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1 **TITLE PAGE**

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3 **Prevalence and clinical characteristics of phenobarbitone-associated adverse effects in epileptic cats**

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ABSTRACT

Objectives: The study objective was to investigate the prevalence and clinical characteristics of phenobarbitone-associated adverse effects in epileptic cats.

Methods: The medical records of two veterinary referral clinics from 2007 to 2017 were searched for cats fulfilling the inclusion criteria of a diagnosis with epilepsy, treatment with phenobarbitone, and available follow-up information on the occurrence of adverse effects. Follow-up information was obtained from the medical records of the primary veterinarian and referral institutions and a questionnaire completed by the cats' owners.

Results: Seventy-seven cats met the inclusion criteria. 58 were affected by idiopathic epilepsy and 19 by structural epilepsy. One or more of the following adverse effects were reported in 47% of the cats: sedation (89%), ataxia (53%), polyphagia (22%), polydipsia (6%), polyuria (6%) and anorexia (6%). Logistic regression analyses revealed significant associations between adverse effect occurrence and both phenobarbitone starting dosage and administration of a second anti-epileptic drug. For each 1mg/kg BID increment of phenobarbitone, the likelihood of adverse effects increased 3.1 times. When a second anti-epileptic drug was used, the likelihood of adverse effects increased 3.2 times. No association was identified between epilepsy aetiology and adverse effect occurrence. An idiosyncratic adverse effect, characterised by severe neutropenia and granulocytic hypoplasia, was diagnosed in one cat. This resolved following phenobarbitone discontinuation.

Conclusions and relevance: The prevalence of phenobarbitone-associated adverse effects was 47%. Sedation and ataxia were most common. These are type A adverse effects and are predictable from phenobarbitone's known pharmacologic properties. In the majority of cases, adverse effects occurred within the first month of treatment and were transient. Idiosyncratic (type B) adverse effects, that are not anticipated given the known properties of the drug, occurred in one cat (1.3% of the study population). Increased phenobarbitone starting dosage and the addition of a second anti-epileptic drug were significantly associated with the occurrence of adverse effects.

INTRODUCTION

Phenobarbitone (PB) is considered the most effective first line antiepileptic drug (AED) used in epileptic cats(1). However, the evidence for PB's efficacy and safety profile in the feline veterinary literature is weak(1). Drug-related adverse effects (AEs) are categorised as type A or type B (also known, respectively, as type I and II AEs).

Type A AEs are those that can be explained by the known pharmacological properties of the agent and are therefore usually dose-dependent and predictable. Type A AEs that may affect individuals receiving PB can be understood by consideration the drug's mechanism of action. PB exerts its anti-epileptic effect by several different means. It is an agonist of the gamma-aminobutyric acid (GABA) A receptor and also modulates this receptor to increase GABA's affinity for it(2). This causes post-synaptic chloride channels to remain open for longer, allowing greater chloride influx into, and hyperpolarisation of, the post-synaptic neuron. Other purported mechanisms of action of PB include inhibition of the excitatory capacity of glutamate(3), inhibition of voltage-gated calcium channels and binding of chloride channels(4). The upshot is an increase in seizure threshold and a decrease in the spread of excitation to surrounding neurons(5). While this provides efficacious seizure control, the overall effect of barbiturate administration is depression of the central nervous system. It can therefore be anticipated that type A AEs such as sedation and ataxia will occur with PB therapy(4). Polyuria and polyphagia are also commonly reported during PB treatment; these are thought to arise through PB's inhibition of anti-diuretic hormone release(5).Type B AEs are not dose-related, are unpredictable and are unrelated to the known mechanism of action of the drug. They can be life-threatening and often require the discontinuation of the offending agent to resolve(6,7).

