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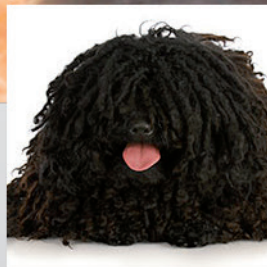
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Fecava lecture*

Duration of vaccine-induced immunity

Karin Möstl[1]

SUMMARY

Changes in vaccination schedules, particularly the prolongation of the booster intervals for some vaccine components, represents a challenge for veterinarians as well as for pet owners. For many years the annual revaccination of dogs and cats was a well-established routine procedure. Some understanding of the scientific background behind these changed recommendations is helpful for veterinarians when making decisions and advising dog and cat owners. This article offers an overview of the current knowledge on the duration of vaccine-induced immunity and the recommendations for booster vaccinations published by expert groups.

Keywords: persistence of antibodies, challenge studies, vaccination, dog, cat

Introduction

Since the 1960s routine vaccination procedures have included yearly revaccination boosters. Baker [1959; cited by Coyne et al., 2001] suggested that approximately a third of pups did not maintain protective titres to canine distemper virus (CDV) for a year after the initial vaccination, which led to the annual revaccination recommendation. However, this recommendation was rather arbitrary and the yearly interval was considered the minimum duration of immunity (DOI) as a safety measure. It was presumed that annual vaccination would not cause any harm and would probably be helpful.

Yearly boosters: necessary?

However, some investigators questioned the necessity of yearly revaccinations and initiated studies to determine the DOI for canine and feline vaccines. R. Schultz started working on the topic in the mid-1970s [Schultz, 2006]. His considerations were based on the observation that dogs and cats, which had recovered from, for example, canine distemper and parvovirus infections, respectively, were completely resistant to reinfection for many years. Additionally, in human medicine most vaccines are given in childhood, but never again. In 1978, Schultz and Scott [1978] published a recommendation for 'an ideal (but not proven) immunization schedule for dogs and cats'. They proposed revaccination every three years against canine distemper, canine adenovirus (CAV) 1 infection, rabies and parvovirus infections in dogs/cats after a series of puppy/kitten vaccinations and a revaccination at one year. During recent decades, various researchers questioned vaccination schedules asking, 'Are we vaccinating too much?' [opinions from various experts collected by Smith, 1995].

Inducing long-lasting immunity

The immunological memory involving B and T lymphocytes, which develop in response to an antigen, plays the key role in long-lasting immunity. Such memory cells are activated rapidly after a second exposure to the same antigen. Additionally, long-lived plasma cells continue to

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produce antibodies to the core vaccines (like CDV and parvovirus) for many years, without any further antigenic stimulation. Schultz [1998, 2006] called these cells 'memory effector B cells'.

The DOI depends on the immunogenic characteristics of the infectious agent, the immunizing strain, the type of vaccine (modified live or inactivated), the degree of attenuation of modified live vaccines, and the use of an adjuvant as well as on individual immune responses of the host. In general, the adaptive immunity to generalizing viruses develops quickly and is highly effective. It induces often a sterile immunity preventing not only disease, but also infection; the DOI may be lifelong. In contrast, immunity develops slowly to bacteria, fungi and parasites and persists for short time periods. Parvovirus infections of the dog (CPV) and cat (FPV), CDV and CAV-1, induce a DOI of many years (probably lifelong), whereas it is much shorter for example for *Leptospira, Bordetella* and canine parainfluenza virus [see review by Schultz, 2006]. Variation may also occur between different vaccines, as demonstrated with rabies vaccines by Kennedy et al. [2007]. These authors also described that dogs under one year of age generate a lower antibody response to rabies vaccination compared to adults with an influence of the animal's size on the antibody response and DOI. Smaller dogs elicit higher antibody levels and a longer DOI than larger breeds of dogs. A similar observation was published by Riedl et al. [2015], who described that an adequate titre increase after CPV vaccination was associated with a body weight <10 kg (p=0.003).

Immunosenescence and inflammageing

In older animals the level of immunity declines because of an impairment of cell-mediated immune functions with age (immunosenescence). HogenEsch et al. [2004] showed that old dogs had a significantly lower lymphocyte proliferative response, but no difference in the concentration of IgM and IgG, compared to young adult animals. Additionally, no differences in protective titres and in post-vaccination titres against CDV, CPV and rabies virus were shown. However, old dogs were shown to be less efficient in mounting primary immune responses [Day, 2010]. In 2005 Kipar et al. [2005] observed an increased activity of monocytes in older cats leading to an increased production of pro-inflammatory cytokines pointing to the process of inflammageing, which is supposed to occur following constant antigenic challenges and the associated production of inflammatory mediators,

which may trigger the onset of inflammatory disease in later life [see Day, 2010].

Determining the DOI

Serology
For the determination of the DOI, serological methods (detection of antibodies in the blood) and challenge infections are used. With serology it cannot be generally assumed that a correlation exists between the antibody titre and the level of protection. While there is a good correlation for parvoviruses, CDV and CAV-1, this is not the case for herpesviruses, where a strong cellular immunity is involved. Additionally, protection against infectious agents replicating and causing damage on mucosal surfaces (like canine coronavirus and canine parainfluenza virus) is probably based on mucosal immune responses.

Also the interpretation of titres is challenging. After an active immunity is established, titres may decline with time, even becoming undetectable. Nevertheless, in cases of infection the immunological memory may be activated so rapidly that the animal is protected against disease. For various infectious agents a high titre may be used to provide evidence of protective immunity, but a low titre does not necessarily indicate susceptibility. Titres may also vary according to the test used and the laboratory performing the test. Therefore, the term 'protective titre' is not applicable (contrary to passively, usually maternally, derived antibody titres). Schultz et al. [2010] claim that the presence of antibodies (following an active immune response), regardless of the titre, demonstrates immunity.

Challenge studies
Challenge studies have the advantage of demonstrating directly whether protection is acquired or not. They require the maintenance of animals in experimental isolation to avoid any field infection for long periods of time – many years – before infecting them (besides unvaccinated, fully susceptible control animals) with virulent infectious agents. Such situations are not directly comparable to real-life environments and may not be reproducible in animals of various ages and with different types of vaccines. Additionally, the ethical concerns have to be addressed.

DOI for core components
Many studies, especially in dogs, were performed in order to obtain information about vaccine-induced DOI. Schultz [2006] described an estimated DOI for CDV and CPV of

at least 7 years. In vaccinated dogs living in a natural environment, Schultz et al. [2010] found antibodies against CDV and CAV-1 for 14 years and against CPV for 10 years. In environments free from CDV and CPV-2, vaccinated dogs remained seropositive without any antigen stimulus for at least 9 years. Following challenge infections after 9 years all animals were completely protected [Schultz et al., 2010]. For CDV, Ottiger et al. [2006] showed that antibody levels did not significantly decrease even in dogs that had received boosters 5-6 years ago. Olson et al. [1997] detected antibodies against CDV indicating immunity in 22/30 dogs which had been imported to Iceland approximately four to ten years earlier from countries where the dogs had been vaccinated against canine distemper. As Iceland was free from CDV infection and CDV vaccination was not permitted in Icelandic dogs, the authors concluded that the DOI against CDV may last much longer than one year. Schultz [2006] claimed that 'immunity to CDV, CPV-2 and CAV-1 persists for a lifetime after vaccination, similar to the persistence of immunity after natural infection'.

In cats, Scott and Geissinger [1999] demonstrated protection against virulent FPV 7.5 years after vaccination with inactivated FPV, FCV and FHV. Protection against FCV and FHV was less effective. Mouzin et al. [2004] described, based on serology, a minimum DOI against the feline core components of 48 months. Recently, Haselberger et al. [2016] found that in clinically healthy, privately owned cats that had been presented to a veterinarian more or less regularly, the time since the last vaccination (twelve days up to 15 years) was not significantly associated with the antibody levels against the core components.

Annual boosters: the cons

Despite the knowledge that the DOI for the feline and canine core components is much longer than one year, the question may arise why not be on the safe side and continue with the yearly revaccination programme. The major reasons against that are:
- that vaccination of already immune animals is not beneficial
- every vaccination entails a small risk of adverse reaction
- it is ethical to avoid medical procedures which are of no benefit.

Lack of benefit

Vaccination of already immune animals does not provide any advantage. Pre-existing antibodies may neutralise the vaccine antigen very quickly, before it can stimulate the immune system. Antibody titres have to be low to allow an immune response to occur. Ottiger et al. [2006] observed that dogs with CPV antibody levels above the cut-off value had had fewer previous vaccinations. Riedl et al. [2015] showed that a booster effect after vaccination against CPV was associated with low pre-vaccination titres. Dogs with high antibody titres (>1:1280, HI assay) did not show any rise in titre after booster vaccination. For rabies vaccination Moore et al. [2015] described that dogs with an out-of-date vaccination status had a higher median increase in titre and reached higher median titres following booster vaccination, compared to dogs with a current vaccination status. Haselberger et al. [2016] showed that cats that had been vaccinated twelve months or less before sampling had lower antibody levels against FPV with increasing age and the number of vaccinations. Therefore, 'over-vaccination' of already immune animals may even be counterproductive.

Risk of adverse events

Vaccine-associated adverse events, which are defined as any undesirable side effect or unintended effect associated with the administration of a licensed vaccine, seem to occur very rarely, although accurate data about their frequency in small animals is only available to a limited extent. In general, the available vaccines are considered very safe, but a small risk of a vaccine-associated adverse event remains with every vaccination. Such adverse events may cover a broad range of clinical signs and severity. Most of them are mild and transient without any need for therapy, many of them only local reactions. However, hypersensitivity reactions and anaphylactic shock may also occur. Special concern is seen with a potential to initiate immune-mediated diseases, for which a causative connection may be difficult to establish because of the time lag. In cats a special risk is recognised for the development of feline injection-site sarcomas (FISS). Different injections may induce FISS, and a potential risk factor may be vaccination with some higher risk for adjuvanted vaccines [Srivastav et al., 2012; Hartmann et al., 2015]. Recently, Finch et al. [2016] looked at risk factors for the development of chronic kidney disease in cats. Their results suggest independent associations for two risk factors for the development of chronic kidney disease: frequent/annual vaccination and the severity of dental disease.

Ethically undesirable

From an ethical point of view, medical procedures that are of no benefit, but are associated with even a small risk of adverse events, are unjustified and should therefore be avoided. It should also be considered that in the case of over-vaccination the pet owner is paying for something that does not result in any positive effect, but may (rarely) cause adverse reactions.

Vaccination guidelines

The current knowledge of DOI, the fact that vaccination of already immune dogs and cats does not result in any positive effect and the consideration that with every vaccination a small risk of adverse reaction remains, are considered by expert groups providing recommendations for booster vaccinations. Vaccination guidelines serve as a bridge between the official requirements and the daily use of vaccines [Thiry and Horzinek, 2007]. They are non-compulsory recommendations, based on current scientific knowledge, and are intended to assist the veterinary practitioner in using vaccines efficiently [Thiry and Horzinek, 2007]. The goal is to achieve lifelong immunity, but to avoid unjustified veterinary medical procedures. For the individual animal the 'vaccine load' should be reduced as much as possible and every vaccination requires a risk / benefit assessment. To achieve 'herd immunity', the goal should be to induce at least a basic immunity in every dog and cat.

Vaccination guidelines are available from various expert groups, such as the WSAVA Vaccination Guidelines Group [Day et al., 2016], the 'Ständige Impfkommission Vet' [Duchow et al., 2013], the ABCD European Advisory Board on Cat Diseases [Hosie et al., 2015] or the AAFP Feline Vaccination Advisory Panel [Scherk et al., 2013]. Currently three year intervals are recommended for the viral core components FPV, CPV, CDV and CAV-1 (modified live vaccines). Day et al. [2016] used an even stricter wording and recommend that 'core vaccines should not be given any more frequently than every three years after the 6 or 12-month booster injection following the puppy/kitten series, because the DOI is many years and may be up to the lifetime of the pet.' The recommendation of three-year booster intervals is already considered for various commercially available vaccines. It has to be mentioned that this recommendation and the data sheets of vaccines refer to a minimum DOI, as dogs and cats that have responded to vaccination with these modified live vaccines maintain a solid immunity for many years without any repeat vaccination. This recommendation does not generally apply to inactivated core vaccines (except for rabies) or non-core vaccines. Bacterial antigens in particular have to be boosted more frequently (e.g. *Leptospira, Bordetella*). Currently available evidence indicating that leptospirosis vaccines may have a protective effect longer than 12 months is lacking. Therefore, yearly revaccination is recommended [Schuller et al., 2015]. Older animals that have been fully vaccinated as pups or kittens do not require a specialized vaccination schedule. Their immunological memory can be boosted. In various cases antibody determination may be helpful and in special cases an individually tailored schedule may be necessary.

Annual health checks

Finally, the importance of the annual health checks for dogs and cats has to be stressed. One aspect has to be vaccination, but contrary to earlier yearly routine vaccination procedures, it should be an occasion to reassess vaccination management and administer selected vaccines depending on the patient's situation. Routine serological testing may also be included to monitor the status of immunity and decide whether revaccination is indicated.

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Fecava lecture*

Top Ten Potential Drug Interactions in Small Animal Medicine

Jennifer M. Reinhart, Lauren A. Trepanier[1]

SUMMARY

Today, comorbidities are increasingly diagnosed in veterinary patients and multiple drug combinations are common. However, as the number of administered drugs increases, so too does the risk for adverse drug interactions. Much of what is known about drug-drug interactions is taken from the human literature, but a growing body of work in veterinary medicine also exists. The purpose of this review is to summarize the current knowledge of potential drug interactions in humans and dogs for ten 'at risk' drugs used in small animal medicine: cimetidine, sucralfate, ketoconazole, fluoroquinolone antibiotics, omeprazole, phenobarbital, clomipramine, furosemide, metoclopramide, and cyclosporine. Increased awareness of these potential drug interactions will enhance therapeutic decision-making and improve the level of care for veterinary patients.

Key words: drug-drug interaction, drug metabolism, adverse drug reaction, polypharmacy

Introduction

In humans, the risk of adverse drug interactions multiplies as the number of administered drugs increases. Drug interactions may lead to loss of efficacy or increased toxicity. Interactions can occur during intravenous drug administration, during oral absorption, at the target site, or during hepatic or renal elimination [1]. Although most of our knowledge of drug interactions comes from data in humans, many of these interactions are likely to occur in dogs and cats as well. An overview of the top ten potential drug interactions in dogs and cats is provided in table 1.

Cimetidine

Cimetidine, a histamine (H2) blocker often used to prevent and treat gastrointestinal ulcers, is a potent inhibitor of several families of cytochrome P450 enzymes in humans, including CYP2D6 and CYP3A4 [2]. Cimetidine can also inhibit transporter pumps and decrease the renal tubular secretion of some drugs [3]. Cimetidine decreases the clearance of many drugs to variable degrees in humans, including theophylline [4,5], lidocaine [6], midazolam [7,8], propranolol [6,9], metronidazole [10] and others. Cimetidine appears to be a much weaker inhibitor of P450s in dogs [11], but effects on renal transporters have not been well studied. Only a few drugs have been studied in dogs, with no effects on the clearance of clorazepate [12] or methadone [13], modestly delayed clearance of theophylline [14], and delayed absorption of cyclosporine [15].

