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Antiepileptic drugs' tolerability and safety – a systematic review and meta-analysis of adverse effects in dogs

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Abstract

Background: The safety profile of anti-epileptic drugs (AEDs) is an important consideration for the regulatory bodies, owners and prescribing clinicians. Information on their adverse effects still remains limited. A systematic review including a meta-analytic approach was designed to evaluate existing evidence for the safety profile of AEDs in canine patients. Electronic searches of PubMed, CAB Direct and Google scholar were carried out without date or language restrictions. Conference proceedings were also searched. Peer-reviewed full-length studies reporting adverse effects of AEDs in epileptic and healthy non-epileptic dogs were included. Studies were allocated to three groups based on their design. Individual studies were evaluated based on the quality of evidence (study design, study group sizes, subject enrolment quality and overall risk of bias) and the outcome measures reported (proportion of specific adverse effects for each AED, prevalence and 95 % confidence interval of the affected population in each study and comparative odds ratio of adverse effects for AEDs).

Results: Ninety studies, including six conference proceedings, reporting clinical outcomes of AEDs' adverse effects were identified. Few studies were designed as blinded randomised controlled clinical trials. Many studies included low canine populations with unclear criteria of subject enrolment and short treatment periods. Direct comparisons suggested that imepitoin and levetiracetam might have a better safety profile than phenobarbital, whilst the latter might have a better safety profile than potassium bromide. However, none of these comparisons showed a statistically significant difference. Comparisons between other AEDs were not possible as a considerable amount of studies lacked power calculations or adequate data to allow further statistical analysis. Individual AED assessments indicated that levetiracetam might be one of the safest AEDs, followed by imepitoin and then phenobarbital and potassium bromide; these findings were all supported by a strong level of evidence. The safety profile in other AEDs was variable, but weak evidence was found to permit firm conclusions or to compare their safety to other AEDs.

Conclusions: This systematic review provides objective evaluation of the most commonly used AEDs' adverse effects. Adverse effects usually appeared mild in all AEDs and subsided once doses and/or serum levels were monitored or after the AED was withdrawn. Although phenobarbital might be less safe than imepitoin and levetiracetam, there was insufficient evidence to classify it as an AED with a high risk of major adverse effects. It is important for clinicians to evaluate both AEDs' effectiveness and safety on an individual basis before the selection of the appropriate monotherapy or adjunctive AED therapy.

Keywords: Systematic review, Meta-analysis, Epilepsy, Canine, Antiepileptic drugs, Safety, Side effects

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Background

In human medicine, a plethora of new antiepileptic drugs (AEDs) have been developed over the years for use either as monotherapy or adjunctive therapy [1]. Many of these drugs are now also used in veterinary medicine. This has led to an increase in the arsenal of AEDs used to treat canine epilepsy. As a rule, AEDs are evaluated on the grounds of their effectiveness and safety through clinical trials and experimental laboratory studies before they are approved for use in patients by the regulatory authorities, e.g. the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA) [2]. The safety profile of drugs is an important consideration for their approval by the authorities and use by prescribing clinicians on their clients' animals [2, 3]. It affects clinicians' decisions to prescribe specific AED(s), as serious adverse effects can lead to chronic complications or even death. Less serious, but nonetheless important, adverse effects can significantly impact quality of life, leading to systematic illness which may increase the overall cost of treatment [3, 4]. Ultimately, the benefits of an effective AED may be outweighed by its adverse effects, and the latter should be always taken into consideration.

Many potential adverse effects for AEDs have been reported, but the evidence behind the severity of these effects or the likelihood of their occurrence has not been systematically compiled [5, 6]. Randomised clinical trials (RCTs) are a considerable source of evidence for some common or expected adverse effects [4]. However, information about serious, rare, and/or long-term adverse effects can typically be found in studies such as case reports, case series and observational studies [7, 8]. Consequently, the clinician will need to search for information from sources other than RCTs [7, 8]. Identification of all relevant studies can be time-consuming and for a busy practitioner it may be more effective to review this information via a systematic review. Systematic reviews are one of the most powerful and reliable tools to assess the severity and the probability of occurrence of AEDs' adverse effects across the spectrum of primary literature [9–12].