Sedation, ataxia, polyuria, polydipsia, and polyphagia have all been reported as type A AEs in cats treated with PB, especially during the initial two weeks of treatment(8). Accurate information on their prevalence, severity and median time to resolution is lacking(9). In dogs, some or all of these dose-related AEs can persist and significantly affect quality of life(10). It is unknown if similar phenomena occur in cats. Idiosyncratic (type B) AEs such as leukopenia, thrombocytopenia, lymphadenopathy, skin eruptions, pyrexia and coagulopathy have been described in a few feline case reports(11–15). The aim of this study

91 was to investigate the prevalence and clinical characteristics of, and risk factors for, PB associated AEs in
92 epileptic cats, which have not been previously evaluated in a large study population.
93
94 **MATERIALS AND METHODS**
95
96 The medical records of two referral veterinary clinics from 2007 to 2017 were retrospectively reviewed to
97 identify cats diagnosed with epilepsy and treated with PB. Inclusion criteria were documentation of two
98 or more unprovoked epileptic seizures (ie reactive seizures were excluded) at least 24 hours apart and
99 availability of follow-up information on the occurrence of AEs. The following information was retrieved
100 from the medical records of the referral institution and primary veterinarian medical records: signalment,
101 diagnostic investigation results, epileptic seizure aetiology (structural, idiopathic) and phenotype (focal,
102 generalized, focal developing into generalized), the occurrence of status epilepticus or cluster seizures,
103 date of PB treatment initiation, PB dosage and serum PB levels over time, duration of PB treatment,
104 administration of a second AED, occurrence of AEs (type and clinical features) and date of AE resolution
105 due to achievement of steady state or following dose reduction or discontinuation of PB. In this study the
106 2015 International Veterinary Epilepsy Task Force (IVETF) definitions for idiopathic and structural epilepsy
107 were applied which are, respectively: 'epilepsy in which the nature of the underlying cause is as yet
108 unknown and with no indication of structural epilepsy' and 'epileptic seizures which are provoked by
109 intracranial/cerebral pathology'.(16).
110
111 The cats' owners were invited to participate in this study by completing a questionnaire. An overview of
112 the study and its aims were provided. The following information was requested via the questionnaire:
113 date of questionnaire completion, PB dosage over time or reason for PB discontinuation, occurrence of
114 any AEs (polyphagia, polydipsia/polyuria, lethargy, ataxia, pruritus, skin lesions, weight gain, changes in
115 sleep pattern, or other AEs to be specified) and their duration following PB initiation or dosage increase,
116 dose reduction or discontinuation of PB due to AEs and subsequent outcome, date of initiation of a second
117 AED and associated outcome, and details of epileptic seizure frequency. When assessed at the referral
118 institutions, all cats were examined by a board-certified neurologist or neurology resident working under
119 supervision of a neurology diplomate.
120

121 Statistical analysis:

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123 Data were analysed using XL Stat (Addinsoft SARL) and Stata (IC v 15.0, Statacorp LLC) and standard

124 descriptive statistics were performed. The frequency of the occurrence of AEs (total number and specified

125 individual adverse effect) was assessed amongst cats meeting the inclusion criteria. The Mann-Witney U

126 test was used to test for differences in PB dosage and serum concentration across cats with onset of AEs

127 and without AEs in the first month. For the AEs occurring with the highest frequency, the influence of

128 epilepsy aetiology ('structural' or 'idiopathic'), the administration of a second AED (binary) and PB dosage

129 (mg/kg) at the onset of adverse effects and PB serum levels (mg/L) on the likelihood of their occurrence

130 was assessed in a mixed binomial/multinomial logistic regression model. As the PB serum levels were

131 numerically higher by a factor of 10 than PB dose levels, and the model assesses odds per unit increase,

132 the PB serum levels were divided by 10. Backward elimination was applied to the four variables initially

133 modelled, with $\alpha \leq 0.1$ the inclusion criterion for retention(17).

134

135 **RESULTS**

136

137 Seventy-seven cats fulfilled the inclusion criteria. Information on sex, breed, epileptic seizure aetiology,

138 including specific aetiology in cases of structural epilepsy, seizure phenotype, and diagnostic tests

139 performed are detailed in table 1.