Because of potential drug interactions with cimetidine, alternative H2 blockers such as ranitidine, famotidine or nizatidine (which are not P450 inhibitors at therapeutic

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Table 1: Potential drug interactions in small animal patients

	Drugs	May increase the toxicity of:	May decrease the efficacy of:	Toxicity may be increased by:	Efficacy may be decreased by:
1	**Cimetidine**	Metronidazole, lidocaine, theophylline, diazepam, propranolol	Ketoconazole, itraconazole, iron supplements		
2	**Sucralfate**		Fluoroquinolones, tetracyclines, erythromycin, theophylline, digoxin		
3	**Ketoconazole**	Cyclosporine, warfarin, digoxin, amitriptyline, midazolam, cisapride, clomipramine, colchicine			Antacids, H2 blockers, omeprazole
4	**Fluoroquinolones**	Theophylline, flunixin meglumine	Mycophenolate mofetil		Sucralfate, iron, calcium, aluminium, magnesium
5	**Omeprazole**	Diazepam, midazolam, carbamazepine, warfarin, digoxin	Ketoconazole, itraconazole, iron supplements, clopidogrel		
6	**Phenobarbital**		Glucocorticoids, clonazepam, clomipramine, lidocaine, etodolac, theophylline, digoxin, propranolol, mitotane, zonisamide, levetiracetam	Chloramphenicol	
7	**Clomipramine**	Selegiline, amitraz		Fluoxetine, ketoconazole, itraconazole, tramadol, dextromethorphan	
8	**Furosemide**	ACE inhibitors, digoxin, aminoglycosides	Bromide, lidocaine (via hypokalemia)	Aminoglycosides	NSAIDs
9	**Metoclopramide**	Ethanol, aspirin, or acetaminophen overdoses; propofol?	Probably does not counteract the renal effects of dopamine	Aceprozamine, fluoxetine	
10	**Cyclosporine**			Ketoconazole, itraconazole, fluconazole, diltiazem, clarithromycin, powdered grapefruit	St. John's wort

concentrations) may have a theoretical advantage [16]. Ranitidine and nizatidine have the added advantage of modest prokinetic effects, which may counteract gastric atony in clinically ill patients [17-19].

Sucralfate

Sucralfate, another antiulcer medication, binds many drugs in the GI tract through its aluminium moiety, forming insoluble complexes and markedly decreasing absorption [20]. For example, the relative bioavailability of doxycycline, a tetracycline antibiotic, is reduced to 20% when given with sucralfate suspension in dogs [21]. Similar results have been documented for minocycline [22]. Sucralfate decreases ciprofloxacin absorption in humans and dogs, although wide inter-individual variation in ciprofloxacin bioavailability likely modulates this effect in dogs [23-26]. Interestingly, sucralfate does not appear to alter absorption of enrofloxacin in dogs [26].

Sucralfate inhibits the absorption of theophylline, digoxin and azithromycin in humans [20,27-28], and these physicochemical interactions likely occur in dogs and cats as well. Impaired absorption of some drugs has also been reported with co-administration of other compounds containing divalent or trivalent cations, including aluminum and magnesium hydroxide [29] and ferrous sulfate [30-31].

Sucralfate drug interactions can be lessened by giving the second drug two hours before the sucralfate, but the opposite regimen is not recommended (i.e. giving the sucralfate first, followed two hours later by the other drug) because of the persistence of sucralfate in the stomach [21-24]. However, because of the difficulty in coordinating dosing at home, sucralfate should be prescribed only with careful thought when other oral drugs are being given. The exception to this is H2 blockers, for which sucralfate slows but does not decrease the extent of absorption. In humans, sucralfate and H2 blockers are given together without loss of efficacy [32-33].

Ketoconazole

The antifungals ketoconazole and itraconazole are best absorbed at acidic pH; therefore, these drugs should not be combined with omeprazole, H2 blockers or other antacids [34]. It is probably wise to discontinue antacids when ketoconazole or itraconazole is being given. Alternatively, if antacids cannot be discontinued, fluconazole can be

considered, if indicated, since fluconazole absorption is not affected by changes in gastric pH [35-36].

Ketoconazole also inhibits the cytochrome P450 enzyme family, CYP3A, which has a wide substrate range and high potential for drug-drug interactions [11,37-38]. Further, ketoconazole is an inhibitor of p-glycoprotein, an important drug efflux transporter in the intestine, kidney, and biliary tree, and a component of the blood-brain barrier [39]. Ketoconazole can therefore decrease the bioavailability and/or clearance of many drugs. For example, ketoconazole co-administration doubles ivermectin exposure (based on area under the curve) in dogs [40]. Although not currently reported, neurologic toxicity could occur if ketoconazole were combined with high doses of ivermectin (e.g. in treating sarcoptic mange) or in p-glycoprotein–deficient breeds [41-42]. Other drugs with impaired clearance from ketoconazole in humans include digoxin [43], amitriptyline [44], midazolam [45-46], clomipramine [47] and cyclosporine [48-49] (See Cyclosporine). A case of suspected ketoconazole-potentiated colchicine toxicity was also recently reported in a Chinese shar pei dog [50].

Fluoroquinolones

Fluoroquinolone antibiotics inhibit the clearance of theophylline [51-52] This has led to theophylline toxicosis in humans, and is attributed to inhibition of the cytochrome P450 enzyme CYP1A2 [51]. Fluoroquinolones also inhibit CYP1A activity in dogs in vitro. Consistent with this, in vivo studies in dogs have demonstrated that plasma theophylline concentrations are increased 30–50% by enrofloxacin [52], 28% by marbofloxacin [53], and 37% by ofloxacin [54].

Other fluoroquinolone drug interactions occur independently of cytochrome P450s. Enrofloxacin delays elimination of flunixin meglumine, possibly by competitive inhibition of renal tubular transporters, leading to higher flunixin blood concentrations in dogs [55]. In humans, ciprofloxacin decreases blood concentrations of mycophenolate mofetil, an immunosuppressive agent, by impaired enterohepatic recirculation of mycophenolic acid (MPA) [56]. MPA is excreted in bile as a glucuronidated metabolite, which is deconjugated by brush border enzymes and subsequently reabsorbed. Ciprofloxacin inhibits this glucuronidase activity, preventing MPA reabsorption [56]. Finally, di- and trivalent cation-containing medications can decrease absorption of some fluoroquinolones, causing decreased plasma concentrations and possible loss of efficacy (see Sucralfate).

Omeprazole

The antacid drug omeprazole, a proton-pump inhibitor, inhibits some cytochrome P450 enzymes in humans (primarily CYP2C19) and may inhibit the clearance of some drugs, including diazepam [57-59], midazolam [60], warfarin [61,62] and carbamazepine [63]. Omeprazole may also lead to digoxin toxicosis, possibly via inhibition of P-glycoprotein efflux of digoxin [64-65]. These interactions have yet to be evaluated in dogs or cats.

Omeprazole impairs conversion of the antiplatelet drug clopidogrel to its active metabolite in humans, leading to decreased antiplatelet efficacy and an increased risk for ischemic cardiac events in human patients [66-68]. However, a recent study in dogs showed that omeprazole at a dosage of 1 mg/kg q 24h did not significantly reduce the antiplatelet effects of clopidogrel [69].

As a potent inhibitor of gastric acid secretion, all proton pump blockers can decrease the absorption of compounds that require an acidic pH for optimal absorption, including iron supplements [70], oral zinc [71], ketoconazole [35] and itraconazole [36]. This same interaction would also apply to H2 blockers such as famotidine, although proton pump inhibitors have a greater antacid effect than H2 blockers in dogs and cats [72-74].

Phenobarbital

The barbiturate phenobarbital is a major P450 enzyme inducer in humans and dogs. Phenobarbital speeds the metabolism of many drugs in humans, including glucocorticoids [75], clonazepam [76], lidocaine [77], etodolac [78], theophylline [79-81] and digoxin [82-83]. Phenobarbital also induces mitotane clearance, and can lead to higher mitotane dosage requirements in dogs being treated for hyperadrenocorticism [84]. Conversely, chloramphenicol is a major inhibitor of phenobarbital clearance and can lead to sedation in dogs being treated with phenobarbital [85-86]. In cats, however, phenobarbital causes minimal cytochrome P450 enzyme induction, and therefore these P450-mediated drug interactions are unlikely to occur in felines [87-88].

Phenobarbital also has clinically significant drug interactions with other anticonvulsants. Clearance of zonisamide is enhanced by co-administration of phenobarbital in dogs, possibly due to induction of CYP3A [89]. Similarly, phenobarbital increases levetiracetam

(Keppra®) clearance, but by a P450-independent mechanism [90]. Phenobarbital lowers the target therapeutic concentrations of bromide needed to maintain seizure control in dogs, although this interaction is likely pharmacodynamic rather than pharmacokinetic [91]. Finally, phenobarbital undergoes autoinduction of its own metabolism, necessitating phenobarbital dosage escalations in some dogs on long-term therapy [92]. These data underscore the importance of routine therapeutic drug monitoring in any animal on phenobarbital, particularly those on combination antiepileptic drugs.

Clomipramine

Clomipramine is a tricyclic antidepressant (TCA) that inhibits norepinephrine and serotonin reuptake in the central nervous system. Pharmacodynamic interactions occur when clomipramine is combined with other drugs that increase synaptic serotonin, leading to 'serotonin syndrome' (twitching, tremor, tachycardia, myoclonic movements, hyperthermia), which can be fatal [93]. Monoamine oxidase inhibitors (MAOIs) are a well-established example in human medicine [94-96]. Although most human MAOIs are antidepressant medications, examples of veterinary MAO inhibitors include selegiline (L-deprenyl, in Anipryl®) and amitraz, found in tick dips and collars (Mitaban®, Preventic®) [93,97]. The potential for an interaction between clomipramine and these drugs has not been directly evaluated in dogs, but the veterinary clomipramine label (Clomicalm®) recommends against giving clomipramine within 14 days of either L-deprenyl or amitraz [98].

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, also inhibit neuronal reuptake of serotonin leading increased concentrations in the synapse. However, the risk for serotonin syndrome in combination with clomipramine appears to be lower than with MAOIs [99]. Other drugs that inhibit serotonin reuptake, to include tramadol and dextromethorphan (in Robitussin®), have the potential for a drug interaction with clomipramine, but the risk appears to be even lower than with MAOIs and SSRIs, at least in humans [100-101].

Clomipramine has several pharmacokinetic interactions. SSRIs can increase plasma clomipramine concentrations by inhibition of CYP2D6 in humans [47]. This can result in cardiac conduction disturbances due to the effects of clomipramine on the cardiomyocyte ion channels

and membrane potential [47-102], and ECG monitoring is recommended when clomipramine and SSRIs are combined in humans [99]. Finally, the metabolism of clomipramine can also be impaired by ketoconazole or itraconazole via CYP3A4 inhibition in humans [47], and clomipramine should probably not be combined with these azole antifungals without strong rationale and careful monitoring.

Furosemide

The loop diuretic furosemide can lead to dehydration and pre-renal azotemia, which will decrease the renal clearance of drugs such as digoxin [103,104]. Furosemide can also cause hypokalaemia and hypomagnesaemia, both of which exacerbate the cardiac toxicity of digoxin [105,106]. These interactions can lead to digoxin toxicity unless serum digoxin concentrations are monitored. In addition, furosemide enhances the nephrotoxicity of amikacin and gentamicin. Because of this, aminoglycosides should avoided in patients that require furosemide, and mannitol may be preferable to furosemide for treatment of acute renal failure caused by aminoglycosides [107]. In combination with high dosages of furosemide, ACE inhibitors can cause hemodynamic changes that can lead to acute renal failure [108]. Initial doses of ACE inhibitors should be conservative when furosemide is also instituted, and clinical status and renal function should be monitored closely, especially over the first 1-2 weeks.

Other furosemide-drug combinations can affect efficacy. Hypokalaemia secondary to furosemide can blunt the antiarrhythmic effects of lidocaine [109]. Serum potassium should be evaluated in patients with ventricular arrhythmias, and potassium supplementation should be considered if furosemide-treated patients do not respond to lidocaine. Furosemide-induced diuresis will also increase the renal loss of bromide and lower serum bromide concentrations, which may lead to seizure breakthrough [110]. The dosage of bromide may need to be increased, for example, by about 50%, in epileptic dogs for which furosemide is later added for heart failure or other disorders. Finally, non-steroidal anti-inflammatory drugs may blunt the diuretic and natriuretic effect of furosemide by impaired renal vasodilation in both dogs and humans [111-113].

Metoclopramide

As a dopaminergic (D2) antagonist and prokinetic agent, the anti-emetic metoclopramide has several important drug interactions. Metoclopramide enhances the absorption of acetaminophen [114], aspirin [115] and alcohol overdoses [116,117] in humans, via increased gastric emptying into the small intestine. Metoclopramide has also been reported to increase cyclosporine absorption in humans, but this was not demonstrated in a canine study (See Cyclosporine) [118,119]. Theoretically, metoclopramide can cause extrapyramidal side effects (tremor) when combined with phenothiazine tranquilizers [120] or SSRIs [121,122]. Tremors can also be seen at standard metoclopramide dosages in dogs with renal insufficiency, necessitating dose adjustment.

In humans, metoclopramide reduces pain on injection of propofol and decreases the amount of propofol needed for anesthetic induction (by 20-25%) by an unknown mechanism [123]. Although metoclopramide is a dopamine antagonist, it has no effect on the use of dopamine for hypotension, which is mediated by D1 receptors [124]. Interestingly, metoclopramide did attenuate dopamine-mediated renal vasodilation in dogs, but only transiently [124].

Cyclosporine

As a substrate for both p-glycoprotein and the cytochrome P450 CYP3A, the immunomodulatory drug cyclosporine has the potential for numerous drug interactions. Drugs that inhibit CYP3A decrease the clearance of cyclosporine, leading to increased blood concentrations and the potential for toxicity. These compounds include, but are not limited to, diltiazem [125], clarithromycin [126,127], ketoconazole and other azole antifungals [48,127,128], and even grapefruit juice and powder [119]. Both cimetidine and metoclopramide have been reported to decrease cyclosporine clearance in humans [118,129]. However, these drugs do not appear to significantly impact cyclosporine concentrations in dogs, perhaps due to a species difference in enzyme-substrate specificity [15,119]. The nutraceutical St. John's Wort induces CYP3A4 in humans and accelerates elimination of cyclosporine, decreasing drug concentrations; this has also been shown in dogs [130-132]. Supplements containing St. John's Wort should be avoided in dogs being treated with cyclosporine.

The interaction between ketoconazole and cyclosporine has been exploited in veterinary medicine to obtain higher blood concentrations for a given dosage of cyclosporine. This allows lower therapeutic dosages of cyclosporine and better affordability for larger dogs [49,133-135]. Recommended dosages are cyclosporine, 2.5–5.0 mg/kg once to twice

daily, depending on the disease being treated [49,133-137], and ketoconazole, 2.5 mg/kg/day [136]. Monitoring of ALT is strongly recommended during treatment, since azole antifungals can lead to increases in serum hepatocellular enzymes [138]. Trough therapeutic drug monitoring of cyclosporine (whole blood drawn just prior to the next dose) may also be helpful, but target cyclosporine concentrations have not been well established for the range of diseases treated in veterinary medicine. Extrapolating from human recommendations, several canine studies have demonstrated a clinical response by targeting cyclosporine concentrations of 400–600 ng/ml [134,135]; however, lower concentrations may be adequate for diseases such as perianal fistula and inflammatory bowel disease [139].

Both fluconazole and clarithromycin have recently been investigated for cyclosporine-sparing effects in dogs [126,128,140]. In one study,(126) clarithromycin (10 mg/kg, q 12 h) increased the area under the curve (AUC) of cyclosporine by 33%, while a second investigation [128] demonstrated a 92% increase in AUC with concurrent administration of fluconazole (4.3 mg/kg/day). Further, fluconazole (5 mg/kg/day) decreased the total daily dose of cyclosporine necessary to maintain therapeutic concentrations (400–600 ng/ml) by 39% in dogs following renal transplantation [140]. Although no direct comparisons have been performed, these data suggest that fluconazole may be a viable alternative to ketoconazole for reducing cyclosporine requirements in dogs, whereas clarithromycin may not be as effective [49,126,128].

Acknowledgements/Conflicts of Interest

Dr. Trepanier has no conflicts of interest to declare.

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Fecava symposium*

Ten animal welfare ideas to apply in small animal practice

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SUMMARY

Many options exist to implement animal welfare in the work place of small animal practice. Simple measures can be taken to minimize fear and stress while handling patients. Animal owners can contribute to reduce their animal's fear when visiting the veterinary clinic. Appropriate analgesia involving both the owners' awareness and procedural pain management are of great importance. Veterinarians can promote animal welfare by advising owners about purchase, animal husbandry and non-violent training methods. They should particularly provide information on sensitive periods during ontogenesis and on breeds with specific physical impairments causing pain, suffering or harm to the animal, since these issues have a special impact on animal welfare. Bite prevention and behavioural therapy are further important consulting areas.