Although evidence for AEDs' efficacy has been recently reported and evaluated in a systematic review [13], it has been suggested that, apart from the efficacy, the selection of the appropriate AED should be also largely influenced by its safety profile [14]. To our knowledge there is only one systematic review in the field of canine epilepsy which evaluated the safety profile of a single AED, potassium bromide, across species and aetiology of seizures [15]. However, a systematic review of the adverse effects observed during treatment with any AED(s) in dogs, as well as AEDs' safety profile comparisons, has not been reported. The aim of this systematic review was to perform an objective analysis of AEDs' adverse effects in dogs, in order to provide evidence-based information on AEDs' safety profiles.

Methods

Search strategy

The literature search aimed to identify all studies assessing or reporting the adverse effects of an AED in dogs. Specifically, studies were evaluated based on the inclusion criteria below:

- Criterion 1-Type of study: Peer-reviewed studies in English (or translated). Experimental laboratory animal studies, clinical trials, observational and descriptive studies were included.
- Criterion 2-Case definition: For the clinical studies, dogs with IE were included as previously defined [13]. Briefly this required dogs within a certain age range, unremarkable interictal neurological status and diagnostic investigation for seizures. For the experimental laboratory animal studies (ELAS), healthy non-epileptic dogs were also included; for the latter a clear diagnostic investigation or health statement should have been reported in the study to exclude the possibility of underlying diseases.
- Criterion 3-Treatment: Dogs treated with any AED available used in canine IE were included. Doses and serum concentrations of AEDs, frequency of drug administration and treatment period were considered important information to record. Dogs treated with methods other than pharmacological intervention, e.g. homoeopathy methods, surgery, food trials, nerve stimulation, were excluded.
- Criterion 4-Outcome: Studies had to assess or report adverse effects following administration of AED(s) in canine subjects. Studies were conducted either to specifically assess or report AED(s)' safety (primary evidence studies) or to assess an outcome other than AED(s)' safety (i.e. efficacy), while also reporting adverse effects (supportive evidence studies). Assessment of the adverse effects should have been performed by the investigators or owner.

Search strategies included use of electronic search engines for publication databases, searching of reference lists of published papers and proceedings of relevant scientific conferences. Electronic databases used were Pub Med (www.ncbi.nlm.nih.gov/PubMed), CAB Abstracts (www.cabdirect.org) and Google Scholar (www.scholar.google.com). Final electronic searches were carried out on 30 February 2015 by the primary and the second author independently, with no date or language restrictions. The search terms used in both search engines were as follows: (dog OR dogs OR canine) AND

[(phenobarbital OR phenobarbitone OR primidone OR PBr OR KBr OR potassium bromide OR bromide OR nimodipine OR zonisamide OR ELB138 OR imepitoin OR levetiracetam OR verapamil OR gabapentin OR gaba OR topiramate OR felbamate OR pregabalin) OR [(treatment OR management) AND (epilepsy OR seizures)] OR (anti-convulsant OR anti-seizuring OR anti-epileptic OR AED) AND (safety OR safe OR adverse-effect OR adverse-effect OR effect OR undesirable effect OR tolerability OR toxicity OR drug toxicity OR reactions OR disease). Hand searching for articles from the reference lists of publications and searching major veterinary neurology conference meeting proceedings from 1970 to 2015 and relative textbook chapters was carried out by the primary and second authors independently. Conference proceedings were searched for the Annual Congresses of the European Society and College of Veterinary Neurology (ESVN/ECVN) and the American College of Veterinary Internal Medicine (ACVIM). Other conference proceedings were searched only if the reference list of identified publications indicated this. All items returned by the search engines, hand searches and correspondence were recorded and entered into the screening process.

Study selection

Restrictions based on publication date or language were not imposed. Studies written in non-English language were assessed initially based on an English translation (Google Translate software) and then verified by a veterinarian fluent in the language of publication.