140

141 **Table 1:** sex, breed, epileptic seizure aetiology and phenotype, and diagnostic test information of 77 cats

142 included in the present study:

		Number	Percentage
Sex	Male entire	5	6.5
	Male neutered	36	46.8
	Female entire	2	2.6
	Female neutered	34	44.2
	Domestic short hair	55	71.4
	Domestic long hair	13	16.9

Breed	Bengal	2	2.6
	British short hair	2	2.6
	Maine Coon	1	1.3
	Tonkinese	1	1.3
	Burmese	1	1.3
	Birman	1	1.3
	Persian	1	1.3
Epileptic seizure aetiology	Idiopathic	58	75.3
	Structural	19	24.7
Structural epilepsy aetiology	Trauma	5	6.5
	Degenerative	4	5.2
	Vascular	4	5.2
	Infectious/inflammatory	3	3.9
	Anomalous	2	2.6
	Neoplastic	1	1.3
Epileptic seizure phenotype	Generalised tonic clonic	51	66.2
	Focal seizures	26	33.8
	Cluster seizures or status epilepticus	36	46.8
Diagnostic tests	Haematology and serum biochemistry	77	100
	Bile acid stimulation test	23	29.9
	MRI of the brain	74	96.1
	Full body CT	2	2.6
	CSF analysis	64	83.1
	FIV/FeLV test	51	66.2
	Toxoplasma gondii serology	35	45.5
	Toxoplasma gondii CSF PCR	12	15.6
	Thoracic radiographs	18	23.4

	Abdominal ultrasound	26	33.8
	Urine organic acid screening	6	7.8

143

144

145 Seventy-six cats underwent advanced imaging of the brain (MRI in 74 cases and whole-body CT, including

146 the head, in 2 cases). Of the 19 cases of structural epilepsy, three cats affected by infectious or

147 inflammatory disease received specific treatment aimed at resolving the underlying disease. The

148 remainder received AEDs in all cases, and three cats also received anti-inflammatory doses of

149 prednisolone.

150

151 The median age of cats at the time of referral was 68.4 months (range 4 - 206.4 months; mean 71.0 ± sd

152 46.3 months). The median age of cats affected by structural epilepsy was 73 months (range: 24 - 150

153 months, mean: 75 months) and the median age of those affected by idiopathic epilepsy was 60 months

154 (range: 4 -150 months, mean: 66 months).

155

156 The median initial dosage of PB was 2.0 mg/kg BID (range: 0.6 - 4.4mg/kg BID; mean: 2.0 ± sd 0.71mg/kg

157 BID). PB loading was performed in five cats; the loading dose was 3mg/kg every six hours, four times, in

158 two patients and it was a total dose of 20mg/kg given in divided doses over 24h in the other three cats.

159 The median duration of PB treatment was 22 months (range 1.5 - 108 months; mean 30 ± sd 27 months).

160 36 cats (46.8%) received a concurrent AED. This was levetiracetam in 34 cases and one case each of

161 zonisamide and imepitoin.

162

163 Median follow-up time was 24 months (range 1.5 - 108 months; mean 30 ± sd 27 months). The primary

164 veterinarians' medical records from the time of referral to the time of data collection were obtained for

165 95% of cats; the remaining 5% had a re-examination in one of the referral hospitals, which provided the

166 information required for follow-up. The owners of 36 cats (46.8%) completed the follow-up questionnaire.

167 The owners of 69.4% of cats reported a reduction of seizure frequency of at least 50% with PB treatment.

168 The seizure frequency was decreased by 25 - 49% in 8.3% of cats, was unchanged in 11.1% of cats and was

169 unknown in 11.1%.

170

171 Type A adverse effects:

172

173 Thirty-six cats (46.7%) experienced one or more type A AEs. These are detailed in table 2.

174

175 **Table 2**: type A adverse effects in 36 cats. Note- several cats experienced more than one adverse effect,

176 so the percentage total is greater than 100:

Adverse effect	Number of affected cats	Percentage
All adverse effects	36	100
Sedation	32	88.9
Ataxia	19	52.8
Polyphagia	8	22.2
Polydipsia	2	5.6
Polyuria	2	5.6
Anorexia	2	5.6

177

178

179 Twenty-five of these cats (69.4%) were affected by idiopathic epilepsy and 11 (30.5%) by structural

180 epilepsy. Median PB dosage at the time of AE onset was 3 mg/kg BID (range 1.25 – 5.0mg/kg; mean 2.89

181 ± sd 0.89mg/kg) in cats who developed AEs compared to a median PB dosage of 2.0mg/kg BID (range 0.6-

182 3.5mg/kg; mean 2.09 ±sd 0.66mg/kg) during the first month of treatment in cats that did not develop AEs

183 (Fig. 1). The difference in dosage between the two groups was statistically significant.

