Long-term efficacy of imepitoin in the treatment of naive dogs affected by idiopathic epilepsy

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Paper

Long-term efficacy of imepitoin in the treatment of naive dogs affected by idiopathic epilepsy

A. Gallucci, T. Gagliardo, M. Menchetti, E. Bianchi, D. Bucci, G. Gandini

The purpose of this study was to evaluate the long-term (12 months) efficacy and tolerability of imepitoin as first-choice treatment in 56 dogs suffering from idiopathic epilepsy and identify possible factors affecting the outcome. Primary treatment success (PTS) was defined as the achievement of a seizure-free interval three times longer than the pretreatment interictal interval (at least three months). Secondary treatment success (STS) was achieved by a decrease in seizure frequency ≥50 per cent compared with the pretreatment frequency. In the long-term follow-up, PTS was recorded in 14 (25 per cent) dogs and responder-dogs (PTS+STS) were 30 (54 per cent) showing significant reduction in the monthly average number of seizures (P<0.001). Median seizure frequency per month was 1.69 pretreatment and 0.3 at 12-month follow-up. Dogs with cluster seizures were significantly reduced (P=0.02). PTS at three and six months was associated with PTS (P=0.006 and <0.001, respectively) and with the status of responder dogs (P=0.002) at 12-month follow-up. Dogs aged >36 months at the start of imepitoin treatment had a positive association to become responder dogs (P<0.001) and achieve PTS (P=0.004). 16 dogs (29 per cent) discontinued imepitoin due to its inefficacy. The receiver operator curve highlighted ≥19 mg/kg twice a day as the most effective minimal dosage. Mild and transient side effects were observed in 16 dogs (29 per cent).

Epilepsy is the most common chronic neurological disease in dogs and, although its true incidence is unknown, it has been estimated to affect approximately 0.6–5 per cent of the total canine population (Podell and others 1995, Bialer and others 2013, Kearsley-Fleet and others 2013, Heske and others 2014, Platt and De Risio 2014). Idiopathic epilepsy (IE) is considered the most common represented canine epileptic disorder (Patterson 2013).

The treatment of canine IE is symptomatic and, in most cases, consists in the lifelong administration of antiepileptic drug (AED) (Bhatti and others 2015). Several factors can affect the overall response to the AED treatment, including the variation in severity in the different breeds and owner-related factors. When compared with human medicine, the percentage of therapeutic success in dogs is generally considered much lower (Volk 2014).

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Recently, the '2015 ACVIM Small Animal Consensus Statement on Seizure Management in dogs' defined the guidelines for IE treatment according to an evidence-based reconsideration of the current literature. The recommendation of the panel concerning the first-line drug to be used in naive IE dogs includes phenobarbital (PB), imepitoin (IMP) and, to a lesser extent, bromide (Br) (Podell and others 2016). The choice of AED is often determined on a case-by-case basis, taking into account AED-specific factors such as tolerability, adverse effects and owner-related circumstances such as lifestyle and financial issues (De Risio 2014a, Bhatti and others 2015, Podell and others 2016).

IMP, licensed in Europe in 2013 after approval by the European Medicines Agency (EMA), is the first AED drug specifically developed for the treatment of single seizures in idiopathic epileptic dogs.

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/medicines/002543/vet_med_000268.jsp&mid=WC0b01ac058008d7a8).

IMP is claimed to have the same efficacy and fewer side effects than PB. A randomised, blind, controlled parallel group clinical field trial did not find any significant differences in the monthly seizure frequency reduction and in the complete suppression of generalised seizures between IMP (75 per cent and 46.9 per cent, respectively) and PB-treated group of dogs (83 per cent and 58 per cent, respectively). The same study showed that the frequency of adverse effects was significantly higher in dogs treated with PB (Tipold and others 2015). IMP acts as a low-affinity partial agonist at the benzodiazepine recognition site of the $GABA_A$ receptor (Bialer and others 2013). In contrast to full agonist drugs, such as PB, IMP does not seem to show tolerance,

dependence and loss of anticonvulsant efficacy during prolonged treatment (Rundfeldt and others 2014). In mice and dogs, no withdrawal signs were noted following discontinuation of the treatment (Löscher and others 2004; Rundfeldt and Löscher 2014; Rundfeldt and others 2014).

The safety of IMP was evaluated under laboratory conditions on a group of healthy beagle dogs, in which no occurrence of relevant adverse events was detected after the administration of 0, 30, 90 or 150 mg/kg IMP every 12 hours for 26 weeks (Tipold and others 2015).

Since the reports of Tipold and others (2015) and Rundfeldt and others (2015), both with an observational period up to six months, no additional reports have been published on the clinical tolerability and efficacy of IMP in field trials. Moreover, the efficacy of IMP has not yet been demonstrated in dogs with cluster seizures (CS) or status epilepticus (SE) (Charalambous and others 2014, Bhatti and others 2015).

