failure. The report of the last cat stated that some relatives of the cat had also died during sedation.

Discussion

In the reports of adverse reactions to veterinary medicines associated with the use of α_2-adrenoceptor agonists, approximately two-thirds of the cats had had clinical, radiological or autopsy findings suggestive of pulmonary oedema. Only two reports mentioned abnormal cardiac necropsy findings. This contradicts the report of Van Der Linde-Sipman et al. (1992), who performed autopsies on 36 cats that had died within six hours after injectable anaesthesia. They found severe hyperaemia and oedema of the lungs and myocardial damage in all of the cats. In most of those cats, no clinical signs had been detected before death, but watery fluid from the nostrils, blue mucous membranes and dyspnoea were seen in some of them. The authors did not specify each cat's anaesthesia protocol, and therefore, it is not known whether the cats with the clinical signs of pulmonary oedema had been administered an α_2-adrenoceptor agonist (Van Der Linde-Sipman et al. 1992). On the other hand, Gaynor et al. (1999)

did not mention pulmonary oedema at all in their report about anaesthesia related complications and mortality in cats that were premedicated with a variety of sedatives, such as acepromazine, fentanyl, oxymorphone, butorphanol, diazepam, tiletamine-zolazepam and xylazine. In our study, most of the cats had been administered more than one drug before the onset of clinical signs, and thus, we were often unable to confirm whether the α_2-adrenoceptor agonist was the specific cause for the suspected adverse reaction.

In our study, the clinical signs of the adverse reactions appeared to be detected in most cases rather soon after the intramuscular administration of the first drugs, even though no exact time was often reported and thus we had to estimate it. The majority of the deaths also seemed to have occurred within the first 15-30 minutes. By contrast, Brodbelt et al. (2008) describe most of the feline perioperative fatalities to have occurred during the postoperative period. This inconsistency may have been caused by the different sources of the material, as Brodbelt et al. (2008) collected anaesthesia records of all cats anaesthetized and sedated at participating veterinary centres, whereas our material consisted of adverse drug reaction reports to the national authority on suspected adverse reactions associated with the use of α_2-adrenoceptor agonist.

In our paper, the most common interventions after detecting an adverse reaction were administration of atipamezole, furosemide and oxygen. Oxygen and diuretics are the treatments of choice in pulmonary oedema (Clarke et al. 2014). Conversely, although atipamezole is widely used for reversing medetomidine and dexmedetomidine induced sedation, only few studies describe its cardiovascular effects in cats (Savola

1989; Verstegen et al. 1991; Dobromylskyj 1996; Granholm et al. 2006), and no reports about its pulmonary effects in this species could be found. Therefore its true benefit in cardiopulmonary anaesthetic complications is difficult to evaluate.

In humans, frothy sputum is pathognomonic sign of pulmonary oedema (Chapman et al. 2005), and it has also been seen in some horses with perianaesthetic pulmonary oedema (Kollias-Baker et al. 1993). In our material, this sign was reported in only three of the 25 cats whose diagnosis was confirmed with radiology or necropsy. Actually, some of the cats with radiologically confirmed diagnosis of pulmonary oedema were reported to have had relatively minor respiratory symptoms. Interestingly also, no specific *post mortem* findings were reported for one cat manifesting frothy sputum. Nevertheless, we concluded that the cats with frothy sputum and no radiological or *post mortem* confirmation had a probable pulmonary oedema.

In humans, perioperative pulmonary oedema is often associated with fluid overload; other precipitating factors are relieving of airway obstruction, neurogenic increase of afterload, pulmonary aspiration, anaphylaxis, sepsis, multiple organ failure and cardiogenic problems (Chapman et al. 2005). Especially cats with cardiac disease are susceptible to pleural effusion or pulmonary oedema induced by overhydration, but markedly decreased glomerular filtration rate may also increase the risk (Lunn et al. 2012). At least in cats that showed the first clinical signs before or immediately after they had received a venous cannula, pulmonary oedema was obviously not caused by intravenous fluid overload.