184

185 [Insert figure 1]

186

187 In cats experiencing AEs, median PB serum concentration at the time of onset of AEs was 36 mg/L (range

188 10.3-70 mg/L; mean 35.04±sd 16.78 mg/L). In cats that did not experience AEs, median PB serum

189 concentration at the first re-check available (range 3 weeks – 3 months after PB treatment initiation) was

190 19.3 mg/L (range 6-40 mg/L; mean 21 ± sd 11.68 mg/L). The difference in PB serum concentration between

191 the two groups was statistically significant.

192

193   AEs were transient in 20 cats. Of these, 13 developed AEs during the inital four weeks of the PB treatment
194   and seven developed transient AEs during ongoing PB treatment. Eight cats showed persistent AEs. It was
195   not possible to determine the duration of the AEs in six cases and in two cases the patients were
196   euthanased, reportedly due to the severity of the AEs.

197

198   Twenty-two cats that developed AEs were administered a concurrent AED. This was levetiracetam in 21
199   cases (dose range 15-20mg/kg; mean 29.3mg/kg; median 20mg/kg every 8 hours) and imepitoin (20mg/kg
200   every 12 hours) in one case. One cat received the alternative AED prior to commencement of PB. In five
201   cases the concurrent AED was started at the initiation of PB treatment, in five cases between two and four
202   weeks following PB initiation, in nine cases more than one month after PB was initiated and the initiation
203   time was unknown in one case. The onset of AEs was up to three weeks after the initiation of both AEDs
204   in six cases, weeks-months before the second AED was added in eight cases, months after the second AED
205   was added in six cats and AE onset was unknown in two cases. The respective likelihood of any adverse
206   effect, sedation and ataxia increased by 3.2, 4.4 and 4.2 times when a second AED was used.

207

208   Type B adverse effects:

209

210   One cat showed lethargy and ataxia in all limbs two months following initiation of PB treatment at
211   2.6mg/kg BID. No epileptic seizures had occurred since starting therapy. Haematology revealed moderate
212   leukopenia with severe neutropenia (0.0 x10^9/l ref. 2.5-12.5 x 10^9/l). Serum biochemistry was
213   unremarkable. The serum PB level was 45mg/L. Bone marrow evaluation (cytology and core biopsy)
214   showed severe granulocytic hypoplasia suggestive of neutrophil aplasia or immune-mediated destruction
215   of neutrophil precursors. PB was decreased by 25% every four days and discontinued after two and half
216   weeks; levetiracetam (20mg/kg TID) and amoxicillin/clavulanic acid (20 mg/kg BID) were commenced. Two
217   weeks later the neutrophil count was 2.27 x 10^9/L and clinical signs had resolved. Six weeks and three
218   months later, the neutrophil levels were 2.85 x 10^9/L and 6.40 x 10^9/L, respectively. This cat was
219   considered to have type A adverse effects (lethargy and ataxia) as well as the type B haematological
220   abnormalities.

221

222   One cat was reported to have consistently elevated ALT two years after PB treatment initiation. Another

223   cat was found to have generalised lymphadenopathy two months after starting PB. These cases were not

224   classified as being affected by type B AEs as the aetiology of the clinical and biochemical abnormalities

225   could not be definitively established from the available history.