The aim of this clinical field study was to contribute to the knowledge of efficacy and tolerability of IMP as a first-line AED in a population of idiopathic epileptic dogs suffering from single and/or CS, with or without SE experience, in a longer follow-up (12 months) than previously reported. An additional purpose was to evaluate the possible association between the efficacy of IMP and specific parameters, such as age, weight, gender, type of seizures (single or cluster), dosage, frequency of seizures, time between the first seizure and the start of the AED treatment.

Materials and methods

A project of a retrospective/prospective study on the long-term efficacy of IMP treatment of idiopathic epileptic dogs was presented at the 2014 Symposium of the Italian Society of Veterinary Neurology. The main aim of the project was to retrospectively collect naive dogs affected by IE that underwent monotherapic treatment with IMP in order to be retrospectively/prospectively evaluated for the efficacy and side effects of the treatment. The project encompassed the possibility to enrol new cases to increase the size of the population.

The medical records of dogs with recurrent seizures, presented for the first neurological examination between 2012 and 2015 at the Veterinary Teaching Hospital (VTH) of the Department of Veterinary Medical Sciences (DIMEVET) of the University of Bologna and in three private practices ('Città di Saronno', 'Schiavi' and 'Ass. Prof. Neurovet'), were evaluated. The establishments involved in the study were all mixed (first opinion and referral) practices.

The dogs included in the study had a diagnosis of IE, which was obtained according to

A. the presence of two or more unprovoked epileptic seizures, occurring as single seizures at least 24 hours apart or repeated episodes of CS;
B. the presence of a normal interictal physical and neurological examination, which were performed by a resident/diplomate in veterinary neurology and, in six cases, by an experienced practitioner;
C. unremarkable laboratory results, including a complete cell blood count and serum biochemistry profile (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, urea, creatinine, total protein, albumin, total bilirubin, glucose, cholesterol, triglycerides, sodium, potassium, chloride, calcium, phosphate) and, in most cases, fasting bile acids and/or ammonia;
D. unremarkable MRI of the brain.

In case of absence of MRI, dogs were included in the study if the age at the first seizure ranged between six months and six years and the abovementioned A, B and C requirements were met. For the purpose of the study, these latter dogs were included if they had a history of at least one year of recurrent seizures and normal interictal neurological examination.

The major requirement for being enrolled in the study was the use of IMP as single AED treatment in monotherapy. The study was conducted following ethical rules and with the approval of the ethical committee of the Bologna University, together with written informed consent of the owners.

The study enrolled all the available cases with sufficient recorded data. The choice of the IMP treatment was made by the owner based on the information provided at the time of the neurological examination and considering the costs and the possible side effects. IMP (Pexion tablet 100 or 400 mg, Boehringer Ingelheim Vetmedica) was administered every 12 hours at the oral dose of 10–30 mg/kg, as recommended by manufacturer's instructions.

Dogs with incomplete seizures information or dogs that previously had treatment with other AEDs were not considered for the study. The dogs with retrospectively evaluated medical records were included in the study if the owners had the post-treatment seizures diary (provided at the onset of the treatment with the drug) adequately filled. During the follow-up, the reasons for discontinuation of the treatment were documented and the dogs that discontinued IMP (or added another AED) due to lack of efficacy before the 6-month and 12-month follow-up were maintained in the study were considered as non-responders.

Results of additional tests, if available, were recorded in selected cases. They included urinalysis, hormonal tests (total T4, free-T4, thyroid-stimulating hormone, adrenocorticotropic hormone (ACTH) stimulation test), coagulation test, protein electrophoresis, chest X-rays and abdomen ultrasound.

MRI was made using either a low-field 0.22 or 0.18 T magnet (Paramed Mr J 2200 and Vet MRI Esaote, respectively) acquiring sagittal, transverse and dorsal T2-weighted and T1-weighted (pre-gadolinium and post-gadolinium) sequences. Additional MRI sequences and cerebrospinal fluid (CSF) examinations were performed in selected cases.

Breed, gender, age at the first seizure and at the beginning of IMP treatment, time elapsed between the first seizure and the beginning of the antiepileptic treatment, number and type of seizures pre-therapy and post-therapy, presence of SE, change of dosage and occurrence of adverse effects (type and duration) were recorded.

Follow-up information was obtained at 3, 6 and 12 months (respectively short-term, medium-term and long-term follow-up) either through recorded follow-up neurological consultations, telephone calls or a questionnaire sent to the owners in due time.

Seizures were classified as single seizures, CS and SE according to the definition of the literature (Mariani 2013, De Risio 2014c, Berendt and others 2015).