Keywords: behaviour, counselling, small animal practice, welfare

Introduction

There is a growing awareness of the need to introduce animal welfare into everyday life. Recently an ethical code has been passed in Germany (Bundestierärztekammer, 2015) that requires veterinarians to use their professional knowledge and abilities to protect the well-being of animals. Small animal practitioners are confronted with a variety of issues regarding animal welfare. At the same time, they have many opportunities to intervene and to optimize these issues during their daily work. The following, ten concepts present ideas for incorporating animal welfare into routine veterinary practice.

Ten ideas

Idea 1: Friendly handling of cats to reduce stress at the veterinary practice

Animal welfare requires cat-friendly handling techniques and measures to reduce fear at the veterinary practice. Rodan (2010) stated that fear and pain are the main reasons for aggressive behaviour of cats when visiting the veterinary clinic. Therefore, fear and stress reduction may decrease the risk of injury to the staff. This can be achieved by changing the structure of rooms and workflows and by following simple handling rules. It is advisable to separate the waiting areas for dogs and cats, to implement noise reducing measures and to create elevated platforms for transport boxes. An important measure is to offer treats to the cats. Anseeuw et al. (2006) stated that cats were often willing to accept treats at the veterinary practice. The use of pheromones in the waiting room is also useful (e.g. Feliway®). It is of the

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utmost importance to eliminate all smells that can cause fear, for example from previously treated cats by cleaning surface areas thoroughly and by getting fresh air into the examination room. When handling cats, minimal restrain is best (Krämer und Krämer, 1992). Minimal handling gives the cat a feeling of control and, as a result, it reacts in a less aggressive way (Rodan, 2010). The treatment room can be arranged in a cat-friendly manner by providing seating benches and elevated areas (Anseeuw et al., 2006). For padding or to cover the treatment table a soft towel or ideally a familiar smelling cat blanket brought along by the owner should be used.

Fearful cats that will not leave transport boxes voluntarily can be examined and treated in the lower portion of the transport box, if the lid is removable (Rodan, 2010). As an alternative or in addition they can be covered by a towel. For additional suggestions to reduce stress at the practice or during hospitalization, please refer to Anseeuw et al. (2006), Rodan (2010), Rodan et al. (2011), Carney et al. (2012), Hammerle et al. (2015) and to the website of the American Association of Feline Practitioners (http://www.catvets.com).

Idea 2: Stress reduction for dogs at the veterinary practice

The majority of dogs exhibit fear at the veterinary practice, as shown by Döring et al. (2009) in their study of 135 dogs. The dogs' behaviour was evaluated during general examination by scoring. Of these dogs, 78.5% were found to be 'fearful'. Young dogs were less fearful than older dogs, males were less fearful than females. Several of the dogs had already had 'bad experiences' with veterinarians. These experiences were found to be related to the fearful behaviour at the practice.

Fearful behaviour can be reduced if the veterinarian applies measures like taking a dog-friendly body position (crouching down, looking away) and using rewards (treats) (Roscher, 2005). When offering treats, the right timing is most important. The treats should already have been given when the dog arrives at the practice, when it enters the examination room as well as when the dog is on the examination table. Thus the veterinarian should not wait until after the examination to give the first treat. Fearful patients should be specifically trained in the practice environment using desensitization and counterconditioning. More information is provided by Landsberg et al. (2013) and Overall (2013).

Idea 3: Advising the animal owner on how to prepare the pet for the practice visit

Dog and cat owners can take several measures to reduce their pet's fear of a veterinary visit. For cats, gentle familiarization with the transport carrier and the transport itself is important (Döring, 2013). A client brochure for cat owners is available on the website of the AAFP (http://www.catvets.com/public/PDFs/ClientBrochures/Cat-to-VetHandout.pdf).

Furthermore, owners should be informed about what they can do during the veterinary visit: bring along a favourite food, favourite toys and a familiar smelling blanket; keep dogs away from the transport box of cats (do not let dogs smell it); behave calmly, which means breathe calmly, stroke the pet slowly, have a calm and quiet voice, praise and reward calm/positive behaviour, ignore fearful/aggressive behaviour, do not shout at or punish the pet (Anseeuw et al., 2006).

For prevention of subsequent problems dogs and cats should be used to being touched all over their bodies, starting as a puppy or kitten. Good socialization with positive contact with a variety of people is crucial. In addition, owners of young dogs and cats should be encouraged to come with their animal to the veterinary practice for 'fun visits'. With the use of treats the animals should become acquainted with veterinary visits in a positive way.

Idea 4: Pain management

Animal owners are required to reduce the pain of their pets (Lorz und Metzger, 2008). But there are owners who do not realize when their pet is suffering from pain. Some organizations provide free information material for pain assessment (IT IS, 2013, WSAVA, 2014; Epstein et al., 2015).

Veterinarians should include pain management in the scope of their surgical activities. Peri- and postoperative pain treatment is essential for animal welfare; it has many positive effects in terms of improved wound healing, rapid convalescence and lowered recrudescence of tumours (ITIS, 2012).

Idea 5: Advice prior to purchase

False expectations on species and breeds are widespread, e.g. that golden hamsters are appropriate pets for children. However, golden hamsters are strictly nocturnal and live solitarily (Gattermann et al., 2001). Therefore, they are

unsuitable for children that want to play with them or pet them during the daytime.

Veterinarians have the expertise to competently advise clients about behaviour and about specific requirements for their husbandry, including any impairments caused by breeding. Animals with critical health issues should not be purchased, such as animals with missing body parts (e.g. missing tail, hairlessness, missing whiskers), with over-typification of certain traits (brachycephaly, dwarfism, giantism, ectropion etc.) or with certain colours which are associated with defects of the sensory organs (e.g. dominant white gene in Persian cats, merle colour in dog breeds; BMVEL, 2002). Dwarf rabbits with homozygous expression of the dwarf gene are not viable (BMVEL, 2002). This means that when breeding two dwarf rabbits, one fourth of the offspring dies. How many owners know that when they buy a dwarf rabbit it probably has some dead siblings?

Idea 6: Advice on animal husbandry
Failures are widespread in pet husbandry, especially for small mammals and birds. The animals are often kept in cages that are too small. Harmful or dangerous accessories like metal running wheels, hamster balls and harnesses are used. Social species are housed solitarily (e.g. rabbits: Rooney et al., 2014). Furthermore, many pets are fed inappropriate food. These deficits contrast the fact that animal owners generally want the best for their pet. When small mammals and birds are brought to the veterinary practice, veterinarians can detect deficits in their husbandry. In these cases, competent advice is of great importance. Good information can be found in books (e.g. Morgenegg, 2005; 2005) and on the internet (e.g. information sheets in German at http://www.tierschutz-tvt.de and the BLV http://www.meinheimtier.ch/de). The husbandry requirements of pet golden hamsters were studied at the University Bern (e.g. Gebhardt-Henrich et al., 2005; Hauzenberger et al., 2006; Fischer et al., 2007; http://www.tierschutz.vetsuisse.unibe.ch/research/former_institute/pdf_documents/index_eng.html).

Idea 7: Advice about socialization
The adequate socialization of companion animals is essential for their well-being. Dogs and cats that are not socialized with humans are permanently exposed to fear. Socialization with conspecifics is also very important to develop adequate social behaviour. Veterinarians should

educate animal owners and breeders about the significance of the so-called sensitive period to avoid later suffering resulting from behaviour problems. In dogs this period is approximately between 3 to 12 weeks after birth (Scott and Fuller, 1965). In cats it is about 2 to 7 weeks after birth (Karsh und Turner, 1988). When advising clients who want to purchase an animal, the focus should be on choosing competent and responsible breeders who offer socialization and habituation (familiarization with everyday stimuli). In small pets the sensitive periods are not clearly defined yet. In rats weeks 4 and 5 after birth were found to be sensitive (Maurer et al., 2008).

Idea 8: Advice on non-violent training methods
Many owners use physical punishment during training and as a reaction to behavioural problems. These methods are not acceptable for many reasons which are explained in the position statements of the AVSAB (2007) and AAFB (2011). In Germany, the use of training methods that result in considerable pain are not allowed (§ 3, German Protection of Animals Act, 2015). Furthermore, one needs reasonable grounds to cause even the slightest pain (§ 1, German Protection of Animals Act, 2015). Since there are plenty of pain-free training alternatives, there is no reason to use painful training measures. The use of electric dog collars is forbidden in Germany (Döring and Erhard, 2008).

Idea 9: Bite prevention
Most dog bites are caused by familiar dogs, often by the family dog (Kahn et al., 2003; Horisberger et al., 2004; De Keuster et al., 2006; Rosado et al., 2009; Reisner et al., 2011).

Children are especially frequent victims (Rosado et al., 2009, Reisner et al., 2011). Veterinarians can play a crucial role in bite prevention through education. They see families with children entering the practice with their newly purchased puppy. Veterinarians can also recognize when dog owners are expecting a child. The most important rule is that the dog and the child should never be left alone - not even for a short moment. Additionally, the child should never annoy the dog, even if it is meant affectionately. It should be forbidden to kiss, hug, or disturb the dog while it is eating or lying down. Valuable information can be found in the German brochures of the TVT (2006) and BLV (2015) as well as on the interactive CD of The Blue Dog (http://www.thebluedog.org).

Idea 10: Behaviour therapy

Behaviour therapy can play an important role in animal welfare (Döring and Erhard, 2006). Some behaviour problems are an expression of the animals' suffering: Dogs that howl or destroy objects when left alone may suffer from separation anxiety. In this case, their behaviour may reflect stress. If pets show stereotypes, e.g. golden hamsters gnawing on the cage bars, this may be an indicator of deficits in animal husbandry. Behaviour therapy aims to eliminate the causes of the problems, thus improving the situation for the animal. It provides the owner with effective, non-violent training methods and leads to a stabilization of the animal-human relationship. Behaviour problems are often the reason animals are surrendered to shelters (Miller et al., 1996; Patronek et al., 1996; Salman et al., 2000; Wells and Hepper, 2000; Diesel et al., 2008; 2010). Gazzano et al. (2008) showed that veterinarians can help to prevent undesirable behaviour in dogs by giving advice to puppy owners.

The AAHA Canine and Feline Behavior Management Guidelines (Hammerle et al., 2015) give an overview of the basic knowledge on ethology that can be very helpful to the practitioner for his daily work.

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Conflict of interest

The authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, this article.

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Fecava lecture*

Deleterious effects of pedigree dog breeding on behaviour

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SUMMARY

Pedigree dog breeding has led to both direct welfare issues caused by selection for exaggerated anatomical features and indirect issues by selecting predominantly for appearance without due consideration of health and behaviour. This paper describes how each of these issues can impact negatively on the dog's behaviour, and suitability as a companion in addition to the health implications commonly discussed. Anatomical features can affect the dog's capacity to carry out normal behaviours, and an observation study of naturalistic dog-dog encounters suggests that dogs with very modified anatomical features, and reduced signalling capacity, are interacted and played with, less often than those with fuller signalling capacity. By selecting predominantly for physical appearance, breeders may also have inadvertently selected dogs ill-suited to the companion environment and with a higher likelihood of developing a range of behavioural problems.

This paper highlights the lack of behavioural data and the dangers in assuming that behavioural differences are genetically controlled, when the effects of rearing environment may be equally strong. There are risks if future selection concentrates on the elimination of specific diseases, whilst still retaining a breed-specific phenotype, and a closed genetic pool. Future breed management plans must therefore take temperament into consideration, and systems to record and monitor behaviour and the occurrence of problems should be considered. We all, veterinarians and behaviourists alike, have a role to play in ensuring we safeguard the behaviour and welfare of future generations of pedigree dogs.

Key words: Pedigree dog, breeding, welfare, behaviour, morphology

Introduction

Over the past few years there has been considerable interest in the welfare concerns associated with pedigree dog breeding in the UK, Europe and beyond.
Following a BBC One documentary, Pedigree Dogs Exposed (BBC 2008) - three key reports (Rooney & Sargan 2009;

Associate Parliamentary Group for Animal Welfare 2009; Bateson 2010), and a number of influential papers (e.g. Asher et al 2009; Summers et al 2010; Packer et al 2013), have been published. Although concentrating primarily on health issues, most of these publications allude to the potential detrimental effects of selective breeding practices upon the temperament and behaviour of dogs. These risks are significant and merit consideration as well as health risks. Hence the Associate Parliamentary Group for Animal Welfare (APGAW: 2009) highlighted the importance of involving behaviourists in the development of breeding strategies and in an independent advisory body; while Bateson (2010) concluded that 'better selection for appropriate temperament combined with effective

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socialisation in the first weeks of a puppy's life' are required. Rooney and Sargan (2009), carried out a survey of experts aimed at prioritising welfare initiatives for improving pedigree dog welfare, and identified two actions of primary importance that refer to behavioural traits: 'the introduction of codes of practice that encourage breeders to consider health, temperament and welfare' and the 'training and accreditation of judges to prioritise health, welfare and behaviour in the show ring'.

Welfare issues surrounding pedigree dog breeding can be divided into two distinct but inter-related categories (Rooney & Sargan 2010):

a) **Increased prevalence of inherited disorders** as a result of a lack of genetic diversity, inbreeding and line breeding, ill-informed breeding choices and over-attention to physical attributes rather than health, welfare and behaviour.

b) **Exaggerated anatomical features that directly reduce the quality of life.**
Issues of both types compromise physical health, but they can also adversely affect the behaviour of certain breeds. However, there is only a limited amount of published data quantifying such behavioural effects, far less than for physical health, making the full extent of the problems difficult to assess.

This paper reviews the literature on the indirect effects of breeding for phenotype on behaviour and also the direct behavioural effects of exaggerated anatomical features. It includes examples from the author's own pilot studies exploring the effects of modification of signalling ability on communication.

Indirect effects of breeding predominantly for appearance

There are likely numerous indirect effects of selective breeding on behaviour since basing choices primarily on appearance means insufficient attention is often paid to temperament or capacity to cope in a domestic environment (McGreevy 2008).

Inferences about selection for temperament are often drawn from comparisons between working and show strains of the same breed. Bateson (2010) stated that 'the only breeds in which artificial selection for desired patterns of behaviour has occurred are the working breeds, the sleeve dogs and possibly those used to help people with disabilities.' Hence one may expect that working strains

would suffer from fewer behaviour problems (or at least fewer of those that may impact upon working ability) than would dogs bred for showing.

In support of this, Duffy et al (2008) found that conformation-bred English Springer Spaniels were reported to be more aggressive towards humans and towards other dogs than field-bred individuals, which they suggest is likely a result of the extensive use of "popular sires" with this temperament type. Similarly, a comparison of 13,097 Swedish dogs of 31 breeds found that dogs bred for showing were more likely to display social and non-social fearfulness, were less playful and curious than dogs from working lines (Svartberg 2005). These findings on first examination seem to point to the conclusion that these traits described are heritable and have been selected for or against in working, but not in to show lines. However, these findings need to be interpreted with care: dogs of working lines may be acquired by owners whose motives, lifestyle, location and approach to training differ significantly to those who choose show-bred dogs. Hence, the apparent genetic effects may be confounded by owner behaviour or rearing environment. In fact, our own studies of working and show Labradors reared in standardised environments show that strains do differ in their adult behaviour, but there are significant differences in the amount of interaction breeders have with their dogs before the age of eight weeks. Puppies from show lines generally have more early human contact, and this in fact may account for some of the differences seen between the adult populations (Rooney et al 2003).

Several studies report breed-specific differences in the incidence of behaviour problems (e.g. Guy et al 2001), and include apparent evidence for a genetic predisposition towards aggression in specific lines of Golden Retrievers as this behaviour tends to occur more in some family groups than others (Knol et al 1997). Also, in Cocker Spaniels a behavioural tendency, which the authors label "dominant-aggressive" behaviour has been shown to vary greatly between different coloured dogs (Podberscek & Serpell 1996; Perez-Guisado et al 2006), suggesting that when selecting for specific colour types breeders may have inadvertently selected for a low threshold for aggressive behaviour. However, as with health problems, an historic lack of systematic data collection on dog behaviour and the incidence of problems, means that comparative levels in the general dog population are unknown.