226

227   Statistical analysis:

228

229   Logistic regression models were run for outcome variables 'adverse effect' (any type A adverse effects),

230   'sedation' and 'ataxia'. The results obtained were very similar for the three models: the initial model

231   significantly explained the data ($X^2_{(4)} \geq 10.6$, $p \leq 0.014$) with 'administration of a second antiepileptic drug'

232   and 'PB dose on the occurrence of adverse effects' being retained in the model ($p \leq 0.011$) but 'aetiology'

233   and 'PB serum level' not making the selection criterion. The final models ($X^2_{(2)} \geq 16.2$, $p < 0.0001$) provided

234   a good fit to the data (Hosmer-Lemeshaw $X^2_{(4)} \leq 4.84$, $p \geq 0.304$); the retrieved odds ratios are provided

235   in fig.2. However, for cats suffering AEs and cats not suffering AEs, PB serum concentration at the time of

236   the onset AE (mg/L) data was not normally distributed (Shapiro-Wilk $W \geq 0.904$, $p \leq 0.006$). A Mann-

237   Whitney U test was used to identify potential significant differences in PB serum concentration between

238   cats suffering AEs and cats not suffering AEs. PB concentrations were significantly higher for cats suffering

239   AEs ($U = 244$, $p < 0.0001$). PB dosage at the time of onset of AEs was significantly higher than that given

240   during the first month of treatment to cats not affected by AEs.

241

242   **Figure 2**: odds ratios for influence of PB dosage and administration of a second antiepileptic drug on the

243   occurrence of adverse effects (95% CLs):

Variable	Any adverse effect	Sedation	Ataxia
PB dosage (1mg/kg BID)	3.1 (1.5-6.3)	3.4 (1.6-7.2)	2.7 (1.3--5.5)
Second AED	3.2 (1.2-9)	4.4 (1.5-13.0)	4.2. (1.2-14.7)

244

245

DISCUSSION

This retrospective study is the first to report the prevalence and characteristics of PB-related AEs in a large population of epileptic cats. The prevalence of AEs was 47%, with sedation and ataxia being most common. These type A AEs can be expected with PB administration, given its known pharmacological properties. Increased PB starting dosage and use of a second AED were significant predictors of the occurrence of adverse effects. Serum PB concentration was significantly higher in cats suffering AEs, though logistic regression analysis determined that this could not be used as a predictor of AEs.

The prevalence of sedation (41.6%), ataxia (24.7%) and polyphagia (22.2%) associated with PB administration in the present study was greater than that reported in a recent systematic review(1), which found 22%, 11% and 11% prevalence of sedation, ataxia and polyphagia, respectively. The prevalence of polydipsia (our study 3%, review 2%) was similar. Additional type A AEs which have been previously reported at a prevalence of less than 10% in cats receiving PB include paraparesis, alkaline phosphatase elevation, weight loss and behavioural change (1). These were not seen in our study population. One study of dogs treated with PB, found that sedation/lethargy, ataxia, polyuria, polydipsia and polyphagia occurred in 50%, 55%, 35%, 40% and 30% of cases, respectively(18). Therefore, type A PB-associated AEs appear to be slightly more common in dogs compared to our feline study population.

In the present study, one cat receiving PB and levetiracetam showed a persistently elevated serum alanine aminotransferase level that remained elevated even after discontinuation of PB. It was not possible to determine, from the available information, the underlying aetiology of the ALT elevation, though this finding has been previously documented in cats receiving PB(1).

Type B AEs that have been reported in cats receiving PB include pseudolymphoma, thrombocytopaenia, stomatitis, coagulopathy, cutaneous eruptions and hyperthermia(1,11–15). These are all rare, occurring in no more than 2% of cats treated with PB. One cat in the present study was reported to show generalised lymphadenopathy two months after starting PB; however, the aetiology of this was unknown so it was not classified as a type B AE. It could not be excluded that this cat was experiencing PB-induced pseudolymphoma but information required for further confirmation of this, such as response to

276 treatment modification, was not available. None of the other previously reported type B AEs were seen

277 in our study population, in which the only type B AE was granulocytic hypoplasia, occurring in one cat

278 (1.3% of the study population). The reported prevalence of haematological abnormalities in dogs treated

279 with PB ranges from 4.2 – 22%(7,19). These are usually subclinical(19), with only 4-5% of affected dogs

280 showing clinical signs(7,19). Immune-mediated peripheral destruction or immune-mediated damage of

281 precursor cells before their release into the peripheral blood are postulated mechanisms underlying PB-

282 induced haematological abnormalities in dogs and humans(6,20). The mechanism for such changes in cats

283 has not been investigated to date.