Outcome

Therapeutic success was defined according to the recent publication of the International Veterinary Epilepsy Task Force (Potschka and others 2015). Primary treatment success (PTS) was defined as the achievement of a seizure-free interval three times longer than the pretreatment interictal interval and lasting at least three months. Secondary treatment success (STS) was defined as the prevention of CS and SE, relevant reduction of seizures frequency considering pretreatment seizures frequency and reduction in seizures severity (Potschka and others 2015). In this study, due to the lack of an objective threshold to define STS and according to the previous definition of therapeutic success, the decrease in seizure frequency ≥50 per cent compared with the pretreatment frequency was used to define STS (Volk and others 2008; Dewey and others 2009; Muñana and others 2012a,b; Packer and others 2014). PTS and STS were assessed evaluating the seizures diary of the owners.

Statistical analyses

The statistical analysis was performed using R (R Core Team 2016). Difference was considered significant for $P \leq 0.05$. Shapiro-Wilk test was used to assess normality.

To perform the analysis, selected numerical variables (weight, age at first seizure and at the start of IMP, dosage and frequency of seizures) were categorised.

Dogs were grouped into three classes according to the *age at the first seizure*: ≤12, >12≤36 and >36 months. According to the *weight*, dogs were divided into three groups: ≤ 10, >10≤20 and >20 kg.

Based on the IMP *dose* received, dogs were divided into three groups: minimum dosage (up to 10 mg/kg twice a day), medium dosage (from 11 to 20 mg/kg twice a day) and high dosage (from 21 to 30 mg/kg twice a day). The dosage changes during the follow-up period were recorded to evaluate the possible association with the outcome.

Frequency of epileptic seizures was investigated distinguishing dogs with low frequency of seizures (dogs experiencing one or less seizures per month) and dogs with high frequency of seizures (dogs having more than one seizure per month). CS were counted considering the total number of epileptic seizures (ie, CS with five separate seizure=five seizures).

With respect to the response to treatment, the general population of dogs was divided into two groups: *responder dogs* (R dogs ('positive outcome'), including R-PTS dogs and R-STS dogs) and *non-responder dogs* (non-R dogs ('negative outcome'), dogs that not achieved a decrease in seizures frequency ≥50 per cent compared with the pretreatment frequency). Further analysis was made on the subpopulation of R-PTS dogs.

Fisher's exact test was used to assess the presence of a relationship between outcome and the different variables (age, weight, gender, type of seizures (single or cluster), dosage, time between the first seizure and the beginning of the AED treatment, frequency of seizures at 3-month, 6-month and 12-month follow-up and side effects).

A paired samples Wilcoxon signed-rank test was used to assess the difference between average monthly seizures frequency at different times (pretreatment, 3-month, 6-month and 12-month follow-up). The difference between R dogs and non-R dogs (as defined at 12-month follow-up) was investigated using a Wilcoxon signed-rank test for independent samples.

A general linear model was set to assess the decrease in CS during the follow-up and a receiver operator curve (ROC) was generated to highlight the most effective minimal dose.

Results

In the period 2012–2015, 161 dogs underwent a first neurological examination at the VTH of the DIMEVET with a final diagnosis of IE. Out of these, 66 dogs received IMP as first-choice AED. In total, 18 dogs were subsequently excluded due to insufficient follow-up recorded data (12 dogs), lost to the follow-up (5 dogs) and discontinuation of IMP after two months because the owner moved to the USA, where the drug was unavailable (1 dog). Forty-eight dogs from the VTH of the DIMEVET met the inclusion criteria and were enrolled in the study. Eight further dogs meeting the same inclusion criteria came from three veterinary practices and joined the study. No reliable data on their respective IE canine population were available. Fifty-six dogs were finally included in the study.

The CBC and serum biochemistry profile in all dogs was shown to be within normal limits. All the additional tests performed, including urinalysis (50 dogs), fasting bile acids and ammonia (50 and 8 dogs, respectively), serum protein electrophoresis (48 dogs), endocrinological tests (17 thyroid functional tests, 1 ACTH stimulation), coagulation test (6 dogs), abdomen ultrasound (21 dogs) and chest radiographs (6 dogs) showed unremarkable results.

MRI of the brain, performed on 12 dogs (21 per cent), showed no remarkable alterations. Two dogs (3.6 per cent) had normal CSF examination.