Recently, large-scale data collection on reported behavioural problems has started to occur, using instruments such as the Canine Behavioural Assessment and Research Questionnaire (CBARQ Serpell 2016; Hsu and Serpell 2003). Findings from studies have supported the hypothesis that selection for particular morphological traits may be accompanied by detrimental behavioural changes. For example, comparisons of 49 common Australian breeds saw reported behaviour to co-vary significantly with morphology (McGreevy et al 2013). In total, 32 undesirable behavioural traits correlated with either height, bodyweight, skull shape (measured as cephalic index (CI): ratio of skull width to length) or some combination thereof. For example, breed height showed strongly significant inverse relationships with a range of reported problems including touch sensitivity, dog-directed fear, separation-related problems, non-social fear, owner-directed aggression. All but one behaviour showed a negative regressions with height, suggesting that the shorter the dog the more likely it is to be reported to show high levels of behaviours often deemed problematic.

Such systematic data collection on dog behaviour facilitates important interbreed and inter-strain comparisons, but caution must be exercised when using questionnaire instruments which rely entirely on owner-reported data that may be affected by natural biases and expectations of how particular breeds should behave. More objective data have started to be collected (e.g. Stone et al 2016), which supports previous findings of a covariance between morphology (size, weight and CI) and behaviour (as measured in a standardised Dog Mentality Assessment). Objective recordings of the behaviour of dogs of all breeds and monitoring of the effects of altered selection pressures are therefore also essential.

Direct effects of breeding for exaggerated anatomical features

Many extreme anatomical traits selected for in particular breeds and even described explicitly in breed standards can result in pain and suffering (Asher et al 2009). However, some cause more subtle effects by preventing dogs from behaving 'normally'. Since provision for the need 'to exhibit normal behaviour patterns' is specified in the Animal Welfare Act (DEFRA 2006), this is a significant concern. However, normal behaviour is not easy to define in a species such as the dog bred for human purposes, which may have lost some of the repertoire of its wild ancestor, or in certain breeds whose behavioural repertoire has been

altered by artificial selection (Bateson 2010). Hence it is challenging to define the level at which behaviour is affected to such a degree that it warrants concern and thus what level of exaggeration is acceptable.

Evidence suggests that physical conformations of certain breeds can restrict their behaviour via a number of mechanisms:

a. Behavioural repertoire can be restricted by **pain or discomfort** resulting from specific anatomical features. For example, some breeds have respiratory deformities (e.g. brachycephalic breeds) which may prevent them from running without shortness of breath. For these dogs, their ability to explore, and exercise may be compromised and their opportunity for natural behaviour and social interactions can consequently be limited.

b. Some anatomical features **physically constrain** the animal rendering it incapable of executing specific behaviours; for example severely reduced limb lengths may restrict dwarf dogs' abilities to run freely. In addition, breeds with short legs and long bodies are less able to play-bow to invite playful interactions with other dogs. Play behaviour is rewarding (Boissy et al 2007), important for normal social development (e.g. Suomi 1982), and high play levels are an indicator of positive welfare (e.g. Jensen et al 1998). Since play signalling is critical to the initiation and continuation of dog play (Bekoff 1995; Rooney et al 2001) an inability to perform these signals may have important behaviour and welfare consequences.

c. Other anatomical modifications have been postulated to **result in fear.** For example, the breed standard, for the Hungarian Puli states 'Long hair overshadows eyes like an umbrella' (The Kennel Club 1998). This obstructs the dog's vision and has been reported to reduce its awareness of its surroundings, increasing the risk that the dog will be startled and react fearfully or aggressively because it cannot adequately assess the context (Houpt 1991). Some breeds are so small that they have been reported to suffer frequent fear and high levels of fearful and defensive behaviours (Duffy et al 2008). Extreme small size may influence their socialisation and diminish their quality of life and may be responsible for some of the associations with reduced body weight and height seen in studies described earlier.

d   Numerous breeds are anatomically modified in such a way that their **capacity to signal is considerably reduced** (Goodwin et al 1997). For example, the stiff legs of the French bulldog prevent it from signalling by the subtle adjustments of height commonly used by dogs of many other breeds (Netto et al 1992). Breeds with flat faces (brachycephalic) are less able to utilise facial expressions; whilst dogs with very short or tightly curled tails (e.g. Leaver and Riemchen 2008), with immobile, drooping or permanently erect ears are less able to signal their intentions. Breeds with very short coats or permanently erected fur are unable to raise their hackles and for breeds with very long or dense fur, nearly all body language communication is obscured. Such extreme anatomical breed traits are postulated to affect a dog's ability to interact with other dogs and to engage in normal social interactions (Bradshaw & Nott 1995).

Goodwin et al (1997) observed differences in the signalling ability of ten breeds of dogs and the number of signals produced correlated inversely with the degree to which the breed was anatomically modified relative to the wolf. They hypothesised that such modification would affect the types of behavioural interactions dogs engaged in, but to our knowledge no studies of 'receiver' dogs' behaviour have been made to date. We therefore carried out a pilot study to investigate whether variations in signalling capacity affect the behaviour of dogs encountering a dog and hence its capacity for social interactions in a natural dog-walking situation (Rooney, Tunnicliff, Browne & Bradshaw unpublished).

We hypothesised that
• Dogs being walked in a park will differ in their response to a target dog dependent upon the target breed's signalling capacity.
• Breeds with the highest signalling capacity will be approached playfully more frequently.
• Breeds with more limited signalling capacity will produce more ambiguous signals and hence promote the most aggressive responses or be avoided most often by dogs they meet.

Twenty-one human subjects were presented with pictures of 20 different breeds of dog (10 medium and 10 large breeds) and were asked to rate their capacity of each to signal using their tail, muzzle, ears and body (on a scale 1-5). Scores for each signalling structure were summed to give a score out of 20, which showed high concordance between scorers (Kendall's W = 0.81; p<0.001). We selected four common breeds with significantly different signalling capacities, yet of similar size, since this may affect other dogs' reactions; the German Shepherd Dog (highest signalling capacity) Labrador Retriever, German Short-haired Pointer, and Boxer (lowest signalling capacity; $F_{(3,16)}$= 77.6, p<0.001).

We recruited four dogs of each breed to act as targets for bouts of dog-dog communication. Each dog was known to be walked regularly on the leash, alone, and was not reported to show aggression to other dogs. Dogs were each recorded on between two to four walks, in a place or at a time when they were likely to meet unfamiliar dogs. Any unknown (object) dogs that came into the visual range of the target dog were recorded. The object dog's response, including its ear and tail position where visible, was observed and whether it approached, avoided or ignored, and the nature of any interaction that occurred was recorded (playful, neutral, submissive, aggressive, or no interaction). The target dogs encountered a total of 396 object dogs. One of the Labradors was seen to initiate significantly different behaviour in dogs it met compared to the others of that breed and so was eliminated from analysis.

The likelihood of an object dog approaching varied significantly with target breed (Fisher's exact=13.5, p = 0.03), but this did not seem to be related to signalling capacity. Labradors were approached most frequently (56%), but they were also avoided the most often (16%), and more often than would be predicted (Standarised residual = 2.2). This may be due to many dogs having had past experiences with this breed, and having modified their behaviour dependent upon whether past experiences were positive or negative.

When examining the nature of interactions, the target breed was found to significantly affect the response of object dogs (Fisher's exact = 24.6, p = 0.01) and the variation could be explained by differences in signalling capacity, as hypothesised. Breeds with higher signalling capacity received the expected frequency of playful, aggressive and submissive responses. However, breeds with lower signalling capacity; German Short-haired Pointers, experienced more than expected "no interaction" (18%), and Boxers received fewer than expected playful responses (20% compared to 39% for Labradors). No significant differences in the frequency of aggressive responses were seen.

This pilot experiment supports the idea that modification

to signalling structures restricts the frequency and nature of social interactions which dogs experience on a walk. This was seen in common breeds which do not have the extreme modifications seen in some rarer breeds. This finding is also of significant concern as several breeds with very exaggerated features are becoming extremely popular in the UK, for example the number of annual Pug registrations increased 4 fold between 2006 and 2015, and the Chihuahua more than doubled in popularity during the same period (Kennel Club 2016). If such dogs appear ambiguous in their signalling and hence do not receive amicable approaches from other dogs, combined with the risk of behaviour problems seen to be associated with small size (McGreevy et al 2013), this presents a significant welfare concern. Therefore, we intend to repeat this study with a large number of breeds including some with more extreme modifications.

In conclusion

In recent years, and in the light of the key publications described above and their recommendations, a number of important initiatives have started to be implemented, aimed at improving the health and welfare of pedigree dogs. Several priority actions identified by Rooney and Sargan (2010) have been put into practice. For example, the Kennel Club has banned first-degree matings (but not second degree as was also suggested) and research has been funded to develop methods for the systematic collection of morbidity and mortality data from all registered dogs (see O'Neill 2014 and O'Neill et al 2014) .

Although these initiatives focus primarily on health, some commendable efforts have been made to consider behaviour and temperament, for example, the independent Advisory Council on the Welfare Issues of Dog Breeding (2012) was formulated, as recommended by many authors with one of its members being an expert in dog behaviour. Before its disbanding, the council made some advance, however, overall progress has been relatively slow and whilst some initiatives may be necessarily so, requiring a long-term commitment, it can be argued that more radical action is still required (RSPCA 2013). In particular progress at ameliorating and quantifying behavioural issues is limited and seemingly underrated in importance.

This paper has highlighted the paucity of behavioural data and the dangers of assuming that behavioural differences are genetically controlled, when effects of

rearing environment may be equally strong. Therefore, consideration and monitoring of behaviour remains critical, and research is needed to address many important unknowns. It is even possible that successful efforts to improve breeders' attention to long term physical health may lead to detrimental effects on temperament and behaviour in some breeds. Selection in certain breeds may concentrate on the elimination of specific diseases, whilst still retaining a breed-specific phenotype, and a closed genetic pool. In the absence of inter-country matings or out-crossing, (as recommended Rooney and Sargan 2010) available mate choices may be limited especially in rarer breeds, which may result in even less selection pressure being exerted on temperament, and new problems may emerge. Therefore, breed management plans must take temperament into consideration and for this, record keeping is vital. In the same way that methods to fully elucidate and monitor the incidence of health problems are being developed, systems to record and monitor behaviour and the occurrence of problems should also be considered. Hence we all (veterinarians and behaviourists alike) have a role to play in ensuring we safeguard the behaviour and welfare of future generations of pedigree dogs.

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Oral antiepileptic drug therapy options in cats

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SUMMARY

Introduction: Epilepsy is one of the most common neurologic diseases of feline patients. Phenobarbital is the most common anticonvulsant used for treating feline epilepsy, but several other suitable drugs are available. The objectives of this paper are a discussion of the oral treatment options for idiopathic epilepsy and to compare the efficacy, side effects and frequency of administration. The aim is to offer guidance for therapeutic decisions.

Materials and Methods: This paper summarizes and analyses several oral therapy options for feline epilepsy. The literature is critically analysed and evaluated, concerning its type and evidence, and in the case of studies, the type of study, number of animals in the study and duration. Recent specialist books and scientific search engines like Pubmed, Ovid, Google Scholar and Scopus were used for literature research. Additionally, reference lists were used to find related records, primary literature about feline epilepsy and diverse anticonvulsants.

Results: Fourteen drugs were described in the literature as anticonvulsants for use in feline epilepsy. Considering their pharmacokinetics, pharmacodynamics, side effects and clinical experience, the authors highly recommend phenobarbital, zonisamide and levetiracetam for clinical use in epileptic cats. The use of gabapentin, pregabalin, bromide, diazepam, carbamazepine, propentofylline, taurine and topiramate is also feasible (moderate/low recommendation), while primidone, phenytoin and valproic acid are not recommended. A review of the studies made it obvious that knowledge about therapy options in feline epilepsy is based on weak evidence. Information on antiepileptic therapy in cats rests upon expert opinion, case reports (Class IV) and a small number of prospective and retrospective studies (Class III). Not a single class-I or class-II study (placebo-controlled, randomized, double-blind trial) describing clinical efficacy is available. Furthermore, the studies are frequently marred by the small number of cats, insufficient time of observation, simultaneous administration of different anticonvulsant drugs and a lack of comparative studies.

Conclusion: Based on the literature, there is a need for additional studies with more robust evidence, such as placebo-blinded and comparative studies, for determining a meaningful treatment regime. Additionally, it is important to increase the number of patients and to extend the duration of the observation period. Until then, the treatment of epilepsy therapy can only be based on poor evidence.

Keywords: epilepsy, cats, oral therapy, phenobarbital, antiepileptic drugs

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INDEX OF ABBREVIATIONS

Br	bromide		**n.d.**	no data
CBZ	carbamazepine		**LEV**	levetiracetam
GABA	gamma(γ)-aminobutyric acid		**PB**	phenobarbital
GP	gabapentin		**VPA**	valproic acid
h	hours		**ZON**	zonisamide
ILAE	International League Against Epilepsy			

Introduction – Feline epilepsy

Epilepsy is one of the most common neurological diseases in small animal practice (Thomas & Dewey, 2008). The prevalence, measured by the population, in different hospitals is 0.5-3.5% (Schwarz-Porsche & Kaiser, 1989; Pakozdy et al., 2010)

There are different opinions regarding the commencement of anticonvulsant therapy in cats. A single epileptic seizure does not require long-term therapy. Only in cases of seizure-accumulation or status epilepticus, should antiepileptic therapy be started (Platt, 2001). However, some authors support aggressive therapy even after a few epileptic seizures (Quesnel et al., 1997). A retrospective study indicated a better outcome after early therapy (Pakozdy et al., 2013). Another author also advocates prompt treatment, because of brain damage caused by each seizure. This leads to the phenomenon of 'kindling', i.e. make further seizures more likely (Rusbridge, 2005).

Generally treatment is initiated because of four indications (Rusbridge, 2005):
- More than one seizure within 12 weeks.
- There are clusters of seizures or status epilepticus.
- Seizure duration is longer than five minutes.
- Seizure frequency is continuously rising.

The goals of anticonvulsant therapy are: a reduction in the frequency and severity of seizures to a minimum, the lowest possible side effects and restoration of quality of life for the pet and the family. Therefore, the possibility of further seizures and the risks of side effects based on long-term therapy should be considered (Thomas & Dewy, 2008). In most cases a long-term therapy is required. Based on the literature, the target of this review is to identify oral therapy options and to compare the efficacy of applicable drugs, their side effects and frequency of administration. Finally, this paper aims to offer guidance for therapeutic decisions.

Material and Methods

The literature was critically considered and evaluated with regards to validity (quality and evidence of literature and in cases of studies; mode, duration of implementation and number of animals per study).

Within the framework of the literature search, the newest veterinary, human neurology, pharmacology books and scientific search engines like PubMed, Ovid, Google Scholar and Scopus were consulted. The following search items were used: "epilepsy cat*", "feline epilepsy", "Epilepsie Katze", "antiepileptic drug* cat*", "idiopathic epilepsy cat*", "idiopathische Epilepsie Katze", "seizure* cat*", "therapy epileptic cat*" and "Epilepsie Therapie Katze". The resulting drugs have been examined in consideration of their pharmacokinetics, pharmacodynamics and clinical use in cats. Furthermore, the Austrian Codex providing the basis of registered trade names of the drugs and reference lists was consulted for continuing research.

To reach a decision: rehabilitation, frequency of administration and side effects were considered. Moreover, the literature was evaluated (quality of literature or study, number of patients and duration of treatment). The guidelines of the ILAE were consulted: class I and class II = placebo-controlled, randomised and double blinded studies, with a high number of cats. Class III = open label studies. Class IV = case reports and expert opinions (Glauser et al., 2006).

Results

Phenobarbital

Phenobarbital (PB), a barbiturate, is used for anaesthesia and the treatment of epilepsy and because of its anxiolytic and sedative-hypnotic effects (Heyer & Macdonald, 1982; Twyman et al., 1989). PB is the initial drug of choice for feline epilepsy (Dewey, 2006; Thomas & Dewey, 2008).

Pharmacodynamics: The anticonvulsant effect of PB is based on different mechanisms. Its effect is mediated by γ-aminobutyric acid (GABA) A receptor. This causes a prolonged gate opening of postsynaptic chloride channels – a boost of GABA efficacy – and therefore an inward chloride ion flux and membrane hyperpolarization (Twyman et al., 1989). At higher concentrations PB causes a presynaptic reduction of calcium dependent action potentials (Heyer & Macdonald, 1982).

