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ORIGINAL ARTICLE

A retrospective evaluation of phenobarbital-induced hematologic changes in 69 cats

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Abstract

Background: Phenobarbital (PB) is used as a first-line treatment for recurrent epileptic seizures in cats. While hematologic abnormalities are well-known side effects of antiepileptic therapy with PB in humans and dogs, little is known about such alterations in cats.

Objectives: The aim of this retrospective study was to investigate the prevalence and clinical relevance of cytopenia during PB treatment in cats.

Methods: In this single-center, retrospective clinical study, 69 cats—with suspected idiopathic epilepsy admitted to the Small Animal Clinic of the University of Veterinary Medicine in Vienna (VMU)—were included. A complete blood count for each patient was performed, and changes in hematocrit, leukocytes, neutrophils, and thrombocytes were documented and graded.

Results: Fifty-three out of 69 cats (76.8%) showed cytopenias with a reduction of at least one cell fraction during PB treatment. The most frequent change was neutropenia (60%), followed by leukopenia (49.3%), thrombocytopenia (24.1%), and anemia (20.3%). Most of the changes were mild or moderate; only one patient (1.5%) showed severe leukopenia and neutropenia, and one was a life-threatening neutropenia (1.5%) with a serum PB concentration within or even below the therapeutic range. These patients did not present with clinical symptoms other than those related to epileptic episodes. Cats who received combination therapy showed lower hematocrits than those who received monotherapy. A tendency for leukocytes and neutrophils to decrease during PB treatment was also seen.

Conclusions: Blood cytopenias may frequently occur in cats on chronic PB therapy, even when serum drug levels are within the therapeutic range. However, clinical signs are typically mild to moderate and rarely severe.

KEYWORDS
cat, hematocrit, neutropenia, phenobarbital, thrombocytes

1 | INTRODUCTION

Phenobarbital (PB) is the most widely recommended anti-epileptic drug (AED) for the treatment of recurrent seizures in cats.[1] Good seizure control—even freedom from seizures can be reached—and a wide therapeutic index renders PB the first drug of choice.[2] Severe systemic effects are uncommon, with sedation being the most reported; nonetheless, other adverse effects, such as ataxia, paraparesis, polyphagia, polydipsia, and/or polyuria, may be seen.[1–3] In dogs, PB-induced hematologic abnormalities (PBIHA) are reported with a prevalence between 4 and 22%.[4,5] Pancytopenia has been associated with PB administration during the first months of treatment, with resolution after treatment discontinuation. As the effect of PB on blood cells in cats has not been examined yet, the objective of the present study was to investigate the prevalence and clinical relevance of PBIHA with a special focus on cytopenias in cats.

2 | MATERIALS AND METHODS

2.1 | Animals and sample analysis

Informed consent was obtained from the owners of all animals described in this work for the procedures undertaken. No additional informed consent for publication was required.

This retrospective study included cats that were presented to the Small Animal Clinic of the University of Veterinary Medicine, Vienna, between 2006 and 2021. The cats were diagnosed with suspected idiopathic epilepsy based on a history of recurrent seizures with no interictal neurologic signs, and unremarkable clinical examinations and serum biochemistry results. Brain MRI and cerebrospinal fluid (CSF) analysis—if available—were also unremarkable. Patients treated with PB with or without other AEDs for at least 2 weeks were eligible to enter the study. Cats with structural brain diseases or neoplastic diseases with hematologic abnormalities were excluded from the study. Patients were included if at least one hematologic examination was available after at least 2 weeks of treatment. Hematologic analysis was performed at the start of the treatment and during therapy monitoring, and total cell counts were evaluated for PBIHA. The hematologic results before PB treatment were defined as a measurement not older than 6 months and before or 3 days after the start of the therapy. An automated complete blood cell count was performed on an ADVIA 2120 (Siemens Healthcare Diagnostics GmbH). Blood smears from all patients were prepared and evaluated according to the standard operating procedures of the laboratory. According to these, all samples with numerical changes that exceeded 25% of the upper or lower limit for each cell population or where scatterplots showed an indistinct separation of cell populations were reviewed microscopically by a senior technician. The investigated hematologic variables included hematocrits, leukocytes, neutrophils, and thrombocyte counts. Samples with thrombocyte counts lower than 150×10^9/L were examined microscopically for thrombocyte aggregates, and samples showing aggregation were withdrawn from the study. The severity of hematologic changes was categorized into mild, moderate, severe, or life-threatening based on the VCOG-CTCAE[6] and the reference ranges of our laboratory (Table 1). Whenever available, the Feline immunodeficiency virus/Feline leukemia virus (FIV/FeLV) status, the duration and dose of PB, and PB serum concentrations were also recorded. An FIV/FeLV test was performed on 43.5% (30) and 52.2% (36) of the cats, respectively. The hematologic analyses were grouped, based on the treatment days: ≤3 (Group 1); 4–180 (Group 2); 181–540 (Group 3); ≥541 days (Group 4); and on the PB serum levels <25 μg/mL, and within (25–35 μg/mL) or above (>35 μg/mL) the therapeutic range. Likewise, the impact of the type of therapy on cell counts, whether PB monotherapy or combination therapy, was evaluated. Serum PB concentrations were measured using a chemiluminescent enzyme immunoassay according to the manufacturer's instructions (Immulite 1000; Siemens Healthcare Diagnostics GmbH). The reference intervals for PB in our laboratory are 10–30 μg/mL.