A two-stage screening process was used [13] and the process was performed by the primary author. Firstly, studies of relevance to the systematic review objectives were identified (stage 1) and, secondly, studies likely to provide evidence of the highest available quality and sufficient detail for assessing the outcome measures and methodology were selected (stage 2). Stage 1 of the screening process identified from the total search results any studies that: (a) fulfilled inclusion criterion 1 and (b) reported findings related to the adverse effects and safety of AEDs administered in dogs. Stage 1 assessment evaluated the retrieved papers' titles and abstracts only. At stage 2, papers were selected for full data extraction according to the inclusion criteria 2, 3 and 4 and were evaluated in detail on the grounds of the quality of evidence and outcomes by MC.

Assessment of quality of evidence

Blinded RCTs (bRCTs) and blinded randomised ELAS (bRELAS) were considered most likely to produce higher quality evidence, followed by non-blinded RCTs (nbRCTs) and non-blinded randomised ELAS (nbRELAS), then non-randomised clinical trials (NRCTs) and non-randomised ELAS (NRELAS), uncontrolled clinical trials (UCTs) and uncontrolled ELAS (UELAS), cohort, case–control and cross sectional studies and lastly case series and reports [16–18]. Accordingly, the studies were allocated based on their design to one of three groups, i.e. bRCTs, bRELAS, nbRCTs and nbRELAS (first group), NRCTs, NRELAS, UCTs, UELAS, cohort, case–control and cross-sectional studies (second group) and case series and reports (third group).

As a general rule, the studies in the first group (bRCTs and bELAS in particular) were considered to provide higher quality evidence, followed by the studies in the second and third group. In addition, a three-part system of evidence quality assessment to indicate the strengths and weaknesses of each study within each group was used [13, 19]: (a) study group sizes, (b) subject enrolment quality and (c) overall risk of bias based on Cochrane [20] and Syrcle's [21] 'risk of bias' assessment tool in order to provide an indicator of confidence associated with the findings of each study. For instance, bRCTs or bRELAS with large group sizes, clear inclusion criteria, thorough diagnostic investigations and low overall risk of bias were considered to provide the highest available quality of evidence.

Study group sizes

This characteristic was categorized for each study using the following system [13, 19]: (a) >50 subjects per group ('good' number of subjects), (b) 20–50 subjects per group ('moderate' number), (c) 10–19 subjects per group ('small' number) and (d) <10 subjects per group ('very small' number).

Assessment of subject enrolment quality

Data on investigations to reach the diagnosis of IE were retrieved to evaluate the quality of subject enrolment in each study as 'well characterized', 'fairly characterized', 'poorly characterized' or 'unclear.' Well characterized diagnoses were defined as diagnostic investigations that included clinical signs and thorough test results consistent with the diagnosis of IE; specifically, the signalment, the absence of neurological deficits between the ictal phases, unremarkable routine biochemical and haematological blood tests and imaging results (including brain MRI and/or CT) and/or normal cerebrospinal fluid (CSF) analysis for all cases of the study. Fairly characterized, used for intermediate situations, were defined as diagnostic investigations that were based on signalment, clinical examination and basic diagnostic investigation (i.e. blood tests only), with only some study cases having had advanced brain imaging and/or CSF analysis. Poorly characterized were defined as diagnostic investigations that were based on signalment, clinical examination and/or basic diagnostic investigation (i.e. blood tests)

only. Unclear related to reports where the approach to diagnosis of IE was not clearly stated (e.g. when clinical signs were not stated and insufficient or no details of diagnostic tests were provided or when dogs with IE were included without reporting details on diagnostic investigation).

For the ELAS, which included non-epileptic healthy animals, 'clearly characterized' were the studies that defined diagnostic investigations and thorough test results to exclude any systemic illness; 'unclear' were characterized when diagnostic investigations to rule out diseases were not clearly stated or when dogs were included and considered healthy without reporting details on diagnostic procedures.

Assessment of overall risk of bias

The overall risk of bias in the clinical trials was assessed based on the criteria of the Cochrane 'risk of bias' assessment tool [20]. Syrcle's 'risk of bias' assessment tool [21] was used to assess the overall risk of bias in ELAS. The latter tool is an adapted version of the Cochrane one and was designed to facilitate critical appraisal of evidence from ELAS.