Pharmacokinetics: PB is rapidly absorbed after oral administration. A single oral dose of 10 mg/kg leads to an absorption half-life of 0.382 hours (h) and a PB-peak after 1-1.5 h followed by a plateau in the serum concentration of 13.5 µg/ml for approximately 10 h. The half-life of the terminal elimination phase and the bioavailability are 76.1 h and 1.20 %, respectively. Therefore, PB is a suitable antiepileptic drug in feline epilepsy (Cochrane et al., 1990a). A study was conducted to show the pharmacokinetics of PB over a longer period of administration (5 mg/kg). In this case the terminal elimination phase of 43.4 h was significantly shorter than for a single oral dose. This may be the result of different populations of cats or an increased enzyme induction and therefore quicker metabolisation of PB by the liver (Cochrane et al., 1990b). PB is metabolized primarily by the liver, only a third is excreted unchanged in the urine. PB is also an auto-inducer of hepatic microsomal enzymes, which can reduce the elimination half-life in cases of long-term administration (Podell, 2013). A steady-state concentration is achieved after approximately 10 days (Schwarz-Porsche & Kaiser, 1989).

Side effects: After long-term administration, common side effects like sedation, ataxia and weight gain/polyphagia are reported (Quesnel et al., 1997; Pakozdy et al., 2013). Starting from a PB-serum concentration of > 140 µmol/L a persistent or a long-lasting sedation is described. In individual cases some cats showed generalized haemorrhages attributable to a thrombocytopenia (Quesnel et al., 1997). A study also showed a negative influence of PB on the blood clotting factors, which could be mitigated by vitamin K supplementation (Solomon et al., 1974). Additionally lethargy, vomiting, limb oedema, generalized pruritus, leukopenia and neutropenia are recognised side effects with PB serum concentrations of 143 µmol/L (Quesnel et al., 1997). In a case-report reversible lethargy, anorexia and ataxia, enlarged lymph nodes and multiple ulcerative and exudative oral cavity lesions were reported (Ducote et al., 1999). Pseudolymphoma-like reactions in cats have not been described, but a case with enlargement of the lymph nodes 3 weeks after starting the therapy. After the therapy was stopped, the lymph nodes returned to normal size (Bho et al., 2011). Blood analysis did not change significantly during PB therapy. Some cats develop a thrombocytopenia, neutropenia and a minor increase of alanine-aminotransferase activity. These cats did not show any symptoms of a liver disease (Quesnel et al., 1997). Nevertheless, one study showed an increase of alkaline phosphatase and alanine transaminase in 4/36 and 11/36 cats, respectively (Pakozdy et al., 2013).

Clinical use: A study conducted in 2010 showed that 40-50% of epileptic cats became seizure-free, 20% were well controlled (one to five seizures per year) and 10 to 15% were moderately (six to ten seizures per year) controlled. Only 30% showed more than 10 epileptic attacks per year. That means 50-80% of cats with primary epilepsy showed therapeutic success with PB-therapy (Pakozdy et al., 2013). Finnerty recorded a seizure reduction of ≥ 50%. The dose was 1.5-8.6mg/kg per day and PB-serum-concentration was between 15 and 45 µg/ml (Finnerty et al., 2014). Initial dose in cats is about 2.5 mg/kg p.o. every 12 hours. Subsequently, the dose has to be adjusted individually with regard to seizure control, side effects and blood parameter changes. Two weeks after initial dose or changes in dosage, PB-serum-concentration should be checked (Thomas & Dewey, 2008). The reference range is about 23 to 30 µg/ml (Smith Bailey & Dewey, 2009). Because of individual differences, PB-serum-concentration can only be approximately assessed in cats (Ducote et al., 1999). During long-term therapy, serum concentration should be checked every 3 to 6 months, because of a potential increase of PB-metabolism induced by PB itself. This phenomenon does not seem as pronounced as in dogs (Boothe, 1998). It has been shown that same dosage produces different reactions in cats; 1.2-3.9 mg/kg PB every 12 hours resulted in an ideal serum concentration in some cases, whereas in other cats, toxic serum concentrations were found. Furthermore, it has been pointed out that an interaction exists between corticosteroids and PB. In cases of increased corticosteroid dosage during PB therapy, a decrease of PB serum-concentration can be observed. Therefore, a higher PB-dosage will be necessary. That is the reason why PB serum-concentrations should be assessed periodically (Quesnel et al., 1997).

Bromide

Pharmacodynamics: There is no exact knowledge about the mechanism of action of bromide. It is supposed that the sedative and anticonvulsant effect is caused by an interaction between bromide and neuronal membranes leading to increased chloride flux, whereby a rise of membrane tension is induced (Boothe, 1998; Potschka et al., 2009). An increased production of inhibitory synapses due to bromide has also been described (Potschka et al., 2009; Volk & Loderstedt, 2011).

Pharmacokinetics: After oral application, bromide is absorbed intestinally and excreted completely by the kidneys (Volk & Loderstedt, 2011). The following insights were obtained after 15 mg/kg potassium bromide application twice a day: the maximal bromide serum-concentration was 1.1 mg/ml, the elimination half-life was 1.6 weeks and a steady state concentration had been achieved after 5.3 weeks. Two weeks after 30mg/kg/day oral dosing, a therapeutic concentration could be achieved (Boothe et al., 2002). A loading dose of 450-600 mg/kg is recommended (Boothe, 1998).

Side effects: In cats, massive side effects may occur after BR administration. At a dosage of 24.2 mg/kg/d, unwanted secondary effects including apathy, polydipsia, vomiting, weight gain, and, after 2 weeks to 23 months of application, coughing have been reported (Boothe et al., 2002). A study conducted in 2001 has also shown disease of the lower respiratory tract. Eleven of 26 cats, treated with potassium bromide, developed a cough during the first seven weeks and 14 months of treatment. Chest X-rays of all cats and bronchioalveolar lavages in two cats showed peribronchial shadings and eosinophil and mixed neutrophil-eosinophil inflammatory reactions, respectively (Orbivich-Wagner, 2001). On the X-ray, changes in bronchial lung patterns and peribronchial shadings are visible not only at the beginning of the treatment, but even seven months after discontinuing potassium bromide (Bertolani et al., 2012). After discontinuing potassium bromide a regression of side effects has been observed (Orbovich-Wagner, 2001). Volk examined the potassium bromide administration to nine cats. In the process, 67% developed respiratory signs during a period of 8.2 months and only in 50% did the signs improve after discontinuing medication (Volk et al., 2006). The underlying cause may be an allergic process caused by bromide administration, because no link could be established between respiratory symptoms and dosage or duration of treatment. An influence of chloride channels on mucociliary function has also been described (Boothe et al., 2002; Klang et al., 2012).

Clinical Use: Bromide can be used in the form of potassium bromide or sodium bromide in a dosage of 30mg/kg/d (Boothe, 1998). Because of its renal excretion and the related protection of the liver, compared to PB, and its long elimination half-life, a good therapeutic outcome was presumed (Smith Baily & Dewey, 2009). A minimization of seizures with a mean total dose of 24.2 mg/kg/d only occurred in 35% of cases (some of them were also treated with PB simultaneously). One study reported a success rate of 89% (Volk et al., 2006). Because of major side effects, primarily on the respiratory tract (35-64% of all cats), bromide should be used only in therapy-resistant cases (Boothe et al., 2002; Dewey, 2006; Volk et al., 2006; Smith-Bailey & Dewey, 2009).

Diazepam

Diazepam is primarily used in veterinary medicine because of its sedative and anticonvulsive properties. But it can also be used in veterinary behavioural modification, for skeletal muscle relaxation and appetite stimulation (Center et al., 1996). Diazepam, the most widely used benzodiazepine in veterinary medicine, is best suited for emergency treatment (Podell, 2013). Apart from diazepam, drugs like clonazepam, clorazepam, midazolam and lorazepam are in use (Dewey 2006).

Pharmacodynamics: The mechanism of action is mediated by the binding of diazepam on the α- and γ-subunit of the GABAA-receptors. This leads to a hypopolarisation and thereby a conformational change and an increase of the binding affinity – resulting in an enhancement of GABA effects on GABAA-receptors. In contrast to PB, diazepam does not have an effect on the duration of bursts, but it increases the frequency of bursting GABA receptor currents (Figure 1) (Twayman et al., 1989; Volk & Loderstedt, 2011). The sedative and anticonvulsive effects are related to its binding to the γ-aminobutyric-acid-benzodiazepine receptor. The behavioural modification and appetite stimulation are related to the drug´s influence on the hypothalamus and limbic centre (Center et al., 1996).

Pharmacokinetics: After oral administration, diazepam is metabolized rapidly by the liver. Approximately 74-
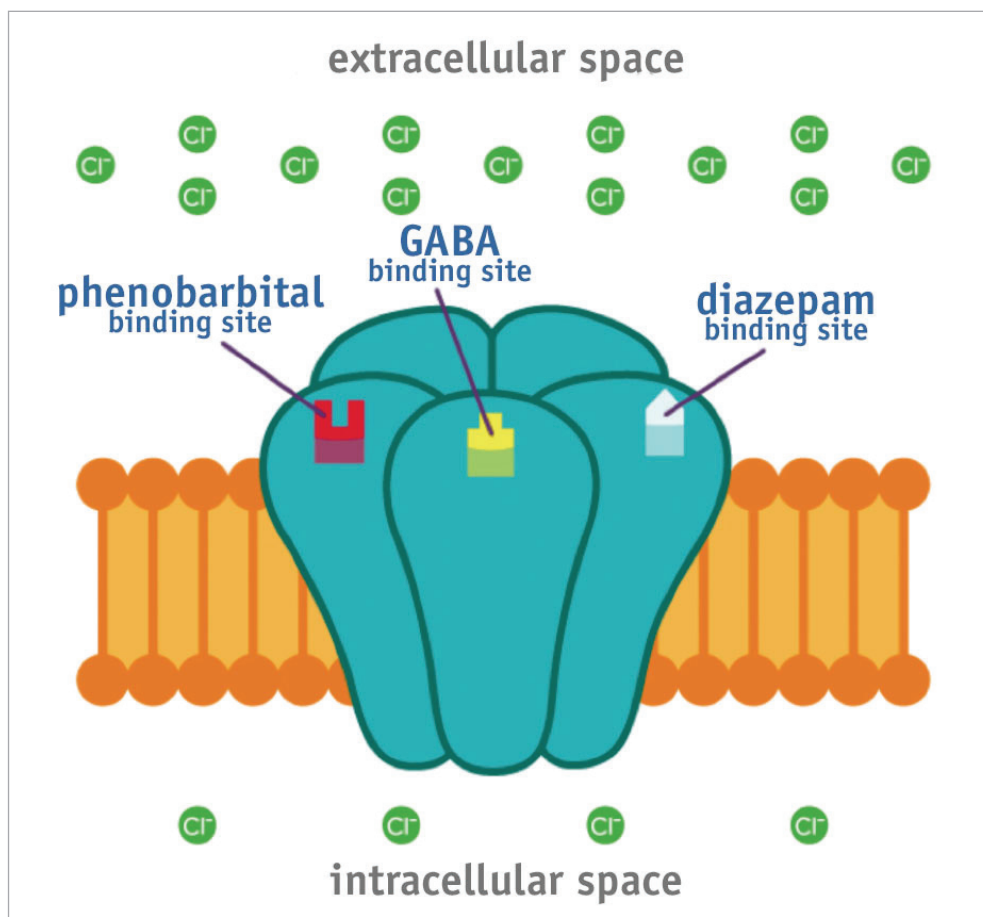
Figure 1:
Presentation of chloride-channels. Caused by the binding of barbiturate (phenobarbital), benzodiazepine (diazepam) or gamma-aminobutyric acid (GABA), an increased permeability for chloride ions is induced. This causes an increased influx and a hyperpolarisaton of the cell membrane.

100% of diazepam, including all active metabolites (nordiazepam, oxazepam), is available in the body. But the bio-availability ranged between 1-3% (Boothe, 1998); 54% is changed to desmethyldiazepam (Cotler et al., 1984). The anticonvulsant property is based on 3 metabolites (Schwarz-Porsche & Kaiser, 1989). Temazepam, oxazepam and desmethyldiazepam occur with oxidative processes and conjugation (Center et al., 1996). The elimination half-life in cats (15-20 hours) is longer than in dogs (Schwarz-Porsche & Kaiser, 1989).

Side effects: In addition to ataxia and hyperactivity, side effects like sedation and increased appetite are the most common side effects of diazepam at serum concentrations around 500 ng/ml (Boothe, 1998). Even behavioural changes, skeletal muscle relaxation, physical dependence and withdrawal-induced tremor, weight loss, rise in body temperature and renewed seizures are recorded (Volk & Loderstedt, 2011; Podell, 2013). There is another, more important side effect that has been documented. Because of inadequate urination, caused by urethrospasm or aggression 11 cats were treated with 1.0-2.5 mg diazepam per os every 24 hours. Even after five to eleven days, signs of liver intoxication could be observed. Eight of them died (Center et al., 1996). The cats were

suffering from icterus, anorexia, vomiting, hypothermia, weakness, dehydration and bleeding tendencies. Blood tests showed increased liver enzymes, hypoglycaemia, hypoalbuminaemia, pathological coagulation times, hypofibrinogenaemia, increased fibrin degeneration and thrombocytopenia. Histological examinations of the livers revealed cholangitis, an enlargement of the gall bladder and acute-subacute lobular massive liver necrosis, characterised by a low number of hepatocytes, blood filled cavities, macrophages and cellular maturity. The cause is uncertain, but a seriously limited performance of synthesis by the liver could be the underlying cause (Center et al., 1996; Hughes et al., 1996). Parenchymal changes like macroscopically visible yellowish spots and histologically identified vacuolated hepatocytes were also reported (Levy et al., 1994). Nevertheless, Folger recommended diazepam as an add-on drug in epileptic cats, because these side effects might be rare idiosyncratic reactions (Folger, 2009).

Clinical use: Some authors deem diazepam an effective anticonvulsant for cats (Schwarz-Porsche & Kaiser, 1989). Historically diazepam was designated as a second-choice drug (Boothe, 1998). In the current state of knowledge, diazepam is not recommended for long-term therapy in epileptic cats (Dewey, 2006; Smith Baily & Dewey,

2009). The common dose for oral therapy is 0.5-2.0mg/kg of diazepam every 8 to 12 hours. To avoid massive sedation, gradual adjustment is proposed and a certain serum-nordiazepam level (reference range: 200-500 ng/ml) should be considered (Podell, 2013). In cats, acquired tolerance does not develop, therefore dose adjustment is not required (Schwarz-Porsche & Kaiser, 1989). The antiepileptic effect of diazepam in cats is pronounced (Dewey, 2006). There are some reviews describing an absence of any seizures in 40% of epileptic cats (Schwarz-Porsche & Kaiser, 1989). During diazepam therapy, continuous blood testing, especially of alanine transaminase and aspartate transaminase, are necessary to identify possible liver damage as early as possible. In cases of alteration, diazepam has to be discontinued (Center et al., 1996; Hughes et al., 1996; Podell, 2013). Some drugs interact with diazepam. For example cimetidine causes a prolonged half-life of diazepam, because of the inhibition of P-450 cytochrome (Center et al., 1996; Volk & Loderstedt, 2011). Even intravenous administration of diazepam cannot be advised for long-term therapy, because of unsafe ingredients and associated Heinz-body anaemia (Center et al., 1996).

Zonisamide

Pharmacodynamics: Zonisamid (ZON), a sulfonamide derivative, has several mechanisms of action. It induces a blockage of T-type calcium and voltage-gated sodium channels. It also has a positive influence on dopaminergic and serotonergic neurotransmission, a carbonic anhydrase inhibition activity and a protection from free radical damage, a promotion of the GABA-effect and an inhibition of glutamate-induced excitation are also mentioned (Leppik, 2004; Dewey, 2006).

Pharmacokinetics: in 2008, the pharmacokinetics and toxicity of ZON was analysed in 5 and 6 cats, respectively. After a single oral dose of 10mg/kg, a maximal plasma concentration of 13.1 µg/ml was measured after 4 h. The elimination half-life amounted 33 hours and steady-state concentration was achieved 2 weeks after initiating the therapy (Hasegawa et al., 2008). ZON is metabolised in the liver by hepatic microsomal enzymes (Orito et al., 2008).