284

285 Some of the cats in the present study were reported to show PB side effects with low serum PB

286 concentrations; five cases experienced AEs with a serum PB concentration of 10-15mg/L. One of these

287 had post traumatic injury following a head trauma of unknown cause eight months prior to the onset of

288 seizure activity. The remaining five had idiopathic epilepsy. The neurological deficits shown by the cat

289 affected by trauma may have been difficult to distinguish from PB AEs. Three of these five cats received

290 levetiracetam in addition to PB, which may explain the occurrence of AEs in these individuals despite

291 relatively low PB serum concentration. Alternatively, it is possible that the small number of cats in this

292 study showing AEs with a PB serum concentration <15mg/L reflects a sensitivity in these particular

293 individuals to PB.

294

295 In the present study, 22/36 cats experiencing AEs were receiving a second AED in addition to PB

296 (levetiracetam in 21 cats, and imepitoin in one case). The addition of a second AED was significantly

297 associated with an increased risk of AEs. It is likely that PB and the second AED have an additive effect, so

298 increasing AEs. It is challenging to determine, in some cases, whether reported AEs should be attributed

299 to PB, the second AED, or both. Lethargy, sedation and ataxia have been previously reported in cats

300 treated with levetiracetam(21–23) and imepitoin(1). Adverse effects of levetiracetam and imepitoin

301 might, therefore, might be indistinguishable from those caused by PB. However, the majority of cases in

302 the present study treated with a second AED had AEs documented before the second AED was

303 commenced (eight cases) or weeks to months after it was started (six cases), making a causative link

304 impossible in the former scenario and unlikely in the latter scenario. It was impossible to determine the

305 relative contribution of the second AED to AEs in some cases, especially when two different AEDs were

306 commenced simultaneously. This problem has also been discussed in the human literature(6). The
307 likelihood of AEs may be increased when two different AEDs are commenced simultaneously, as AEs were
308 reported in all five cases in which two AEDs were started at the same time in a previously untreated cat.
309
310 In the majority of cases, AEs occurring within a short time of PB treatment starting, being noticed in the
311 first month following PB initiation in 26/36 cats. In four cases, AEs were reported a significant time after
312 initiation of PB treatment. In two cases AEs were reported six months after starting PB, but in both these
313 cases AEs occurred following a dose increase due to poor seizure control and inadequate serum PB
314 concentrations. In two cases, both with idiopathic epilepsy, AEs occurred six years after starting PB. In one
315 case this was attributed to excess serum PB concentration (38mg/L). The PB dose was reduced from 2.9
316 to 2.1mg/kg every 12 hours and AEs resolved. Another cat developed sedation and ataxia six years
317 following initiation of PB treatment but no further information on this case was available. Euthanasia,
318 reportedly due to PB AEs, was a rare event, only occurring in two cases. The two cats which were
319 euthanased both had structural epilepsy (following presumptive diagnoses of neoplasia in one case and
320 degenerative disease in the other) and progression of these conditions may have been difficult or
321 impossible to distinguish from AED AEs.
322
323 AEs were transient in 20/36 affected cats. Broadly, the transience of PB-induced AEs can be attributed to
324 the development of pharmacokinetic and/or pharmacodynamic tolerance(4). Pharmacokinetic tolerance
325 occurs in dogs treated with PB whereby PB induces hepatic microsomal cytochrome P450 activity,
326 increasing PB clearance(24). This results in reduced serum concentration over time, despite the dosage
327 remaining unaltered. Hepatic enzyme induction does not appear to occur in the cat(25), possibly due to
328 low levels of CYP2C(26). Pharmacodynamic tolerance is likely to account for the transience of AEs seen in
329 the present study. Pharmacodynamic tolerance is determined by the interaction of the therapeutic
330 molecule with receptors which can be altered over time by processes such as desensitization, receptor
331 loss and exhaustion of mediators(27).
332
333 The majority of the 19 cats affected by structural epilepsy did not receive specific treatment for their
334 underlying disease. Only the three cats affected by inflammatory or infectious disease received specific,
335 definitive therapy aimed at resolving the structural brain disease. The remainder of cats with structural

336   epilepsy received AEDs and in three cases also received anti-inflammatory doses of prednisolone. Some

337   cats with structural epilepsy may have experienced progression of disease which could affect mentation,

338   gait and possibly appetite and thirst- signs that could be difficult to distinguish from PB AEs.