Descriptive data

Twelve dogs (21.4 per cent) were mixed breed, six dachshund (10.7 per cent), six pinscher (10.7 per cent), four Yorkshire (7.1 per cent), three labrador retriever (5.3 per cent), three French bulldog (5.3 per cent), two miniature Schnauzer (3.5 per cent), two Rottweiler (3.6 per cent), two beagle (3.6 per cent), two Pomeranian (3.6 per cent), one Volpino Italiano (1.8 per cent), one Border collie (1.8 per cent), one Brittany spaniel (1.8 per cent), one English bulldog (1.8 per cent), one chihuahua (1.8 per cent), one Czechoslovakian wolfdog (1.8 per cent), one Pekingese (1.8 per cent), one cocker (1.8 per cent), one Australian shepherd (1.8 per cent), one boxer (1.8 per cent), one Siberian husky (1.8 per cent), one German shorthaired pointer (1.8 per cent), one pug (1.8 per cent) and one giant schnauzer (1.8 per cent).

In total, 32 dogs were males (two neutered) and 24 were females (nine neutered). Median weight was 12.75 kg (range 2.5–42; IQR 17.5). Median age at the first seizure was 28.5 months (range 4–108; IQR 27.5), while median age at the beginning of IMP treatment was 36 months (4–108; IQR 30). Median time elapsed between the first seizure and the start of IMP treatment was 10 months (0–144; IQR 19.25).

Outcome and statistical results

In total, 56 (100 per cent), 53 (95 per cent) and 40 (71 per cent) dogs reached the 3-month, 6-month and 12-month follow-up while under IMP treatment, respectively. In the 3 and 13 dogs that missed the 6-month and 12-month follow-up, IMP was discontinued for lack of efficacy and replaced or combined with another AED. These dogs were still included in the study as non-R dogs.

At 3-month, 6-month and 12-month follow-up, there were, respectively, 36 (64 per cent), 29 (52 per cent) and 30 (54 per cent) R dogs. At the same end points, PTS was recorded in 23 (41 per cent), 12 (21 per cent) and 14 (25 per cent) dogs, respectively.

Conversely, the non-R group counted 20 (36 per cent), 27 (48 per cent) and 26 (46 per cent) dogs (Table 1).

There were 17 (30 per cent) and 39 (70 per cent) dogs with low and high pretreatment seizure frequency, respectively. Thirty-three dogs (59 per cent) experienced single seizures (thirty-two generalised and one focal). Seizure type and frequency at the different follow-up end points are detailed in Table 1.

The median of the monthly seizure frequency during pretreatment and at 3-month, 6-month and 12-month follow-up was 1.69 (range 0.5–20; IQR 3.67), 0.7 (range 0–10; IQR 2.08), 0.9 (range 0–15; IQR 2.62), 0.3 (range 0–6; IQR 1.28), respectively, calculated on R dogs (Table 1).

Pretreatment interictal time had a median of 23 days (range 2–60; IQR 25.75) (calculated on the last six months for dogs with a history of epileptic seizures pretreatment lasted more

TABLE 1: Descriptive statistics of outcome and seizures type and frequency of the investigated canine idiopathic epileptic population

Variables	Pretreatment n=56	3 months n=56	6 months n=53	12 months n=40
Outcome				
Positive	—	36 (64%)	29 (52%)	30 (54%)
Negative		20 (36%)	27 (48%)*	26 (46%)**
Seizures frequency				
High frequency	39 (70%)	22 (39%)	20 (38%)	8 (20%)
Low frequency	17 (30%)	11 (20%)	21 (39%)	18 (45%)
Seizure-free	–	23 (41%)	12 (23%)	14 (35%)
Average monthly seizure frequency (median)	1.69 (0.5–20) IQR 3.67	0.7 (0–10) IQR 2.08	0.9 (0–15) IQR 2.62	0.3 (0–6) IQR 1.28
Type of seizures				
Single seizures	33 (59%)	22 (39%)	33 (62%)	24 (60%)
Cluster seizures	23 (41%)	11 (21%)	8 (15%)	2 (5%)
Status epilepticus	3 (5%)	0	1 (2%)	0

*3 and **16 dogs that discontinued imepitoin due to lack of efficacy were included in the study as non-responder dogs (negative outcome)

than six months) and at 12 months of IMP treatment had a median of 100 days (range 5–180; IQR 151.25) (calculated on the last six months). The same data calculated only on the dogs that achieved PTS at 12-month follow-up was 180 days (range 180–180; IQR 0) and the pretreatment median was 34 days (range 6–60; IQR 26.5). When compared with the pretreatment value, R dogs showed a significant reduction of the monthly seizure frequency in short-term (P<0.01), medium-term (P<0.001) and long-term follow-up (P<0.001) (Fig 1).

Table 2 reports the association between variables and outcome, both of R-PTS and R dogs, of the investigated canine idiopathic epileptic population.

Dogs with a seizure-free condition at the three-month and six-month follow-up were positively associated to achievement of PTS (P=0.006 and <0.001, respectively) at the 12-month follow-up. Dogs with a seizure-free condition recorded at the six-month follow-up (N=12) were still seizure-free for the rest of the study.