Side effects: In order to verify possible side effects, 20mg/kg of ZON was administrated to six cats per os for nine weeks, 50% (three cats) developed neurological symptoms of ataxia and somnolence and gastrointestinal

symptoms of anorexia, vomiting and diarrhoea. Blood tests had not shown any changes but the plasma concentration in these cats was about 46.3µg/ml. This concentration is almost equivalent to the human neurotoxic concentration (30.0-40.0 µg/ml); 10mg/kg ZON also administered for nine weeks did not lead to any side effects (Hasegawa et al., 2008). After intravenous administration (30mg/kg and 60mg/kg), side effects like vomiting, hypersalivation, ataxia and poor general condition were reported (Wada et al., 1990).

Clinical use: An oral dose of 5-10mg/kg ZON once a day is recommended (Smith Bailey & Dewey, 2009; Thomas, 2010). The anticonvulsant potency was analysed. Generalized seizures, triggered by electrical stimulation of the visual cortex, were analysed. An intravenous administration of 60mg/kg in these cats reduced the seizures to partial seizures and considerably shortened the duration of electric discharge (Wada et al., 1990). Within 2 weeks after abruptly discontinuing medication, no withdrawal signs like status epilepticus or a rise of seizure-frequency were documented (Hasegawa et al., 2008). ZON can also be used as add-on therapy (Dewey, 2006). With regards to its hepatic metabolism by microsomal enzymes, it is important to note that other drugs, even those metabolized in the liver, reduce the half-life period and the plasma concentration of ZON (Orito et al., 2008; Podell, 2013). Because of few insights into ZON-therapy in cats, routine application isn´t recommended. Moreover, further studies are required (Dewey, 2006).

Levetiracetam

Levetiracetam (LEV) is one of the newest anticonvulsant drugs and may be representative of a new class of antiepileptic drugs (Leppik, 2001; Carnes et al., 2011). Besides neuroprotective properties, a reduction of seizure-related brain damage is reported. Because of its anti-kindling effects, LEV reduces the probability of an increase of seizure-frequency (Thomas & Dewey, 2008).

Pharmacodynamics: LEV (s-α-ethyl-2-oxo-1-pyrrolidine-acet-amid) works in a novel way (Carnes et al., 2011). Pharmacological researches found an interaction with the neuronal synaptic vesicle 2A (SV2A) in the central nervous system. The exact mechanism of action has not been clarified yet. Furthermore, a partial suspension of N-type voltage gated calcium channels and suppression of the inhibitory effect of Zn^{2+} on GABA- and glycine currents are
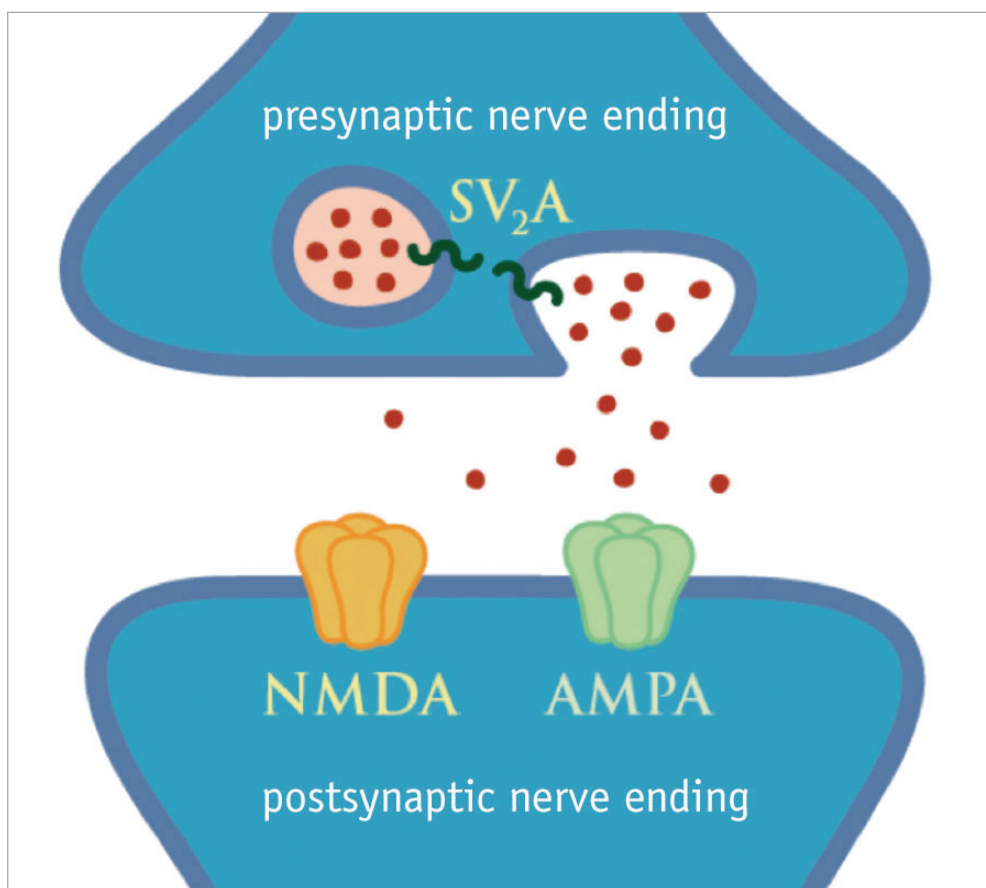
Figure 2: Schematic drawing of the action mechanism of levetiracetam. Levetiracetem may induce an interaction with the neuronal synaptic vesicle protein 2A (SV2A). This reduces the release of the excitatory neurotransmitter glutamate. As a consequence, glutamate receptors like NMDA (N-methyl-D-aspartate) and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionylacis) are not stimulated to a normal extent. Therefore less excitation is caused.

suspected (Rigo et al., 2002; Lynch et al., 2004). In 2006 a neuroprotective effect of LEV was shown in mice after subarachnoid bleeding and traumatic brain injuries (Wang et al., 2006).

Pharmacokinetics: Because of its high water solubility, LEV is absorbed rapidly and completely after oral administration. Caused by the renal metabolism and low protein binding (<10%) in the liver, LEV is free of non-linear elimination kinetics, autoinduction kinetics, drug-drug interactions and does not displace highly protein-bound drugs (Leppik, 2001). LEV is the drug of choice in patients with liver disease (Dewey, 2006). After a single oral or intravenous administration of 20 mg/kg LEV in 10 cats, LEV is metabolized by the kidneys and even 10 minutes post administration, plasma concentration, within the reference range, was achieved and maintained for 10 hours. The therapeutic reference range (5-45 µg/ml) in cats and dogs is based on human medicine. One study showed a mean maximum concentration of 25.54 µg/ml and a mean time to peak serum concentration of 1.67 h after oral administration, and mean maximum concentration of 37.52 µg/ml after intravenous administration, an elimination half-life of 2.95 h and 2.85 h respectively and an oral bioavailability of 100% (Carnes et al., 2011). Smith-Baily found a similar outcome= a mean serum maximum

concentration of 25.5 µg/ml after 2 h and an elimination half-life of 2.9 h (Smith Bailey et al., 2008).

Side effects: After a single oral or intravenous dose of 20 mg/kg LEV, cats showed good toleration. Apart from hypersalivation after oral administration, no clinical or haematological changes were found (Carnes et al., 2011). Even during long-term therapy, no considerable side effects occurred. Only two self-limiting side effects (lethargy and inappetence) were observed (Smith Bailey et al., 2008).

Clinical use: Due to its excellent tolerability and efficacy, LEV is highly recommended for anticonvulsant therapy in cats (Smith Bailey et al., 2008; Carnes et al., 2011). The short half-life period of LEV requires regular administration every 6 hours (Carnes et al., 2011). However, since this requires high compliance and since studies have suggested that its efficacy continues even after concentrations have dropped below the reference range, an administration of 20mg/kg p.o. or i.v. every 8 h is acceptable (Thomas & Dewey, 2008; Carnes et al., 2011). Dosage can be increased step-by-step till therapeutic success is achieved or side effects occur (Dewey, 2006). Dosage should be decreased in cats with renal dysfunction because of renal elimination (Smith Bailey et al., 2008). As there is no clear relation between serum drug concentration and efficacy

for LEV, and in view of its high safety, routine therapeutic drug monitoring is not necessary (Dewey, 2006). In cases of lacking therapy success, considerable side effects or too high values of serum-concentration during PB treatment, LEV can also be used as add-on drug. Smith-Bailey reported a significant reduction of seizures (≥ 50 %) in 3 months after 20mg/kg of LEV was administered as an add-on drug additional to PB in poorly controlled cats. Some cats even showed a 100% improvement (Smith Bailey et al., 2008).

Although PB remains the first-choice drug for cats with idiopathic epilepsy, LEV is an attractive alternative anticonvulsant choice (Smith Bailey et al., 2008). Cluster seizures and status epilepticus can be treated with an initial dose of 40-60 mg/kg p.o. or i.v. for 10 minutes. Subsequently 20 mg/kg LEV must be administered every 8 h, till a seizure-free period of about 48h is achieved (Volk & Lodersredt, 2011).

Gabapentin

Pharmacodynamics: There are different hypotheses for the mechanism of action of gabapentin (GP). Its anticonvulsant, anti-nociceptive, anxiolytic and neuroprotective properties are based on different mechanisms. Although GP is similar to gamma(γ)-aminobutyric acid, it does not work in the same way. Studies and hypotheses report a transport of GP by amino acid transporter and an increase of GABA-concentration, an antinociceptive effect by binding on α-2-δ-subunit of voltage gated calcium channels, increase of blood serotonin concentration and neuroprotective effects by inhibition of glutamate synthesis (Tyler et al., 1998; Cheng & Chiou, 2006; Manuef et al., 2006). The anticonvulsant effect is based on an increased release and the impact of GABA in the brain and a blockage of neuronal sodium channels by binding (Dewey, 2006).

Pharmacokinetics: GP is increasingly used in feline epilepsy therapy. In order to collect pharmacological data, GP was administered to six cats. The following data were raised after oral administration: Bioavailability: 88.7%; half-life period: 3 h; the maximal plasma concentration was reached after 100 minutes (Siao et al., 2010). GP is metabolized by the kidneys (Podell, 2013).

Side effects: there are no recordings about tolerability of GP in cats. In dogs, sedation, ataxia and weight gain, caused by increased appetite, were observed (Thomas & Dewey, 2008).

Clinical use: Because of renal excretion, GP does not affect and is not affected by other antiepileptic drugs with hepatic metabolism. In cases of renal dysfunction, the GP dosage should be reduced (Podell, 2013). A dosage of 5-10 mg/kg GP every 8 to 12 hours is only based on empiric experiences (Dewey, 2006). Neither bibliographical references with regard to dosage, nor studies relating to efficacy of GP in cats could be found. Only one author reported therapeutic success in cats (Olby, 2005). Bailey and Dewey, however, related a minor impact (Smith Bailey & Dewey, 2009).

Pregabaline

Pharmacodynamics: Pregabalin (PG) is a derivate of gabapentin with a mechanism of action of voltage-gated calcium channels. The reduction of calcium influx generated in this way, effects a lower distribution of the exciting neurotransmitter glutamate (Taylor et al., 2007; Smith Bailey & Dewey, 2009).

Pharmacokinetics: after a single oral dose of 4 mg/kg PG the following findings were collected: absorption half-life: 0.54 h, elimination half-life: 10.4 h, maximum serum concentration after 2.9 h (Cautela et al., 2010). Side effects: As in dogs, slight sedation and ataxia can occur in cats (Cautela et al., 2010; Podell, 2013). However, there is no accurate data mentioning PG-tolerance in cats.

Clinical use: Because of a half-life period of 10.4 h, administration every 12 h makes sense. An initial dose of 1-2mg/kg or 2-4mg/kg twice a day is reported (Cautela et al., 2010; Volk & Loderstedt, 2011). Studies proved successful in the treatment of partial and generalized tonic-clonic seizures with PG. The pharmacodynamics of PG provides hope that PG may improve in future (TAYLOR et al., 2007).

Taurine

In cases of cellular damage, radioactive radiation, restricted mental skills and epileptic seizures, a decrease of taurine concentration has been noticed (Van Gelder, 1972). Pharmacodynamics: Taurine causes a blockage of neuronal discharges in the brain, counteracts the toxicity of cardiac glycosides and regulates cellular potassium concentrations (Van Gelder, 1972).

Pharmacokinetics: Taurine is metabolized into isethionic acid, which is an important component for the transmission of neural impulses (Van Gelder, 1972). Side effects: even in high dosages (800mg/kg or 1500mg/kg) no clinical side effects were documented in cats. In one cat slight changes in electroencephalography were noticed. The generated data indicates a good tolerability of taurine in cats (Van Gelder, 1972; Van Gelder et al, 1977),

Clinical use: Because of the inhibitory actions of taurine on neurons, its impact on potassium concentration and its presence in high concentration during rapid protein synthesis, Van Gelder investigated the action of taurine on colbalt-induced seizures. The results indicate that repeated injections of taurine (100mg/kg or 75 mg/kg) reduce or abolish seizure incidence and the duration of seizures. After administration of taurine, GABA and glutamic acid levels recovered from a decrease, caused by the seizures, to a normal level. No adverse reactions were noted as a result of taurine administration. In summary, taurine is a possible choice for seizures, caused by cerebral damage (Van Gelder, 1972). In contrast to photically-induced seizures, taurine has no protective action against kindled amygdaloid convulsions. These results indicate that taurine is only useful in certain types of seizure-generating conditions (Wada et al., 1975). A case report describes the progression of spontaneous, chronic, tonic-clonic seizures in a cat after taurine administration. Administration of 300mg taurine s.c. twice a day for two days followed by 100mg taurine once a day p.o. for one month produced a reduction of seizure frequency. These changes were also shown by electroencephalography. Abrupt cessation led to a rise of frequency. Only slow reduction achieved a seizure-free period for at least three months. (Van Gelder et al., 1977).

Valproic Acid

In human medicine, valproic acid (VPA) is used in the treatment of absence seizures, generalized seizures and febrile convulsions (Löscher, 1985).

Pharmacodynamics: Caused by an inhibition of GABA-α-oxoglutarate-aminotransferase and the inhibition of succinic semialdehyde dehydrogenase, VPA leads to a GABA increase. Furthermore, VPA induces an activation of glutamic acid decarboxylase, causing an increase of GABA-pool in neurons. These findings would explain the anticonvulsant action of VPA (Löscher, 1980). Changes in sodium conductivity lead to an inhibition of electrically-

induced repetitive high frequency discharges in mice (Mclean & Macdonald, 1986; FREY, 1988). This change is more likely an extension of repolarization of sodium channels (Boothe, 1998).

Pharmacokinetics: VPA is rapidly metabolized in the liver (Boothe, 1998). After an intravenous administration of 40 mg/kg sodium-valproate or an oral administration of 40-60 mg/kg/q12h, the following findings were noted: mean elimination half-life: 4.82 h after intravenous and 4.8 h after oral administration, bioavailability: 90%, maximal plasma concentration: 0.25-2 h after administration (Dreimann, 1992).

Side effects: Side effects including slight sedation and reduced appetite were observed for a period of 3 to 6 h after oral or intravenous application. During a two-week continuous study, weight loss and vomiting were observed (Dreimann, 1992) as well as gastrointestinal symptoms and an increase of hepatic enzymes (Boothe, 1998). Pellegrini also reported drowsiness, reduced reaction to extreme stimuli and reduced activity (Pellegrini et al., 1978). Some cats developed alopecia (Zoran et al., 2001).

Clinical use: In penicillin induced generalized seizures, a single administration of 50-130mg/kg valproate led to a reduction of epileptic convulsions, especially in the first three hours. Even during long-term therapy (25-100mg/kg three times a day) the seizures decreased significantly. This condition remained for at least some weeks. During this period, sodium valproate was unverifiable in plasma (Pellegrini et al., 1978). To achieve a therapeutic plasma level, dosage or application-frequency has to be increased. This would result in considerable adverse reactions. Short half-life period and side effects argue against clinical use (Dreimann, 1992). Other antiepileptic drugs also have a negative influence on the half-life period of VPA (Boothe, 1998). A metabolic drug tolerance cannot be ruled out, because of a reduction of the half-life period after long-term therapy (Dreimann, 1992).

Carbamazepine

Carbamazepine (CBZ) is an anticonvulsant and psychotropic drug used primarily in the treatment of epilepsy, bipolar disorders and diabetic neuropathy as well as glossopharyngeal, post herpetic and trigeminal neuralgia and arrhythmia (Schmutz, 1985).