Each of the following study components was categorized as presenting a 'high', 'low' or 'unclear' risk of introducing bias to the study findings: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting of outcomes and other sources of bias. For ELAS, two further components-random housing and baseline characteristics of dogs - were also assessed and mentioned as part of the "other sources of bias" section. Case series and reports as well as observational studies were considered to be of high overall risk of bias.

Level of the studies' evidence

The level of evidence provided for the safety profile of each AED was based on the overall quality of evidence of the studies. The level of evidence was allocated according to a previous similar system [13, 19] which was extensively modified for the needs of the current study: 'strong' evidence was provided for the safety profile when at least one bRCT and/or bRELAS reported or assessed the adverse effects of an AED; 'weak' evidence was provided for the safety profile when bRCTs and/or bRELAS were not available.

Assessment of outcome measures

The outcome measure of this study was the evaluation of the safety profile of AED(s) administered in dogs. The adverse effects were organized by body system (e.g. neurological, gastro-intestinal, dermatological, etc.) and types, including type I (dose dependent and predictable) and type II (idiosyncratic-dose independent and unpredictable). Different terms used by the studies but describing the same adverse effects (e.g. drowsiness and somnolence, wobbly gait and ataxia, lethargy and sedation, etc.) were considered synonymous and only one term was selected for use in the analysis. The outcome measure was assessed according to the methods below:

Proportion of specific adverse effects for each AED

This was expressed as a percentage and calculated for each AED by dividing the number of studies that reported a specific adverse effect by the total number of the studies for this AED. If an AED was used as a monotherapy and adjunctive therapy, further calculations were also performed for each sub-category.

Prevalence and 95 % confidence interval of the affected population in each study

Prevalence was expressed as a percentage and calculated for each study by dividing the number of subjects that developed adverse effects during the specified study period by the total size of the study population. The 95 % confidence interval (95 % CI) of the proportion of study animals that developed adverse effects related to the AED(s) was calculated by standard methods [22]. This was used as a further indicator of an AED's safety profile. If the 95 % CI of affected dogs (based on 95 % CI calculations) were ≥ 50 %, then it was considered that the majority of the study population experienced adverse effects.

For each study, the period of treatment, AED's doses and serum levels were reported with the aim to evaluate the association of these values with the prevalence of each AED's adverse effects.

Statistical analysis

For the comparison groups' studies, a further approach was conducted to identify statistical differences between studies with regards to reported adverse effects. For each AED study, the total number of patients experiencing adverse effects and/or the number of patients experiencing specific adverse effects (e.g. sedation, ataxia, polyuria, etc.) in all therapeutic groups were retrieved. The odds ratio (OR) was then estimated in order to indicate the increased or decreased odds of observing a specific adverse effect(s) in total for an AED compared to its control group (comparison AED or placebo or untreated animals). Statistical analysis was undertaken following the guidelines of the Handbook of the Cochrane Collaboration 5.0. The OR for dichotomous data was calculated using the random-effects model in Review Manager 5.3. Heterogeneity between studies was calculated using the Chi square test and was considered to be heterogeneous when $P \leq 0.1$. I^2 values of no more than

25, 26 to 74 % and no less than 75 % were considered as "low", "moderate" and "high" heterogeneity, respectively. Associations were considered to be statistically significant at $P < 0.05$. P values between 0.05 and 0.1 were considered as statistical trends of potential interest.

Results

Description of studies

By 29 December 2015, the search strategy had identified a total of 368 unique citations; 347 from the electronic searches of PubMed, CAB Abstracts, Google Scholar and manual searches from the publications' reference lists, 16 from manual searching of major conference proceedings and 6 unpublished studies included as part of published data. Two hundred ninety two items fulfilled stage 1 screening criteria. Of these, 90 final studies (published between 1981 and 2015) also fulfilled stage 2 selection criteria and were thus selected for review.