339

340   Our study found that 75.3% of seizuring cats were affected by idiopathic epilepsy and 24.7% had structural

341   epilepsy. A previous study has classified the seizure aetiology in cats as reactive, structural and idiopathic

342   in 22%, 50% and 25% of cases respectively(28). Other studies have found the prevalence of idiopathic

343   epilepsy to range from 30 - 60%(8,29–32). The inclusion criteria of our study, which required participating

344   cats to have experienced 2 or more seizures at least 24 hours apart, meant that reactive cases were

345   unlikely to be included. The ratio of idiopathic to structural aetiology was greater in our study compared

346   to previous investigations(28,31). Possible explanations for this are: our study population may be different

347   to that of the other studies (reflective of different geographical or genetic background), the two centres

348   involved in our study attract a different caseload compared to other centres or that the difference is

349   simply due to chance.

350

351   While evaluating the efficacy of PB for seizure control in cats was not the primary purpose of this study,

352   our data reveals that 69.4% of cases achieved a seizure frequency reduction of at least 50%.This parallels

353   previous studies which have shown that the PB treatment is successful in the majority of epileptic

354   cats(30,33). A limitation of this finding is that information on seizure frequency after treatment was only

355   available for 31 cats. There was no obvious correlation between epilepsy aetiology and efficacy of

356   treatment.

357

358   There were several limitations in this study, some of which are inherent in retrospective investigations.

359   Diagnostic and treatment protocols and the dosage of both PB and any concurrent AED was not

360   standardised. Different laboratories were used to analyse blood samples and measure serum

361   phenobarbitone concentrations. In many cases the rationale for the addition of the second AED was not

362   available. The information and detail in medical records was variable. Only a small minority of cases (5%)

363   had follow-up assessment by a board-certified neurologist or resident working under the supervision of a

364   specialist. Recall bias was possible when follow-up was conducted by interviewing owners or by

365   questionnaire. In some cases of structural epilepsy, progression of the underlying disease may have been

366   difficult to distinguish from PB AEs. While the timing of blood sampling to test serum PB concentration
367   with respect to PB administration varied between cases, this may not be a limitation of the study.
368   Following administration of PB to healthy cats, the serum concentration has been shown to increase for
369   up to two hours, then plateau for around 10 hours(34). The half-life of PB in cats has been reported to
370   range from 43.4 to 76 hours(25,34) and in dogs is 46.3-88.7 hours(35,36). 91% of epileptic dogs have been
371   shown to have no therapeutically relevant changes in the serum PB concentration during the 12 hour
372   dosing interval(37) and it is possible that the situation is similar in cats, meaning that timing of sampling
373   for PB serum concentration may not be important in the majority of cases.

374

375   **CONCLUSIONS**

376

377   The prevalence of PB-associated AEs was 47%, with sedation and ataxia being most common. These are
378   type A AEs and tended to occur within the first month of treatment before diminishing, likely with the
379   development of pharmacodynamic tolerance. A type B AE occurred in only one cat. Increasing PB starting
380   dosages and the addition of a second AED were significantly associated with the occurrence of AEs.

381

382

387

388   **Author note:**

389

390   This paper was presented in part as an oral abstract at the European College of Veterinary Neurology
391   Congress, 2018, Copenhagen.

392

393   **Conflict of interest:**

394

395   None declared.

396

401

402 **Ethical approval:**

403

404 This study was approved by the Ethics Committee of the Animal Health Trust (approval number AHT62-

405 2016)

406 .

407 **Informed consent:**

408

409 Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animals

410 described in this work for the procedures undertaken. No animals or humans are identifiable within this

411 publication, and therefore additional informed consent for publication was not required.