Pharmacodynamics: Carbamazepine ensures a prolonged repolarization of inactive sodium channels. If an action potential is generated, no repetitive discharge will occur, because of inactivity of neurons (Frey, 1988; Dreimann, 1992).

Pharmacokinetics: The pharmacokinetics were analysed after a single dose of 20 mg/kg and long-term therapy with 10 mg/kg q12h. Maximal plasma concentrations of CBZ (6-17.3 µg/ml) were reached after 0.5-2 h. It was possible to observe a prolongation of half-life period (9.9 h) by 10-25%. Carbamazepine-epoxide, an antiepileptic metabolite of carbamazepine, was observed already after 15 minutes after administration. Its half-life period was 12.2 h. Due to a prolonged half-life period, development of metabolic tolerance can be excluded in case of long-term therapy (Dreimann, 1992).

Side effects: Side effects of vomiting, mydriasis and reduced general condition have been described. After an administration of 40 mg/kg ataxia, disorders of accommodation, dysphagia and sedation to the edge of apathy occurred. At that time, plasma concentration was 14 µg/ml. After inadvertent administration of 20 mg/kg over a longer period, a cat developed tonic convulsions, hyperpnoea and unconsciousness (Dreimann 1992).

Clinical use: To determine the impact of CBZ in the cortex of cats, 2.5-10mg/kg was delivered intravenously. This allowed a reduction of seizure duration, a prevention of propagation and an elimination of the high-frequency parts of focal seizures (ITO et al., 1977). With its long half-life, the production of an anticonvulsant metabolite, absence of developing tolerance and low plasma protein binding as well as few additional side effects, CBZ can improve the quality of life of patients. It can be used instead of diazepam or phenobarbital in a dosage of 10 mg/kg q12 h (Dreimann, 1992).

Primidone

Pharmacodynamics: Primidone is an anticonvulsant of the barbiturate class, but its effect is mainly based on its active metabolite phenobarbital, which is also an anticonvulsant. The exact pharmacodynamics of primidone itself, has not been explored until now. Nevertheless, a synergetic influence on PB is reported (Ebert et al., 2002). Pharmacokinetics: Primidone is metabolized by liver enzyme activity. The therapeutic reference range is

equal to the therapeutic reference range of PB (Boothe, 1998). Half-life period ranged between 6.75 and 7.5 h and maximal mean serum concentration of primidone (19 µg/ml), phenylethylmalonamide (12 µg/ml) and phenobarbital (6 µg/ml) were reached after 2.4-8 and 8-12h respectively. Primidone was metabolized to PB only to a small extent, so serum concentrations of primidone and phenylethylmalonamide were higher than of PB. In contrast to dogs, there are no insights into the induction of microsomal enzymes in the cat. The findings indicate a different metabolism of primidone in cats than in dogs (Sawchuk et al., 1985).

Side effects: Secondary effects like slight sedation and ataxia were monitored after oral administration of 20 mg/kg of primidone twice a day. Neither blood values nor EEG-results showed any changes. Patho-histological examinations revealed diffuse cholangiohepatitis in control groups as well as in primidone treated cats. Therefore no correlation between hepatopathy and primidone administration was found. It is yet to be clarified, if long term therapy or higher dosages will cause liver damage as in in dogs (Sawchuket al., 1985). Only one report documented an application of 50 mg/kg primidone in a cat, which caused extreme depression, anorexia and considerable weight loss (Schwarz-Porsche & Kaiser, 1989). Solomon reported an absence of impact of primidone on the coagulation system in cats (Solomon et al., 1974).

Clinical use: Six cats, treated with a low dose of primidone, showed different therapeutic successes. Two cats became seizure-free during treatment, in two cats seizure frequency was reduced and two cats did not show any improvement (Schwarz-Porsche & Kaiser, 1989). According to Boothe (1998), Sawchuk et al. (1985) used an insufficient dosage to achieve a therapeutic concentration. The medical effect and side effects of primidone as an effective anticonvulsive dosage have yet not been determined for cats. Therefore, primidone is not recommended for the treatment of feline epilepsy (Boothe, 1998).

Phenytoin

Phenytoin, also known as diphenylhydantoin, is not a common anticonvulsant drug (Boothe, 1998).

Pharmacodynamics: Caused by a displacement of sodium and a reduction of the transmission of neuronal impulses, phenytoin has a stabilizing effect on synaptic connections.

Thereby the level of synaptic excitability will decrease and epileptic seizures will be absent. Furthermore, a reduction of calcium flux is initiated. This stabilization of burdened neurons happens without CNS-depression (Boothe, 1998).

Pharmacokinetics: Phenytoin is metabolized to meta- or parahydroxyphenytoin. Because of a high protein binding during the metabolism, an interaction with other drugs is possible (Boothe, 1998). In cats, phenytoin is eliminated very slowly. The elimination half-life is about 24-108 h and steady state concentration was determined with 25-35 µg/ml (Roye et al., 1973).

Side effects: A dosage of 10 mg/kg p.o or i.v. for 22 days resulted in excessive plasma concentrations and toxic side effects such as lethargy, ataxia and reduced appetite (Roye et al., 1973). Also Schwarz-Porsche reported of loss of appetite, vomiting, weight loss, increased liver enzymes, sialosis, and an inhibition of insulin and antidiuretic hormone secretion. (Schwarz-Porsche & Kaiser, 1989; Boothe, 1998). Further side effect like mydriasis, hypersalivation, tachypnoea, muscle relaxation, ataxia, and a reduction of spontaneous activity were recorded (Wada et al., 1990):

Clinical use: To determine the effect of phenytoin on the feline cortex, 5-10mg/kg of phenytoin was given intravenously. EEG recordings showed a reduction of seizure duration, inhibition of propagation and an elimination of the high-frequency portions of focal seizures (Ito et al., 1977). In order to clarify if phenytoin can also be used in add-on therapy, Schwarz-Porsche combined phenytoin and diazepam in cats. One cat showed an improvement (no seizures during at least 6 months with a steady state concentration of 6.5-7.1 µg/ml), the other only developed side effects (Schwarz-Porsche & Kaiser, 1989). During an administration of 15 mg/kg, no relevant EEG changes were found. But a plasma concentration of 15.6 ± 2.5 µg/ml showed a seizure suppression and an absence of resulting discharges (Wada et al., 1990). A dosage of 2-3 mg/kg/day is recommended for use in cats (Roye et al., 1973). Because of low efficacy and frequent side effects, the clinical use of phenytoin in feline epilepsy is only acceptable in individual cases or as an add-on therapy. Liver values and phenytoin plasma concentration should be regularly monitored (Schwarz-Porsche & Kaiser, 1989). Some references classify phenytoin as a toxic drug for cats (Thomas & Dewey, 2008).

Topiramate

Pharmacodynamics: Topiramate is a sulphamate-substituted derivate of a monosaccharide. A blockade of propagation of epileptic seizures in the brain is caused by an increased GABA activity (Podell, 2013).

Pharmacokinetics: There are no insights into the pharmacokinetics of topiramate. Therefore no statement about elimination half-life and therapeutic range can be made (Podell, 2013). An elimination half-life of only 2-4 hours was documented for dogs (Thomas & Dewey, 2008).

Side effects: No clinical studies have been published. Sedation and anorexia were the only documented side effects (Podell, 2013).

Clinical use: Topiramate should be administered in a dosage of 12.5-25 mg p.o. q8-12 h (Podell, 2013). Due to a lack of research and possible side effects of topiramate in cats, topiramate is only used in exceptional cases (Ebert et al., 2002). No reliable data was found.

Propentofylline

Propentofylline does not have any restraining effect on neuronal activity, it does not primarily act as an anticonvulsant drug (Deleo et al.,1988). Its main impact, the improvement of haemodynamics (peripheral and central), make it ideal for use in geriatric dogs. In human medicine, propentofylline is becoming more and more important, because of its possible use in Alzheimer´s diseases and vascular dementia (Kapl & Rudolphi, 1998).

Pharmacodynamics: Due to propentofylline, a xanithin derivate, a blockage suspension of the adenosine-transport and phosphodiesterase is induced. Thereby an increase of extracellular adenosine concentration and intracellular cyclic AMP- and cyclic GMP-concentration were caused. The result is an increase of neuroprotective effects (Kapl & Rudolphi, 1998).

Pharmacokinetics: No data relating to the pharmacokinetics of propentofylline in cats have been published so far.

Side effects: No data relating to the side effects of propentofylline in cats were found.

Clinical use: Effects like an enhancement of cognitive skills, an inhibition of several inflammatory processes and a positive effect on synthesis and secretion of nerve growth factors were observed in experimental studies on rats and mice (Goto et al., 1987, Shinoda et al., 1990; Si et al., 1996). Propentofylline also counteracts ischaemic brain damage and reduces the formation of seizures (Deleo et al., 1988). Propentofylline is not licenced for cats. Nevertheless it can be used as an antiepileptic drug in a dosage of 5 mg/kg twice a day (Rusbridge, 2005).

Discussion

In the course of this study, different oral anticonvulsant drugs for cats were determined and summarized in regards to their pharmacodynamics, pharmacokinetics, side effects and clinical use. Furthermore, these drugs were examined in relation to the evidence. Diverse studies, case reports, reviews and book chapters on 14 drugs were found. Besides common anticonvulsant drugs, different reports of amino acids and a vasodilator, which were reported to be effective in epileptic cats exist.

Drugs

The following 14 drugs were reported for oral therapy of epilepsy in cats (see table 1)
- Common anticonvulsant drugs: phenobarbital, bromide, diazepam, zonisamide, levertiracetam, gabapentin, pregabalin, valproic acid, carbamazepine, primidone, phenytoin, topiramate
- Amino acids: taurine
- Vasodilator: propentofylline

1. Highly recommended

Phenobarbital
There are many publications regarding the use of PB in cats. Although the references only show low evidence and a certain effort with regard to the required clinical monitoring, the high number of publications, good efficacy, slight or good controllable side effects, low costs and acceptable frequency of application support the clinical use of PB in feline epilepsy. PB remains the first-choice drug.

Zonisamide
The evidence of the majority of references is classified as category IV and III. Nevertheless, zonisamide is recommended for clinical use, because of its antiepileptic efficacy and low side effects. A worthwhile advantage of zonisamide is its single administration per day. Every other drug has to be administered several times a day.

Levetiracetam
With few side effects and a reasonably good antiepileptic efficacy in cats, LEV can be used in cats.
However, it requires strict compliance by the owner, as it needs to be administered three times daily. The evidence for the recommendation is poor, as there are few publications, which mainly describe the pharmacokinetics of LEV.

2. Moderately recommended

Gabapentin
No studies exist regarding the efficacy or possible side effects of gabapentin in cats. Statements about efficacy and dosage (partly empiric) are only based on expert opinions. The necessary 3 times-a-day administration is also a disadvantage.

Pregabalin
Only two references (category III and IV) about pregabalin were found. None of these address the efficacy of pregabalin in cats or possible side effects. Nevertheless, the pharmaco-kinetics of pregabalin indicates a feasible administration.

Bromide
The administration of bromide to cats has been within the focus of many publications. Their evidence is low, because of low numbers of animals and missing category-I studies. During potassium bromide application, respiratory signs can occur. In this case, different drugs were usually given at the same time. In our opinion, potassium bromide can be used in exceptional cases such as therapeutic resistance. Continuous control examinations and blood monitoring are necessary.

Diazepam
The tolerability and efficacy of diazepam were documented by different category III and category IV studies. In spite of its good efficacy, diazepam should not be used in epileptic cats for long term therapy, because of its potential considerable side effects on the liver.

3. Less recommended

Taurine
Taurine is not used in practice. Nevertheless, studies have

Table 1: Antiepileptic therapeutic options for cats - Overview

Active substance	Half-life	Side effects	Recommended in cats?*
Phenobarbital	76 hours after single administration 43 hours after long term therapy	sedation, ataxia, PU/PD/PP, haemorrhages, thrombocytopenia, reduction of vitamin K-dependant coagulation factors, lethargy, vomiting, oedema, generalized pruritus, hepatic enzyme induction: alanine aminotransferase, alkaline phosphatase, leukopenia, neutropenia PB-Hypersensitivity: lethargy, anorexia, ataxia, lymphatic enlargement, ulcerations in oral cavity, swollen reddened paws, halitosis, hypersalivation, pseudolymphoma	++
Zonisamide	33 hours	ataxia, somnolence, anorexia, vomiting, diarrhoea, hypersalivation, reduction of general condition	++
Levetiracetam	3 hours	hypersalivation, lethargy, inappetence	++
Gabapentin	3 hours	No data	+
Pregabaline	10 hours	No data	+
Bromide	1.6 weeks	lethargy, polydipsia, vomiting, weight gain, cough, disease of lower airways, feline asthma	+
Diazepam	15-20 hours	ataxia, sedation, PP, hyperactivity, behavioural changes, relaxation of skeletal muscles, psychological addiction after withdrawal: tremor, increase of body temperature, new seizures. Liver intoxication: icterus, anorexia, vomiting, bleeding tendency, increase of liver enzymes, hypoglycaemia, hypoalbuminaemia, hypofibrinogenaemia, extended coagulation time, thrombocytopenia, cholangitis, liver necrosis	+
Taurine	No data	no side effects even at high doses	±
Carbamazepine	10 hours After long-term treatment (prolonged by 10-25%)	vomiting, mydriasis, reduction of general condition, ataxia, disorder of accommodation, dysphagia in high dosages: sedation, lethargy	±
Propentofylline	No data	No data	±
Topiramate	No data	sedation, inappetence	±
Primidone	7 hours	slight sedation, ataxia with 50 mg/kg: depression, anorexia and weight loss	-
Phenytoin	24-108 hours	lethargy, ataxia, reduced appetite, vomiting, weight loss, increase of liver enzymes, sialosis, inhibition of insulin and ADH-secretion, mydriasis, hypersalivation, tachypnoea, muscle relaxation	-
Valproic acid	5 hours	Slight calming, reduced appetite, weight loss, vomiting, increase of liver enzymes, gastrointestinal symptoms	-

*   Grade of ACVIM panel recommendation (after Podell et al, 2016):
++ high recommendation (likely to be effective)
+   moderate recommendation (most likely to be effective)
±   low recommendation (may not be effective)
–   not recommended (may be ineffective and/or dangerous to the patient)

shown a reduction of certain forms of epilepsy. Because it has no secondary effects, taurine may be used as an add-on drug in the future.

Carbamazepine
All information about the administration of carbamazepine in cats is based on a single reference (category III). Serious side effects such as dysphagia and sedation or apathy oppose its clinical use in cats.

Propentofylline
There are no references on the treatment of feline epilepsy with propentofylline. Further investigations are required to document the efficacy and side effects of propentofylline during long-term therapy.

Topiramate
References about administration, side effects and efficacy are only based on expert opinions (category IV). A 3 times-daily application also limits its use in feline epilepsy.

4. Not recommended

Primidone
Because of short study periods and low numbers of participants, evidence in available references is sparse. Furthermore, efficacy and side effects during the treatment of feline epilepsy in an effective dosage over a longer period are not proven so far. To recommend primidone, further studies are necessary.

Phenytoin
Because of serious side effects and low efficacy, phenytoin cannot be recommended for clinical use in cats. Continuous and accurate monitoring of serum concentrations would be necessary during the therapy. This also requires good owner compliance. The information about phenytoin therapy is based on weak evidence.

Valproic Acid
There are no known studies on the effects and side effects of valproic acid in useful dosages. Because of anticipated side effects, short half-life and poor evidence, valproic acid is not recommended for cats.
To draw up evidence-based therapy guidance, each drug has to be examined in terms of applicability with regard to long-term therapy and monotherapy. Therefore references need to be analysed critically. The ILAE developed guidance to assess the evidence of all publications.

Placebo-controlled, randomized and double-blind trials, which include a high number of cases or participants, are collectively referred to as category I and II. Open label trials rank among category III. Category IV includes expert opinion and case reports (Glauser et al., 2006).

Data about the therapy of feline epilepsy and the efficacy of various drugs is mainly based on expert opinion, case reports (category IV) and a few prospective and retrospective studies (category III).

With oral treatment options, only a few prospective studies (in this case studies with the highest evidence) were found. Most of them deal with the pharmacokinetics of possible drugs and only a few record their side effects or efficacy.