The vast majority of studies were allocated in the second (i.e. non-blinded, non-randomised and uncontrolled studies) and third (i.e. retrospective case series and reports) group. A few studies included more than one sub-study (i.e. a clinical trial and/or ELAS and/or retrospective case series part); accordingly, such studies were included in more than one group. Therefore, study designs represented were five bRCT [23–27], two nbRCT [28, 29] and seven nbRELAS [25, 30–35] in the first group, six NRCTs [36–41], 11 NRELAS [42–52], 22 UCTs [44, 48, 53–71], six UELAS [34, 72–76] and one cross sectional study [3] in second group, and 19 retrospective case series [77–95] and 16 case reports [96–111] in the third group. In addition, five unpublished studies described adverse effects and were reported briefly in EMA report; thus all these were considered as one study [112] and were not included in any category as there was insufficient information as far as their design was concerned.

Overall, the 90 selected studies reported 12 AEDs. In all studies but one [43], the AEDs were orally administered. Within each study, one or more AEDs were evaluated as a monotherapy and/or adjunct to other AEDs.

Disease characterisation

In the majority of the studies, the inclusion criteria for diagnosing IE were not well characterized. According to the described grading system for subject enrolment quality, 16 studies [27, 33, 53, 61, 63, 64, 68, 80, 81, 90, 96, 97, 100, 101, 110, 111] enroled treatment groups of well characterized IE, 13 studies [3, 44, 48, 54–57, 62, 66, 67, 77–79] enroled treatment groups of fairly characterized IE, and 14 studies [23–26, 39, 58, 59, 65, 74, 82, 84, 88, 108, 109] enroled treatment groups of poorly characterized IE. In 26 studies [28, 29, 36–38, 50, 60, 69, 70, 75, 83, 85–87, 89, 91–94, 98, 99, 102–106], the diagnostic procedures for enrolment of cases with IE were unclear.

As far as the ELAS including healthy animals were concerned, eight [31, 36, 45, 46, 50–52, 73] enroled treatment groups of clear and 14 [25, 30, 32, 34, 35, 37, 38, 42, 43, 47, 49, 72, 76] enroled treatment groups of unclear or unknown diagnostic investigation for ruling out other diseases. In one report, a dog was non-epileptic and was treated with phenobarbital and chlomipramine due to anxiety and aggression, but the diagnostic investigation for this was unclear [107].

Study group sizes

The vast majority of studies reported the total number of dogs evaluated. The majority of studies evaluated small or very small study size groups. Thirteen studies [25, 26, 40, 50, 62, 69–71, 75, 82, 88, 90, 113] evaluated groups with a good number of dogs, 13 studies [23, 24, 32, 37, 39, 65, 74, 77, 79, 80, 91, 94, 95] evaluated groups with a moderate number of dogs, 26 studies [3, 28, 34, 36, 38, 44–46, 48, 53, 54, 56–61, 63, 64, 66, 70, 75, 81, 83, 84, 114] evaluated groups with a small number of dogs and 38 studies [33–35, 39, 42, 43, 51–53, 55, 67, 68, 72, 73, 76, 78, 85, 87, 89, 92, 93, 96–100, 102–111, 115, 116] evaluated groups with a very small number of dogs. In two studies, the study group size was unclear [47, 49].

Signalment and baseline characteristics of study subjects

Baseline characteristics (such as breed, age and sex) of total enroled dogs were reported to some extent for all 90 studies. Clear presentation of statistical comparison of intervention groups with respect to signalment and baseline disease characteristics was not commonly encountered.

In all studies reporting baseline data, the recruited dogs represented multiple breeds, both sexes and a wide range of ages at study entry (median 5, mean 4, range 0.5-7 years). Major affected breeds were crossed-breeds and pure breeds such as Labrador and Golden Retrievers followed by German Shepherd dogs, Beagles, Boxers and Poodles. In the majority of the studies more males were affected compared to females, though these differences were not evaluated statistically.

Methodological quality of included studies

The vast majority of studies revealed high and/or unclear risk of bias for all the components (Fig. 1). As stated in the methods, retrospective case series and reports were not included in the methodological quality assessment as these were considered to be at an overall high risk of bias.

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