412

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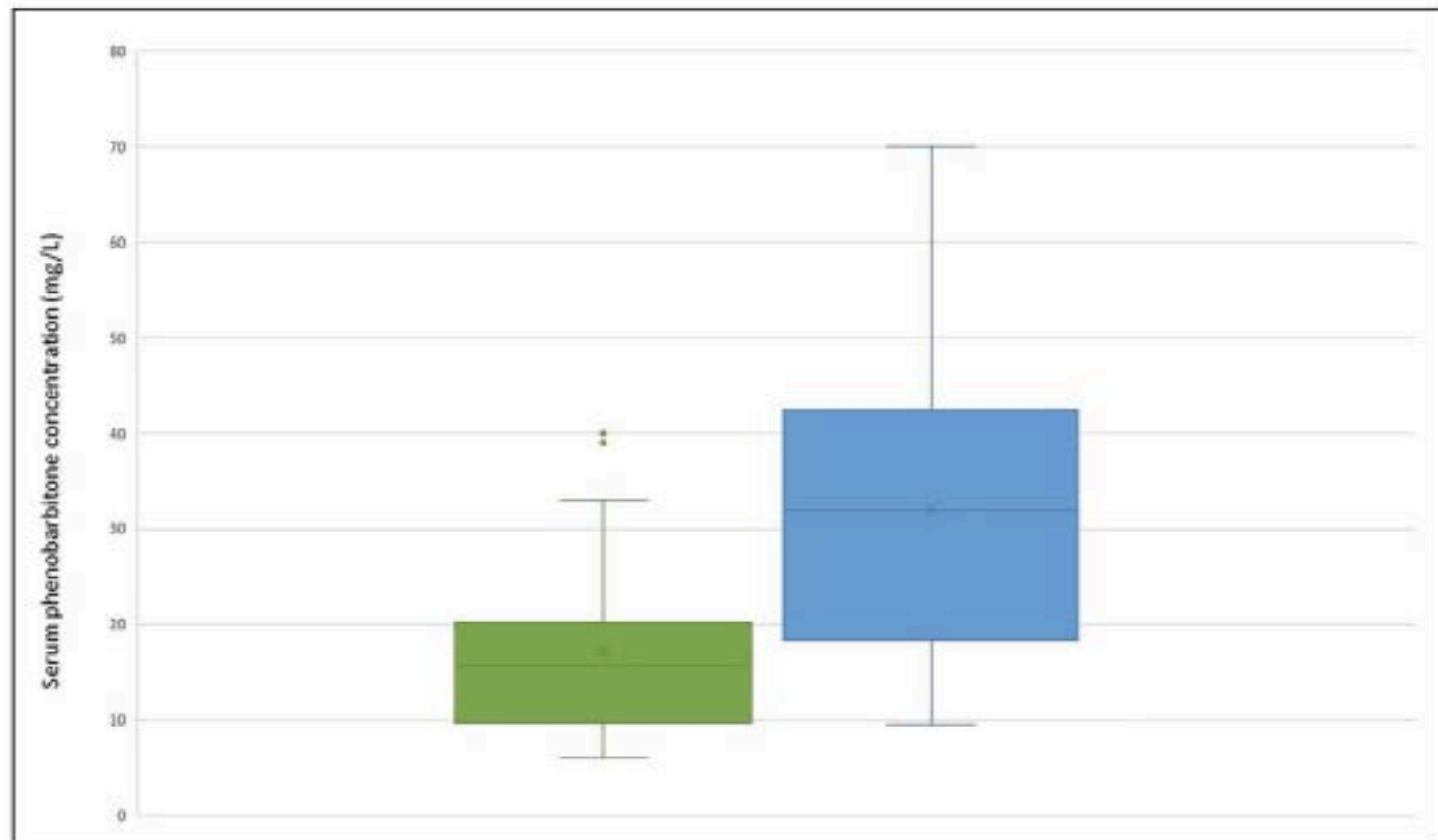
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Figure 1 Phenobarbitone serum concentration at the first re-examination in 41 cats that did not develop adverse effects (green) vs serum phenobarbitone concentration in 36 cats with adverse effects (blue). The box represents median serum phenobarbitone concentration and interquartile range, and the cross represents the mean serum concentration