There are no placebo- controlled, randomized and double-blind trials focusing on the clinical efficacy of diverse antiepileptics. Only two randomized crossover studies were found. These trials only refer to pharmacokinetics and cannot be taken into account, because the main focus of our paper is the clinical efficacy of different antiepileptic drugs. Missing category I trials are a major point of criticism. Recently, double-blind, placebo-controlled trials were conducted in epileptic dogs. On this occasion a positive influence of placebos was documented. In 10% and 29% of cases, no further seizures occurred or a reduction of ≥ 50% was achieved (Munana et al., 2010, Hardy et al., 2012). This kind of study is, because of its quality evidence, necessary to assure a reliable statement about the effects and side effects of possible drugs and to create a scientifically-based therapeutic plan.
Also the number of participants has a profound impact on the significance of a therapy plan. Only in four retrospective studies (three of them about PB), did the number of participants exceed 25 (26, 30, 36, 30) (Quesel et al., 1997; Orbovich-Wagner, 2001; Pakozdy et al., 2013; Finnerty et al., 2014). The other trials achieved their results with less than 20 animals or only with one (case report). In addition, treatment durations were short, so that potential side and long-term effects could not be observed. The question arises whether a small number of participants and short study duration allow a generalized statement about side effects and efficacy of proven drugs. Also the long-term study (Pakozdy et al., 2013) faces the restriction that animals were treated for various durations and received an additional antiepileptic drug.

In many studies and case reports additional anticonvulsant drugs were administered (Quesnel et al., 1997; Smith-Bailey et al., 2008; Klang et al., 2012; Pakozdy et al., 2013). Therefore, different effects could not be assigned to the corresponding drug. As a result, the validity of the study decreases. To make a precise and explicit statement, therapies with different drugs during the same time should be critically examined because of possible interactions. Substances for testing must be used in single therapies to verify possible side effects.

Another important criterion is the absence of comparative studies. PB for example is recommended as the first choice drug (Thomas & Dewey, 2008), but no study shows a better outcome after PB treatment compared to another drug . The effects of diverse anticonvulsant drugs can only be analysed and compared in placebo controlled, randomized and double-blind studies (category I). Only then, can a statement be made, without a justification based solely on low side effects, half-life and expert opinion. Ethical aspects and compliance limit the feasibility in veterinary medicine.

Conclusion

Fourteen different drugs were found for the oral treatment of feline epilepsy, but knowledge is based on poor evidence and veterinarians must be aware of this. To achieve more reliable evidence, category I studies, comparative studies, crossover studies, as well as higher numbers of participants and a longer duration of treatment are indispensable. Until then, therapy recommendation has to be based on other, less significant evidence. Different treatment regimes have to be tried and maybe rejected. Next to the effect of drugs, other factors like possible side-effects and necessary control examinations (serum concentration monitoring) have to be considered. Other very important criteria are available dosage forms, application frequency, practicability, compliance of pet owners and the patients, as well as the costs.

It must also be mentioned, that no single antiepileptic drug is approved for cats. A reclassification is essential.
Other therapeutic options should be considered. For example, surgical interventions (conventional or radiosurgery) may gain importance, because of growing possibilities (Podell, 2013).

Table 2: relevant antiepileptic drugs (dosage/galenic form)

Active substance	Dosage	Brand names (examples) Galenic formula	Dosage[*]
Phenobarbital	2.5 mg/kg q 12h	Phenoleptil 12.5 mg-tablets (100 pieces) OR Epiphen Solution 4% w/v Oral drops (only in UK!)	12.5 mg/5 kg q 12h = 1 tablet twice a day. OR 0.3 mL q 12h
Zonisamide	5 mg/kg q 24h	Zonegran 25 mg hard capsule (28 pieces)	25 mg/5 kg q 24h = 1 capsule a day
Levetiracetam	10 mg/kg q 8h	Magistral preparation: Levetiracetam 50 mg-capsules (60 pieces) OR Syrup 100mg/mL (Keppra, Levebon)	50 mg/5 kg q 8h = 1 capsule 3 times a day OR = 0.5 mL 3 times a day
Potassium bromide	15 mg/kg q 12h	Magistral preparation is required: Potassium bromide 75 mg-capsules (60 pieces)	75 mg/5kg q 12h = 1 capsule twice a day
Diazepam	0.5 mg/kg q 12h	Gewacalm 5 mg-tablets (50 pieces)	2.5 mg/5 kg q 12h = ½ tablet twice a day
Gabapentin	10 mg/kg q 8h	Magistral preparation: Gabapentin 50 mg-capsules (60 pieces)	50 mg/5 kg q 8h = 1 capsule 3 times a day
Pregabaline	2 mg/kg q 12h	Magistral preparation: 10 mg-capsules (60 pieces) based on Lyrica 25 mg - capsules (56 pieces)	10 mg/5 kg q 12h = 1 capsule twice a day

[*] Dosage for a 5kg cat

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Nursing the critical care patient – part 2: monitoring

Katherine Howie[1]

SUMMARY

Once the emergency patient has been stabilised and any hypovolaemia, hypoxia or perfusion deficits have been reversed, on-going monitoring and treatment are required. For example, trauma patients will need stabilising of the hypovolaemia, improvement of their clinical status and monitoring of perfusion parameters before investigating and stabilising secondary issues such as wound management, fracture management, bladder management and nutritional support.

Excellent nursing care and management alongside well-developed nursing plans to ensure continuity of care will improve patient outcomes and shorten hospitalisation periods.

Monitoring Equipment

There are various monitors available for use in veterinary practice and all will have benefits to our patients. However, as with any equipment there is room for operator error and machine malfunction. Knowing the benefits and limitations of any equipment used is important, and veterinary nurses need to be able to troubleshoot potential problems and along with the veterinary surgeon decide if the equipment is the problem or if the patient actually has a problem.

Monitors do have a place in any veterinary environment and alongside good observational skills can give vital information about the patient's status often in a minimally invasive manner.
As well as knowing how to use the equipment properly and accurately it is also important to know the limitations of each piece of equipment and be able to troubleshoot problems.

The most valuable monitor any patient can have is an observant conscientious veterinary nurse. No piece of even

the most sophisticated equipment is of any use if it is the sole form of monitoring. There is so much to be learnt from observing, watching, listening and feeling during the examination of patients that a monitor may not pick up on. Also, accurate recording of vital parameters including the time, initials of the individual taking the recording is essential and required.

Heart rate, respiratory rate and temperature

In critical patients, these should be monitored continuously or at intervals of 5-15 minutes in the early part of their admission to the hospital. Sometimes it is useful to plot these parameters on an anaesthetic recording chart to see trends in the patient's vital signs.

The **heart rate** is checked frequently but can be a non-specific parameter. Tachycardia (heart rate > 160bpm) can have many reasons, including hypovolaemia, cardiogenic shock and massive haemorrhage. Other causes should be considered if the patients are not showing signs of clinical compromise, including stress, anxiety, noise phobia in dogs, excitement or exercise just before attending the clinic.

It is also important to monitor the patient's pulse quality on an on-going basis: is it normal or weak and thready? Does the patient have peripheral pulses?

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Are the pulses bounding? Any change in these pulses should be reported to the vet immediately.

When monitoring patient trends, the whole picture needs to be looked at (monitoring the heart rate and thorough chest auscultation, ECG, peripheral pulses and perfusion). The difference between a patient`s heart rate and femoral pulse rate can mean they have pulse deficits which could indicate arrhythmias caused by myocardial hypoxia, acid-base or electrolyte abnormalities.

Respiratory rate is monitored frequently particularly in dyspnoeic patients or patients with heart failure or traumatic injury. But a lot of information can also be gained from the patient's respiratory effort: is it inspiratory or expiratory, are the patient's elbows abducted (sign of air hunger), is the patient assuming one position and does it struggle of become more dyspnoeic if placed in a different position? Are there any paradoxical abdominal movements which could indicate a ruptured diaphragm? This is all useful information to ensure patient comfort but also for the vet as many assessments in respiratory patients need a hands-off approach.

Temperature is often monitored in emergency patients however due to the nature of the procedure there seems to be some reluctance to continue with regular monitoring once the patient has been treated and seems to be recovering. Normal recommendations for temperature recording in ECC patients should be every 2-4hrs in certain patients. Temperature has been shown to correlate well with perfusion and cardiac output so regular monitoring should be considered.

Patient demeanour

Any patient that goes from bright alert and happy to miserable depressed and quiet should be assessed systematically. If the patient is fairly responsive upon admitting then it should become more responsive and alert with suitable interventions from the veterinary team. A change in demeanour does not necessarily mean they are deteriorating but investigating the reason for the change is important.

Clinical reasons for changes in demeanour can be drug-induced, caused by inadequate analgesia or by a deterioration of the patient's condition. Although a change in demeanour is always a cause for concern it can also be caused by something in the environment (e.g. sudden loud noises causing anxiety and stress, vacuum cleaning noise, oxygen alarm, male instead of female nurses or vice versa). Whatever the cause of the change it should be investigated by the veterinary surgeon and treated as required.

Urine output and fluid balance

Following a trauma, patients can have physical problems when urinating such as a fractured pelvis or they may become anuric, oliguric or be in acute renal failure. Monitoring urine output in emergency patients is an excellent indicator of the patient's perfusion status – if urine output is normal then perfusion to the major body systems is usually adequate.
* Normal urine output is approximately 2ml/kg/h
* Oliguria is defined as between 0.5-1.5ml/kg/h
* Anuria is defined as <0.5ml/kg/h

Increases in urine output may be due to high fluid therapy rates. It is also possible for the disease process itself to cause an increase in urine output (polyuria) such as uncontrolled diabetes mellitus or chronic renal failure. In these cases there will be an overall loss of fluid from the intra-cellular and interstitial spaces and the patient can become dehydrated.

Monitoring urine output can be carried out in several ways dependent upon the underlying condition and the veterinary surgeon's choice.
Some methods of monitoring output include:
* An indwelling catheter connected to a closed collection system. This is particularly useful for recumbent patients and patients with bladder dysfunction leading to urine overflow or inability to pass urine
* Free-catching urine: this can be undertaken simply and easily by the veterinary nurse – just catch the volume of urine passed then measure and record this volume on the patients records
* In case of recumbent patients unable to have a urinary catheter, weighing of incontinence sheets and bedding before and after use can give a rough estimation of urine passed (1 gram is roughly equivalent to 1 ml of urine).

Alongside monitoring and recording of urine output intra-venous fluid volumes administered should be recorded alongside any other intake such as oral intake of water.

Losses of vomitus and diarrhoea should also be recorded. Once the volume of the emergency patient has been stabilised, regular monitoring of bodyweight and fluid balance should be considered as an essential part of the nursing plan.

Blood Pressure

Blood pressure monitoring is probably the most commonly used measurement alongside clinical examination in the emergency patient and will often be carried out a regular basis. Blood pressure gives us essential information about the patient's delivery of oxygen and nutrients to cells and organs and if a patient is improving from a hypovolemic crisis – or deteriorating. Cases of hypertension associated with fluid overload are also seen.

A patient with a normal systolic pressure will have good perfusion, delivery of oxygen and nutrients around the body. They are not likely to have any major issues with cardiac output or blood flow. There are exceptions to this –in some emergency patients a normal systolic blood pressure is seen on admission and then a reducing pressure as the patient's status changes.

Normal blood pressures in dogs is systolic 140/diastolic 75 mm Hg (mean 100) and in cats systolic 130-180 / diastolic 90-120 mm Hg. Cats have a marked 'white coat effect' (blood pressure elevated by stress). If a metatarsal, metacarpal or other peripheral pulse can be palpated, the patient is likely to have a systolic pressure above 80mm/Hg –obviously this can be unreliable.

Doppler Method
The Doppler method of measuring systolic pressure is considered the most accurate non-invasive monitoring for systolic pressure in small animal patients. The Doppler system gives information on systolic pressure only.

Oscillometric Monitoring
Oscillometric blood pressure monitoring gives information on systolic, diastolic and mean arterial blood pressures. It is normally carried out using a multiparameter monitor attached to the patient and is pre-set to take readings on a regular basis. The monitor inflates the blood pressure cuff and as the cuff deflates it picks up oscillations in blood flow to give us these readings on the screen.

Invasive blood pressure monitoring
Invasive blood pressure monitoring is considered the "gold standard" of blood pressure monitoring. However, due to the technical skill and equipment required it is rarely used in practice.

For all blood pressure monitoring systems, it is essential to ensure accurate readings.
- The patient should be calm before readings are taken to avoid false readings
- The chosen artery should have all the hair removed from around it to enable good contact between the blood pressure probe and skin (in the case of Doppler monitoring)
- Cuff size should be 40% of the circumference of the limb – measure the limb with a measuring tape and ensure accuracy in this area. If the cuff is too small, false high readings may be obtained, and if it is too large, false low readings. This may affect treatment which could be detrimental to the patient.
- Patient movement should be limited during measurements
- Take three readings and take the average to further ensure accuracy

Electrocardiogram

While use of an ECG can seem daunting, they do give valuable information on the emergency patient. Patients presenting with arrhythmias (with or without impact on cardiovascular function) in emergencies are common. Whilst it is not expected for veterinary nurses to interpret every abnormal ECG, veterinary nurses should be able to set up, monitor and recognise an abnormal ECG.

Pulse oximetry

Pulse oximetry, commonly used in veterinary practice with patients under general anaesthesia, it is commonly used in emergency patients to monitor oxygen saturation of haemoglobin. Haemoglobin is the main carrier of oxygen around the body with 99% of oxygen molecules being bound to haemoglobin. Normal haemoglobin level and oxygen supply levels give readings of 98-99% on the pulse oximeter.

In emergency patients where the respiratory system may be compromised or where the patient may have a low

circulating volume of red blood cells (e.g. haemorrhage or other anaemia), much lower SPO2 readings are seen. Many hypoxic patients will not show cyanotic mucous membranes until the hypoxia is severe - often less than 90%, by which time they are severely compromised.

The probe for the pulse oximeter can be placed on any mucous membrane, usually the tongue or the lip. If this is not tolerated, the vulva or prepuce can also be used. Any patient with a SPO_2 of less than 95% can be considered as hypoxic and should have oxygen supplementation. If there is a concern that the patients lacks adequate red blood cells to carry haemoglobin then blood transfusions may be considered.

Nutritional support

Nutritional support is an essential part of the nursing plan and should be considered as soon as the patient has been stabilised. The gastro-intestinal system in the emergency patient can become highly compromised. If patients are not supported with appropriate nutrition during the critical and recovery period this may cause delayed healing times, complications associated with gastro-intestinal tract issues such as ileus and the potential for long-term damage to the gastro-intestinal tract if it is non-functional for any period of time.

"Patients don`t get better when they eat – they get better because they eat" (Louise O. Dwyer)

Patient comfort and 'tender loving care'

Patient comfort should be considered an essential part of the nursing plan and considerations for the type of housing and bedding the patient needs. A lot of information in these areas can be gathered from careful questioning of the client once their pet is more stable, for example:
- What type of bedding is the pet used too?
- Do they like to urinate on grass/gravel or concrete (dogs), wood litter, and gravel based litter or normally outdoors (cats)?
- Is there anything in a hospital environment they may be fearful of (broom, mops, vacuum cleaner)?
- What type of bowl does the animal normally eat from (metal, ceramic or human plates and bowls)?
- Is there anything the pet particularly dislikes? E.g. other dogs or cats, gender dislikes (particularly in dogs), does not like having ears /feet/paws touched

- Is there anything that can be done in the hospital environment the pet really enjoys? Grooming, exercise (obviously depending on condition of patient), play sessions, having somewhere to hide.
- Do they have a particular routine at certain times of day? If so can we try and mimic that routine?

As well as the monitoring of vital parameters, consider the patient as a whole and take on board a holistic approach to nursing to include the patients likes and dislikes and time set aside in our nursing plans for just tender loving care. It will have a positive impact upon the patient and their emotional wellbeing in the hospital and it does wonders for the staff too!

Conclusion

Once the emergency patient has been stabilised and restored intra-vascular volume, provided oxygen and instigated emergency treatment development of a longer term nursing plan to ensure all of the animals needs are met is important. On-going monitoring, recording of vital parameters and early recognition of when things might not be going to plan is a crucial part of the veterinary nurse's role and will increase survival rates in our emergency patients.

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