Dogs with a seizure-free condition at the 3-month follow-up showed a positive association to become R dogs (P=0.002) at the 12-month follow-up. Dogs with single seizures and seizure-free condition at the six-month follow-up were positively associated to become R dogs (P=0.03) at the 12-month follow-up (Table 2).

Dogs with pretreatment low frequency of seizures were positively associated with PTS at all the end points of the follow-up (P=0.02, 0.004 and 0.02, respectively) and showed a positive trend to become R dogs at the three-month and six-month follow-up (P=0.08 and 0.06).

Dogs ageing >36 months at the start of the IMP treatment had a positive association to become R dogs at all the follow-up end points (P=0.004, 0.001 and <0.001, respectively) and R-PTS at 6-month and 12-month follow-up (P=0.009 and 0.004) (Table 2). The other parameters, including weight, time elapsed between the first seizure and the beginning of the IMP treatment, were not associated with the outcome at any time of the follow-up (Table 2).

Twenty-three dogs (41 per cent) experienced CS (all generalised) before the treatment (average of seizures per cluster: 4.1; range 2–15). During IMP treatment, CS were observed in 11 (21 per cent; average seizures: 3.3; range 2–4), 8 (15 per cent; average seizures: 4; range 3–6) and 2 dogs (5 per cent; average seizures 4; range 4–4) at 3-month, 6-month and 12-month follow-up (Table 1).

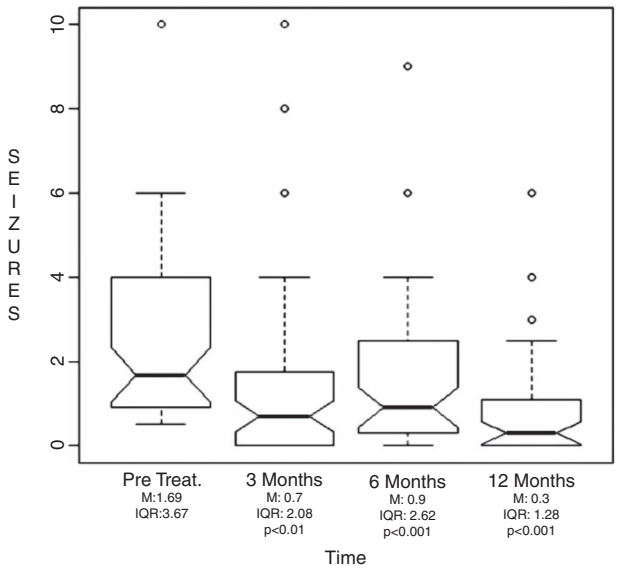

FIG 1: Median of the average monthly seizures reduction in responder dogs at 3-month, 6-month and 12-month follow-up compared with the pretreatment value (P<0.01, <0.001 and <0.001, respectively). Notches represent 95% CI

CS turned to single seizures in, respectively, 8 (35 per cent), 12 (52 per cent) and 11 (48 per cent) dogs at 3-month, 6-month and 12-month follow-up and reached PTS at the same follow-up end point in 9 (39 per cent), 5 (22 per cent) and 5 (22 per cent) dogs. Nine dogs with CS did not improve and were considered non-R dogs due to the change of treatment during the study. When compared with the pretreatment value, the whole number of dogs with CS showed a significant reduction at 6-month and 12-month follow-up (P=0.04 and 0.02, respectively) (Fig 2). During the study, dogs suffering from CS were treated with diazepam administered per rectum and no other AEDs were added.

Three dogs (5 per cent) experienced SE before the treatment. Out of these, one discontinued the treatment at six months, and the other two turned to single seizures (one R and one non-R). One dog (2 per cent) with single seizures experienced one episode of SE in the first six months of IMP treatment and was responsive to the intravenous injection of a bolus of diazepam (1 mg/kg).

At the beginning of the treatment, the dogs received a median dosage of 15 mg/kg twice a day (range 8–23; IQR 6.12). In 13 dogs (23 per cent), the dosage was increased within the first three months of therapy to improve the efficacy and in 1 dog (2 per cent) the dosage was reduced by the owner because the seizures disappeared. Table 3 shows IMP dosage at the different follow-up end points. No further adjustment of the IMP dosage was recorded at the medium-term and long-term follow-up. Not all the 16 dogs (29 per cent) that did not complete the study due to lack of efficacy of IMP monotherapy reached the maximum dosage. This was mainly due to economic restraints of the owner. No R dogs discontinued therapy due to IMP costs.

The ROC showed the optimal dosage differentiating R dogs from non-R dogs was ≥19 mg/kg twice a day (area under the curve 0.82; 95 per cent CI 0.71 to 0.92; sensitivity 77 per cent; specificity 70 per cent) (Fig 3).