2.2 | Data analysis

Standard descriptive statistics were performed, including the minimum, maximum, and median of all collected data. Statistical analysis was performed with the statistical add-in software for Microsoft Excel, Analyse-it (version 5.65, Leeds, UK). Quantitative variable distributions were assessed for normality using the Shapiro–Wilk test. The nonparametric Wilcoxon–Mann Whitney and Kruskal Wallis tests were used for between-group comparisons of quantitative variables, while the Steel test was used for comparisons with the

TABLE 1 Grades for the severity of hematologic changes based on the recommendations of the veterinary cooperative oncology group (VCOG) and the reference values of our laboratory.

	Hematocrit (%)	Leukocytes ($\times10^9$/L)	Neutrophils ($\times10^9$/L)	Thrombocytes ($\times10^9$/L)
Increased	>47.0	>15.0	>12.75	>430
Within range	27.1–47.0	6.0–15.0	3.60–12.75	180–430
Mild	25.1–27.0	4.0–5.9	1.50–3.59	100–179
Moderate	20.1–25.0	2.0–3.9	1.00–1.49	50–99
Severe	15.0–20.0	1.0–1.9	0.50–0.99	25–49
Life-threatening	<15.0	<1.0	<0.50	<25

control group (≤3 treatment days, PB serum concentration within the therapeutic range). Values of $p < .05$ were considered statistically significant.

3 | RESULTS

The medical records of 69 cats with the diagnosis of idiopathic epilepsy (epilepsy of unknown origin) were retrospectively evaluated in this study. The median age of the cats at the time of first presentation was 5 years (range 6 months to 14.7 years). Thirty-five (50.7%) cats were male (one intact, 34 neutered), and 34 (49.3%) cats were female (three intact, 31 spayed). European shorthair cats were the most represented breed, with 63 (91.3%) cats, followed by 3 Maine coon cats (4.3%) and one (1.4%) each of European longhair, British shorthair, and Russian blue. The median body weight was 4.2 kg (range 2–10 kg). Twenty-nine (80.6%) cats tested negative for FeLV and FIV, six (16.7%) cats were FeLV negative but had an unknown FIV status, and one (2.8%) cat was negative for FeLV but positive for FIV. This cat did not present with hematologic abnormalities during the study period. Twenty-eight (40.6%) cats received PB monotherapy, and 40 (58%) received PB therapy combined with levetiracetam (LEV). One (1.4%) cat received LEV (36.17 mg/kg/d) and imepitoin (25.84 mg/kg/d) at the same time as the PB therapy and was included in the combination therapy group. Fifty-three (76.8%) cats showed cytopenias during PB therapy. For these patients, a total of 312 hematologic analyses before (52) and during PB (260) treatments were available, with a median of three per cat (range 1–14). Neutropenia was found in 60% (39/65) of cats, leukopenia in 49.3% (34/69), thrombocytopenia in 24.1% (7/29), and anemia in 20.3% (14/69) (Table 2). Sixteen (23.3%) cats had a decrease in one peripheral blood cell type, 27 (39.1%) had a decrease in two, 9 (13%) had a decrease in three, and one (1.4%) had a decrease in all. Thirty-four patients developed leukopenia (median 4.8×10^9/L, range 1.2–6), and 39 developed neutropenia (2.45×10^9/L, range 0.06–3.66) during the treatment. Leukopenia and neutropenia persisted during the study period in 20 out of 34 patients (58.8%) and 26 out of 39 patients (66.7%), respectively, being mild in most of the cases. Neutropenia was moderate in five cases, severe in one, and life-threatening in one. These patients, except for one cat with moderate neutropenia whose FeLV/FIV status was unknown, tested negative for FeLV/FIV.

One cat developed severe leukopenia and neutropenia in the third blood analysis after 571 days of PB treatment, reaching values of 1.22×10^9/L and 0.18×10^9/L, respectively. Although this patient developed life-threatening neutropenia, clinical examinations were unremarkable. The serum biochemistry panel only showed a mild increase in liver enzyme activity, most likely related to PB therapy. Hematocrits and thrombocyte counts were within the reference values. This cat tested negative for FeLV/FIV. Due to a worsening of neurologic symptoms, the patient was euthanized. A pathologic examination showed bilateral hippocampus malformations and sclerosis due to an intraventricular meningioma. A bone marrow evaluation could not be performed due to poor cell preservation.

