Responses to successive anti-epileptic drugs in canine idiopathic epilepsy


PHARMACORESISTANCE to anti-epileptic drugs (AEDs) can be a source of frustration for owners and veterinarians alike in the treatment of canine idiopathic epilepsy (IE), with ongoing seizures having a significant negative impact upon the quality of life of affected dogs and owners (Chang and others 2006, Wessmann and others 2014). Finding an effective AED that reduces seizure frequency to an acceptable level (generally classed as more than 50 per cent reduction in veterinary medicine), or results in remission (seizure-freedom) can be a long process, with several AEDs trialled before optimum treatment is reached (Packer and others 2014). With more AEDs becoming available to veterinary patients, knowing whether (and when) to include further therapies can be challenging for practitioners, when faced with the balance between seizure control and side effect profiles.

In human epilepsy, response rates to first-line and further AEDs have been studied in several populations, with the probability of seizure control diminishing progressively with successive AED treatments. Kwan and Brodie (2000) reported response rates (as a proportion of the population) of 47, 15 and 4 per cent for first-line, second-line and third-line drugs, respectively (Kwan and Brodie 2000). Similarly, Mohanraj and Brodie (2006) reported response rates of 50.4, 10.7 and 2.3 per cent, respectively, with just 0.8 per cent responding to any further drugs (Mohanraj and Brodie 2006).

If the initial AED fails to control seizures, the prognosis for seizure control may be poor. Failure to respond to the first AED has been demonstrated to predict becoming refractory at two-year follow-up in a study of children with temporal lobe epilepsy (Dlugos and others 2001). In a further study, of those patients unresponsive to the first AED, 76 per cent failed two or more AEDs and 38 per cent failed at least four (Perucca and others 2011). These patients were also at an increased risk of experiencing adverse health outcomes, including disability, morbidity, mortality and reduced self-reported quality of life than those that responded (Perucca and others 2011).

This may depict a bleak picture for patients unresponsive to the first AED; however, it has been highlighted in other studies that a notable proportion of patients who fail to respond to the first AED may respond to subsequent AEDs, for example, around one-third of child and adult patients have been seen to respond to a second AED (Elkis and others 1993) or further AEDs (Perucca and others 2011). In veterinary medicine, various AEDs are used for the management of IE in dogs; however, data on their efficacy remain limited, with most evidence derived from non-blinded, non-randomised uncontrolled trials and case series (Muñana 2015). In addition, the response rate for successively used AEDs is poorly reported, despite polytherapy commonly being used. In this study, we describe response rates to first-line, second-line and third-line AEDs.

Data from dogs treated at a multibreed canine-specific epilepsy clinic at the Royal Veterinary College Small Animal Referral Hospital (RVC SARH) between 2005 and 2011 were retrospectively collected from RVC’s electronic patient records. Clinical data were originally gained via standardised owner questionnaires for patients with epilepsy at their first appointment, and longitudinal follow-up data were gained via telephone interview with the dogs’ owners. All dogs received a uniform diagnostic protocol, with only dogs reported to be diagnosed with IE, for which a cause was not identified (no remarkable findings on interictal neurological examination, haematology, biochemistry, brain MRI and cerebrospinal fluid examination), included in the study.

Dogs were only included in the study if they were receiving at least one AED, recorded as whether they received a first-line AED (phenobarbital (PB)), second-line AED (potassium bromide (KBr)) and/or a third-line AED (levetiracetam or others). Non-responsiveness to an AED was classified as a less than 50 per cent reduction in seizure frequency, despite being within the reference range for the prescribed AED and titrated to the maximum tolerated effective dose. As these data were derived from a clinical population, decision making leading to the maximum dose of any AED was made by both the clinician and the owner, taking into account adverse effects of the drug and its efficacy.

A total of 196 dogs were included in the study, with 72 per cent male and 57 per cent neutered. The median age presented to hospital was 1129 days (720–1830) and median age at diagnosis 815 days (509–1440). The median follow-up time was 604.5 days (300–862.5). Cluster seizures had been experienced by 55.1 per cent of dogs, and status epilepticus by 20 per cent. Overall response rates (with response defined as more than 50 per cent reduction in seizure frequency) to the first-line, second-line and third-line AEDs (as a proportion of the whole population) were 57.2, 10.7 and 6.1 per cent, respectively. Only 57.2 per cent of dogs responded to one AED alone (PB). Of the nearly two thirds of dogs (62.8 per cent, n=123) of dogs that did not respond to the initial PB monotherapy, 65 per cent (n=80) received a second line drug (KBr) as an adjunct therapy, of which nearly one third (26.3 per cent, n=21) responded. Finally, of the over two thirds of dogs (75.8 per cent, n=99) that did not respond to the PB and KBr combination, 54.2 per cent (n=52) received an additional third line drug (levetiracetam in 27 of cases), of which over one third (37.5 per cent) responded (Fig 1). When remission (seizure freedom) is taken as the standard for response, only 28 dogs overall (14.2 per cent) achieved this, with all of these dogs reaching seizure freedom on one AED alone. Half of all dogs
(50.3 per cent) had been pretreated with AEDs by the referring veterinary surgeon (RVS) before arrival at the RVC SARH, while the other half (49.7 per cent) had AED therapy initiated at their hospital appointment. A chi-squared analysis indicated there was no significant difference in response rates (more than 50 per cent reduction) to second-line and third-line drugs between dogs that had been pretreated by the RVS and those that initiated AED treatment at the RVC SARH (P>0.05).

In human medicine, response to the first AED has been shown to be higher, for example, nearly half of adult patients (e.g. 49.5 per cent; Brodie and others 2013; 47 per cent; Kwan and Brodie 2001) and 55 per cent of child patients (Yilmaz and others 2014) becoming seizure free on the first-ever AED, in comparison with only 14 per cent in this study. In human epilepsy, response to treatment is often defined as achieving seizure freedom on an unchanged treatment for 12 months (Mohananraj and Brodie 2006), a standard currently higher than that commonly used in veterinary medicine. From this, it is clear that we have not yet found the ‘perfect AED’ to treat canine IE. PB is the most commonly used first-line AED in canine epilepsy, and in a previous study of PB and KBr as first-line treatments, complete seizure freedom was achieved in 85 and 52 per cent, respectively, of treated dogs; however, this was with only six-month follow up and could reduce over time (Boothe and others 2012). The lower success rates seen in the current study may reflect dogs with a more severe seizure phenotype, as half had been referred to a neurology specialist after unsuccessful pretreatment at their RVS, whereas in the study by Boothe and others (2012), all recruited dogs had not received previous AEDs.

Drug refractory epilepsy is defined by the International League against Epilepsy as failure to achieve sustained seizure-freedom after at least two appropriate AED trials (Kwan and others 2010). Despite this definition, there is widespread belief among human neurologists that patients should have to fail to respond to three or more AEDs to be considered pharmacoresistant (55 per cent respondents), with some believing four AED failures (14 per cent) or all available AED failures (19 per cent) are required to classify patients this way (Hashimi and others 2008). This study demonstrated that one-fifth (37.2 per cent) of dogs that received a third-line AED after treatment failure with two AEDs were responsive to this drug (achieving more than 50 per cent reduction in seizure frequency). In light of this finding, with careful consideration, the addition of third-line drugs may be appropriate in some cases, but further research is required to determine which medication may be most efficacious in this scenario. Finally, expectations of improvement in seizure frequency should be modified by the finding that only dogs who responded to the first AED became seizure-free in this study.

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References


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