Side effects

Sixteen dogs (29 per cent) experienced side effects (in two dogs more than one side effect was simultaneously observed): eight dogs (14 per cent) showed excitability, six (11 per cent) sedation, two (4 per cent) polyphagia, one (2 per cent) mild generalised tremors, one (2 per cent) gastrointestinal disorders and one (2 per cent) increase of aggressiveness. All the recorded side effects were transient and disappeared within the first 10 days of treatment. Side effects were not significantly associated with any of the analysed variables (Table 4).

Discussion

The present study was aimed to give a contribution in establishing the long-term efficacy and tolerability of the monotherapic treatment with IMP in a population of idiopathic epileptic dogs in field conditions. While many papers have aimed to investigate the properties of IMP in a research setting (Löscher and others 2004, 2013, Rieck and others 2006, Rundfeldt and Löscher 2014, Rundfeldt and others 2014), the scientific reports on the clinical safety and efficacy of IMP in field trials are limited to the papers of Tipold and others (2015) and Rundfeldt and others (2015). To date, there were no clinical data on IMP efficacy and safety for follow-up longer than six months (Rundfeldt and others 2015, Tipold and others 2015).

In this study, IMP showed to be efficacious in 54 per cent of treated dogs and produced a seizure-free state (PTS) in 25 per cent of dogs at the end of the 12-month follow-up. The authors' ROC depicted an optimal minimum dosage ≥19 mg/kg every 12 hours. At the six-month follow-up, their results differ from those of Tipold and others (2015) both in the reduction of the monthly seizures frequency (52 per cent v 75 per cent) and in suppressing seizures (21 per cent v 46.9 per cent). Possible reason to explain these data may stay in the different nature of the two studies.

TABLE 2: Association between variables and outcome (primary treatment success (PTS) and total) of the investigated canine idiopathic epileptic population (N=56)

Variables	PTS referred to the general population	Responders (PTS+STS) referred to the general population
Age at first seizure	3 months: P=0.65	3 months: P=0.16
(≤12; >12≤36 ; >36 months)	6 months: P=0.46	6 months: P=0.06 (trend NA for ≤12 months)
	12 months: P=0.24	12 months: P=0.14
Weight	3 months: P=0.71	3 months: P=0.1
(≤10 kg; >10≤20 kg; >20 kg)	6 months: P=0.51	6 months: P=0.54
	12 months: P=0.07 (trend NA for ≤10 kg)	12 months: P=1
Gender	3 months: P=0.46	3 months: P=0.32
	6 months: P=0.05 (NA for intact female)	6 months: P=0.03 (NA for intact female)
	12 months: P=0.14	12 months: P=0.14
Type of seizures (pre-treatment)	3 months: P=1	3 months: P=0.57
	6 months: P=1	6 months: P=0.79
	12 months: P=0.89	12 months: P=0.59
Type of seizures (3 months)	12 months: P=0.006 (PA for SF)	12 months: P=0.002 (PA for SF)
Type of seizures (6 months)	12 months: P<0.001 (PA for SF)	12 months: P=0.03 (PA for SS and SF)
IMP dosage*	3 months: P=0.17	3 months: P=1
(minimum, medium, high)	6 months: P=0.01 (NA for high dosage)	6 months: P=0.06 (NA trend high dosage)
	12 months: P=0.01 (NA for high dosage)	12 months: P=0.06 (NA trend high dosage)
Pretreatment frequency of seizures†	3 months: P=0.02 (PA for low dosage)	3 months: P=0.08 (trend low: PA)
(low, high)	6 months: P=0.004 (PA for low dosage)	6 months: P=0.06 (trend low: PA)
	12 months: P=0.02 (PA for low dosage)	12 months: P=0.7
Time between first seizure and onset of IMP treatment	3 months: P=0.49	3 months: P=0.99
	6 months: P=0.11	6 months: P=0.25
	12 months: P=0.44	12 months: P=0.26
Age at the start of IMP treatment	3 months: P=0.07 (trend PA for >36)	3 months: P=0.004 (PA for >36)
(≤12 ; >12≤36 ; >36 months)	6 months: P=0.009 (PA for >36)	6 months: P=0.001 (PA for >36)
	12 months: P=0.004 (PA for >36)	12 months: P≤0.001 (PA for >36)

*IMP dosage: minimum dosage (up to 10 mg/kg twice a day), medium dosage (from 11 to 20 mg/kg twice a day) and high dosage (from 21 to 30 mg/kg twice a day)
†Pretreatment frequency of seizures: low frequency of seizures (dogs experiencing ≤ seizures per month) and dogs with high frequency of seizures (dogs having >1 seizure per month)
IMP, imepitoin; NA, negative association; PA, positive association; SF, seizure-free; SS, single seizures; STS, secondary treatment success