Although myocardial damage has been associated with pulmonary oedema in cats that died after injectable anaesthesia (Van Der Linde-Sipman et al. 1992), in our data this association was not evident. Cardiac abnormalities had not commonly been detected with ultrasonography or in necropsy even when pulmonary oedema had been diagnosed with radiographs or necropsy. However, it is possible that undiagnosed cardiac diseases existed in some cats, as cardiomyopathy is rather common in apparently healthy cats (Paige et al. 2009). Furthermore, we cannot assess the reliability of the reported *post mortem* and radiological findings, as the experience and training of the veterinarians performing those studies were not stated.

Pulmonary oedema may occur secondary to upper airway obstruction at least in humans (Firdose & Elamin 2004; Chapman et al. 2005), dogs (Kerr 1989) and horses (Kollias-Baker et al. 1993). Although not clearly stated in the reports, we expect that most of the cats were not intubated, as the clinical signs of pulmonary oedema were often detected rather soon after the intramuscular drug injection. Therefore, upper airway obstruction cannot be ruled out as a potential cause of the pulmonary oedema also in these cats.

Perianaesthetic reflux has been reported in cats (Galatos et al. 2001; Adami et al. 2011), and it occasionally leads to regurgitation of gastric contents to the mouth (Galatos et al. 2001). Furthermore, pulmonary aspiration has been associated with pulmonary oedema at least in humans (Chapman et al. 2005). In our material, the presence of regurgitation could not be evaluated. Moreover, vomiting was mentioned in the reports of a few cats with suspected pulmonary oedema, and thus, aspiration may have been one of the causative factors.

Anaphylaxis might have been a possible cause of pulmonary oedema at least in some of the cats, and in one cat with pulmonary oedema it was actually suspected based on necropsy findings. Clinical manifestations of anaphylactic reactions are species dependent, but in the cat, the predominant "shock organ" is the respiratory tract (Shmuel & Cortes, 2013). Published reports of anaesthesia-related anaphylactic reactions in small animals are rare (Armitage-Chan 2010). In humans, neuromuscular blocking agents and antibiotics are common causes of perioperative anaphylaxis (Krishna et al. 2014), and especially betalactam antibiotics are often involved in severe anaphylaxis (Renaudin et al. 2013). In our material, none of the cats with suspected pulmonary oedema were reported to have received neuromuscular blocking agents, but some of them had been administered betalactam antibiotics.

The α_2-adrenoceptor agonists enhance systemic vascular resistance in cats (Golden et al. 1998; Lamont et al 2001; Pypendop et al. 2011), resulting in increases in left ventricular preload and afterload (Golden et al. 1998). At least in theory this might increase the risk of pulmonary oedema, as a neurogenic increase of afterload is a precipitating factor in humans (Chapman et al. 2005). In sheep anaesthetized with sevoflurane, massive capillary congestion and alveolar oedema were present within a few minutes of dexmedetomidine administration (Kästner et al. 2006). In rats, increased permeability of pulmonary endothelium has been proposed to cause xylazine-induced pulmonary oedema (Amouzadeh et al 1993), whereas in sheep hydrostatic stress has been suggested to be the underlying cause of dexmedetomidine-induced pulmonary oedema (Kästner et al. 2006). The effects of α_2-adrenoceptor agonists in feline lungs and their aetiology warrant further investigations.

In our study, approximately one-fifth of the cats with suspected pulmonary oedema were reported to have died. However, the mortality rate of cats due to anaesthesia-related pulmonary oedema cannot be estimated based on these reports, as the sample was probably biased; the severity of the symptoms and the outcome of the cat may have affected the motivation of the veterinarian to report the case to Fimea. Neither can the frequency of feline anaesthesia-related adverse reactions be estimated from previous reports on pharmacovigilance (Linnett 2006, Davis et al. 2013, 2015), as it is most likely that the adverse reactions are underreported, especially when an adverse reaction is expected (e.g. mentioned in the SPC).