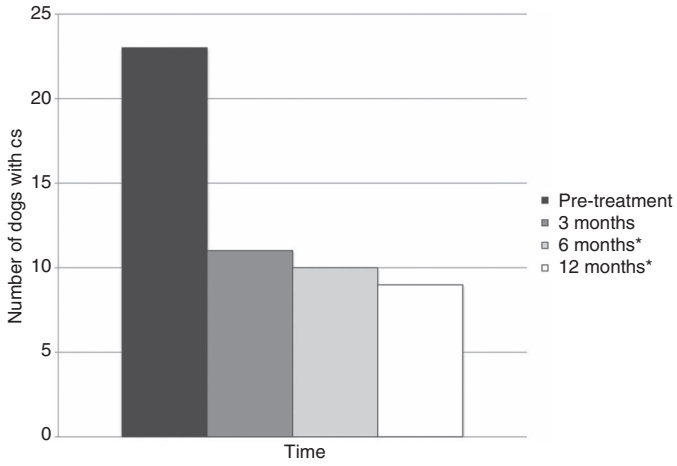

FIG 2: Number of all dogs (responder and non-responder dogs) with cluster seizures (CS) at the beginning of the treatment and at 3-month, 6-month and 12-month follow-up. When compared with the pretreatment value, the number of dogs with CS showed a significant reduction in the medium and long-term follow-up (*P=0.04; **P=0.02)

TABLE 3: Imepitoin dosage in the investigated canine idiopathic epileptic population

Variables	Initial dose M=15 (8–23) IQR=6.12	3 months n=56* M=20 (10–31) IQR=7.25	6 months n=53* M=20 (10–31) IQR=7.25	12 months n=40* M=20 (10–31) IQR=7.25
Minimum dose	9 (16%)	5 (9%)	5 (9%)	5 (12.5%)
Medium dose	45 (80%)	37 (66%)	37 (70%)	30 (75%)
High dose	2 (4%)	14 (25%)	11 (21%)	5 (12.5%)

No further adjustment of the imepitoin dosage was recorded after the three-month follow-up.
M, median

Caution needs to be adopted in trying to compare the percentage of therapeutic success between different studies due to the extreme variability in terms of AEDs used, inclusion criteria and follow-up duration (Heynold and others 1997, Berendt and others 2007, Arrol and others 2012). Not many reports detail the seizure-free state at a specific follow-up end point (De Risio 2014a) and the recent revision of the definition of seizure-free state (Potschka and others 2015) prevents an effective comparison of their results with those of previous studies. According to the results at six-month follow-up of a randomised clinical trial, PB and Br seem to have higher percentages of seizures-free dogs (85 per cent and 52 per cent, respectively) compared with those with IMP (Boothe and others 2012).

Adverse effects, which were recorded in 29 per cent of the dogs, were mild and transient, disappearing within 10 days from the beginning of the treatment. The authors' results are in agreement with the findings of Tipold and others (2015) and Rundfeldt and others (2015). Their statistical analyses failed to find any association between dosage and all the other investigated factors, but most of their population was not treated at the maximum dosage and cannot exclude that a higher dosage may produce higher incidence of side effects.

In a recent paper comparing a small population of dogs treated with first-line AEDs, dogs treated with PB experienced ataxia compared with control and IMP-treated dogs (Suiter and others 2016).

In accordance with the findings of Löscher and others (2004), the authors did not find withdrawal effects such as those described for PB (Bialer and others 2013). None of the dogs that discontinued the treatment had withdrawal seizures. In the authors' opinion, the absence of withdrawal effects represents an important benefit suggesting that, in the case of lack of response, IMP can be safely and quickly replaced by other AEDs without relevant withdrawal side effects.

The present study has several limitations, the most important being the lack of a placebo control group excluding any

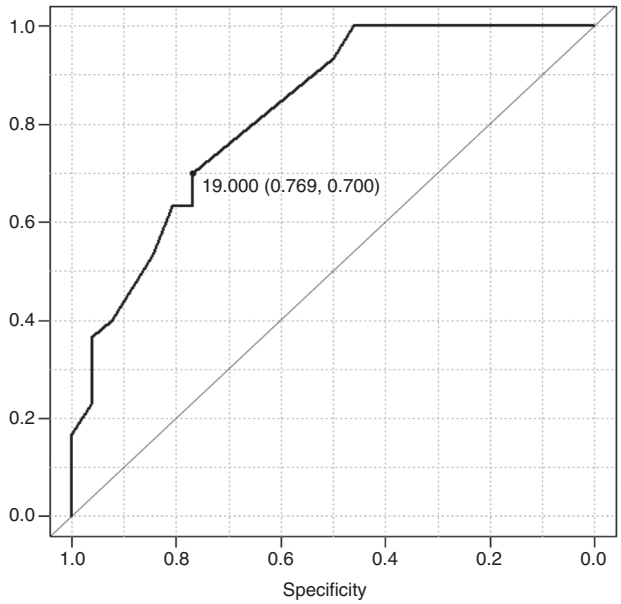

FIG 3: The receiver operator curve showed that dosage ≥19 mg/kg every 12 hours could be considered the minimal effective dose, with a sensitivity of 77% and a specificity of 70% (area under the curve: 0.82; 95% CI 0.71 to 0.92) based on responder or non-responder dogs

TABLE 4: Association between side effects and variables of the investigated canine idiopathic epileptic population

Variables	Side effects (P value)
Age	0.53
Weight	0.7
Gender	0.14
Type of seizures (pretreatment)	0.21
Imepitoin dosage	0.2
Time between first seizure and onset of imepitoin treatment	0.34

possible improvement in seizure frequency not attributable to the treatment. Possible sources of bias include the ways in which the population was selected and the diagnostic protocol. The cost of the drug may have selected small-breed dogs and neurologists may have preferred to treat in a different way the most severe cases, resulting in a population with a different breed distribution compared with other studies. MRI was performed in a minority of cases (21 per cent) due to owner's financial restrictions and, despite the strict inclusion criteria, other type of epilepsy could not be totally excluded. However, the possibilities of structural epilepsy in dogs younger than six years with more than one-year history of seizures with a normal interictal neurological examination are considered unlikely (Smith and others 2008). Finally, the relatively small number of dog population may have limited the power of the statistics.

Despite the above-mentioned limitations, the study provides some significant data. The result may suggest that early IMP therapeutic efficacy is maintained over time. Dogs with a seizure-free condition at the 3-month and 6-month follow-up were positively associated to achievement of PTS at the 12-month follow-up. Furthermore, seizure-free dogs at the first follow-up had a positive association to become R dogs (P=0.002) at the 12-month follow-up.

Dogs treated with higher dosage of IMP showed a negative association to become R-PTS dogs and a negative trend to become R dogs at 6-month and 12-month follow-up. These findings may confirm the necessity to have higher dosages in dogs affected by more aggressive IE.

The positive association of pretreatment seizure low frequency with PTS at all the follow-up end points may suggest that less severe IE are more responsive to the IMP treatment. In this study, the high median time between the first seizure and the start of IMP treatment (10 months) and the median monthly seizure frequency (1.69) may reflect the involuntary selection of a population of dogs affected by less severe IE.

CS are considered one of the clinical risk factors for refractoriness and dogs with CS are less likely to achieve remission and have a lower survival time and increased requests for euthanasia (Monteiro and others 2012, Packer and others 2014). To date, according to EMA indications (based on the results of the study of Tipold and others 2015) and the results of a randomised, double-blind, controlled parallel group clinical field trial, there were no specific data to recommend using IMP monotherapy in the treatment of IE dogs affected by CS (Rundfeldt and others 2015).

Our study provides some interesting preliminary data on the use of IMP in treating CS. In this study, the number of dogs with CS was significantly reduced at 6-month and 12-month follow-up and, at the end of the one-year follow-up, only two dogs were still experiencing CS. Twenty-two per cent of the dogs with CS reached a PTS at the 12-month follow-up. Nevertheless, it has to be noted that 39 per cent dogs with CS stopped the monotherapic treatment with IMP and were transferred to other protocols. These preliminary findings need to be confirmed by further more appropriately designed studies on a larger population.

In this study, intact females were associated with a negative outcome at the six-month follow-up. It is interesting to note that the vast majority of intact females (14 out of 15) had the oestrus between four and seven months after the beginning of IMP treatment. In dogs, a recent study found an association between heat and the onset of seizures in intact females with presumptive IE, and hypothesised a possible role of the proconvulsant effects of oestrogen or the loss of the protective effect of progesterone against seizures (Van Meervenne and others 2014b). However, little is known about the influence of sex hormones on epilepsy in dogs and further research is needed to evaluate the possible role of sterilisation on epilepsy (Van Meervenne and others 2014a).

Conclusion

This study provides some new data on the long-term results of the IMP monotherapic treatment in a population of idiopathic epileptic dogs. At the end of the 12-month follow-up, 25 per cent dogs reached a seizure-free status and 54 per cent dogs showed a positive response to the treatment. Results of this study suggest that the most effective IMP minimum dosage is ≥19 mg/kg every 12 hours.

The results suggest that IMP, when effective, produces an enduring control of the seizure activity. More adequately designed studies are necessary to evaluate the efficacy of IMP in dogs with CS that, in this study, produced a relevant reduction.

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Competing interests GG is a member of the Canine Epilepsy Advisory Group of Boehringer Ingelheim.

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