In general, marked variation exists in the extent and precision of describing the events in the reports of adverse reactions to veterinary medicines. That was especially the case in the earlier reports, which were handwritten on a paper form, improving somewhat after a uniform electronic form was taken into use in EU in 2005. Thereafter veterinarians could copy information directly from their electronic register of patients and paste it easily to the electronic form. For the causality assessment it is essential that the reports include all details of the medication and a thorough description of the event. Thus the importance and necessity of the complete information of suspected adverse reactions reports cannot be overemphasized.

In conclusion, pulmonary oedema is a perilous condition that may appear in cats soon after administration of α_2-adrenoceptor agonists. Its aetiology is not fully understood in cats, but at least in our material it was probably not generally caused by intravenous overhydration.

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Table 1 Frequencies of clinical symptoms reported in cats with suspected adverse drug reaction associated with the use of α_2-adrenoceptor agonists (n = 89), and numbers of cats with *post mortem* and/or radiological examination conducted. In one report of a cat that had died, the presence of pulmonary oedema (PE) could not be evaluated due to scanty information.

	Probable PE n = 37	Possible PE n = 24	Likely not PE n = 28
First clinical signs (minutes)	13 (1 - 2880)	15 (10 – 120)	10 (3 – 2880)
Excess fluid or frothy sputum (n)	11	1	0
Crackles on auscultation (n)	18	20	1
Dyspnoea (n)	16	14	8
Abdominal breathing pattern (n)	3	2	3
Apnoea (n)	5	1	7
Cyanosis (n)	11	3	6
Other respiratory signs* (n)	5	7	5
Tachycardia (n)	1	2	2
Cardiac arrhythmias (n)	7	2	0
Cardiac arrest (n)	4	0	4
Opisthotonus/cramp/seizure (n)	16	7	13
Vomiting (n)	2	1	2
Prolonged recovery (n)	0	0	2
Mydriasis (n)	4	2	2

Other clinical signs** (*n*)	2	4	2
No clinical signs described (*n*)	1	2	2
Thoracic radiography (*n*)	21	1	1
Died*** (*n*)	11	3	6
Necropsy (*n*)	6	1	3

*such as tachypnoea, superficial breathing, wheezing, coughing, hypoxaemia

**such as too light or too deep sedation, salivation, reddish eyes

***in five reports, the outcome was not clearly stated; these cats therefore excluded when counting the number of cats that had died

Results are presented as number of cats (*n*) or median (range).

Table 2 Reported interventions in 84 cats after detecting clinical signs. In five reports, the interventions were not described, and in one report the presence of pulmonary oedema (PE) could not be evaluated due to scanty information. These six cats were excluded from the table.

	Probable PE *n* = 37	Possible PE *n* = 22	Likely not PE *n* = 25
Intubation (*n*)	6	1	5
Oxygen (*n*)	27	13	7
Resuscitation (*n*)	14	2	5
Furosemide (*n*)	28	21	11
Atipamezole (*n*)	28	20	18
Glucocorticoid (*n*)	6	2	1

Intravenous fluid (*n*)	0	1	1

Results are presented as number of cats (*n*).

Table 3 Age of the cats, time from drug administration when clinical signs suggestive of pulmonary oedema were first noted and frequencies of some clinical symptoms reported in cats with suspected pulmonary oedema associated with the use of α_2-adrenoceptor agonists cross-tabulated with outcome. Excluded from the table were one dead and two survived cats with no clinical signs reported and four cats whose outcomes were not clearly stated.

	Survived *n* = 41	Died *n* = 13	*p*
Age (years)	5.8 ± 5.0	6.0 ± 3.4	0.899
First clinical signs (minutes)	15 1 - 300	10 5 - 40	0.213
Excess fluid or frothy sputum (*n*)	6	5	0.109
Crackles on auscultation (*n*)	31	5	0.020
Dyspnoea (*n*)	23	5	0.346
Abdominal breathing pattern (*n*)	5	0	0.321
Apnoea (*n*)	2	4	0.025
Cyanosis (*n*)	11	2	0.485

Cardiac arrhythmias (*n*)	8	0	0.176
Cardiac arrest (*n*)	0	4	0.003
Opisthotonus / cramp / seizure (*n*)	13	9	0.024

Results are presented as number of cats (*n*), mean ± standard deviation or median (range).