The second patient, a 1.3-year-old cat, developed moderate leukopenia due to severe neutropenia (0.06×10^9/L) on the second blood analysis after 114 days of treatment. Leukocytes reached reference values on day 163 (lost to follow-up) due to lymphocytosis (10.3×10^9/L), while neutrophils remained low. Lymphocytes were mostly mature, with some reactive cells present. Despite severe neutropenia, the clinical examination of this patient was unremarkable. This patient tested negative for FeLV/FIV and did not show other cytopenias.

Fourteen patients showed a decrease in the hematocrit (median 25%, range 21–27). Anemias were mild in 11.6% and moderate in 8.7% of the cats (Table 2). When subsequent measurements were available after the first appearance of anemia, hematocrit values normalized within the duration of therapy, except in five patients. In all cases, anemia was non-regenerative; two cats showed azotemia, two had hyperproteinemia, and in one, no further information and follow-up were available.

Thrombocytopenia was present in 24.1% (7 out of 29) patients (median 144×10^9/L, range 63–179) (Table 2), being moderate in two cases and persisting only in one case; none of these patients showed signs of bleeding. The thrombocyte concentration was available only in 29 cats since thrombocytes were not requested for all patients, and samples with aggregates were excluded from the study.

PB doses were recorded in all cats. Sixty-six cats received PB twice a day, one cat once a day (3.42 mg/kg), and two cats three times a day. The total daily median PB dose was 6.15 mg/kg (range

TABLE 2 Frequency and severity of hematological abnormalities; *n* refers to the number of patients with a hematologic analysis; the lowest value of all measurements during the period of study was evaluated.

	Hematocrit	Leukocytes	Neutrophils	Thrombocytes
	n = 69	*n* = 69	*n* = 65	*n* = 29
Increased			1.5% (1)	
Within range	79.7% (55)	50.7% (35)	38.5% (25)	75.8% (22)
Mild	11.6% (8)	31.9% (22)	49.2% (32)	17.2% (5)
Moderate	8.7% (6)	16% (11)	7.7% (5)	6.9% (2)
Severe		1.5% (1)	1.5% (1)	
Life-threatening			1.5% (1)	

0.88–27.17 mg/kg). LEV was in 40 (58%) cats with a total daily median of 40.54 mg/kg (range 4.1–97.32 mg/kg) LEV dose. Those patients who received PB in combination with LEV had significantly lower hematocrits than those who received PB as monotherapy ($p < .05$), while no influence of treatment on leukocyte, neutrophil, and thrombocyte counts was observed. The measurement of PB serum concentrations was available 192 times for 67 cats, with a median of 27.5 µg/mL (range 6–79.2 µg/mL). Lower leukocyte counts were observed in patients with serum PB concentrations in the therapeutic range (25–35 µg/mL) than those with PB below or above the therapeutic range ($p < .05$), while no significant differences were found between the therapeutic range of PB in serum and hematocrit, neutrophils, and thrombocytes. A significant difference was noticed between cell counts before and after PB therapy in the measurements of leukocytes and neutrophils ($p < .05$; Figure 1). Additionally, there is a trend towards a decrease in the leukocyte and neutrophil counts as the treatment time increases, while no influence of treatment time on the hematocrit or thrombocyte count was observed.

4 | DISCUSSION

In this retrospective study, 69 cats under PB as monotherapy or combination therapy with a suspected diagnosis of idiopathic epilepsy were investigated for the occurrence of PBIHA. Fifty-three out of 69 cats (76.8%) showed, during the study period, cytopenia with a reduction in at least one cell line, neutropenia (60%), and leukopenia (49.3%), the most common changes, followed by thrombocytopenia (24.1%) and anemia (21.7%). Even if most of the observed cytopenias were mild to moderate, the changes in the cases of leukocytes and neutrophils became severe or even life-threatening, although these were not clinically relevant during the observation period.

The most reported dose-dependent adverse effects in cats—treated with PB—were sedation, pelvic limb ataxia, polyuria, polydipsia/polyphagia, weight loss, increased alanine transaminase/alkaline phosphatase activities, and behavioral changes.[7,8] Idiosyncratic drug reactions are not only unpredictable but mostly unavoidable and occur in only a small proportion of patients at therapeutic doses. The most common are cytopenia, lymphadenopathy, pseudolymphoma, skin eruptions, pyrexia, and coagulopathy.[7,8] Furthermore, the effect of PB on the liver is well known, leading to hepatic enzyme induction; however, these changes have not been observed in cats.[9]

Compared with a study in PB-treated dogs by Pakozdy et al. where PBIHA was reported in 22% of cases, the prevalence of PBIHA in our studied cats was much higher. Interestingly, we found an absence of clinical symptoms related to cytopenias, especially severe neutropenia, compared with their study, in which 5% of the patients suffered from severe clinical cytopenia-related diseases.[4] In another study, the estimated prevalence of PBIHA in dogs was 4%, and all dogs showed nonspecific clinical signs.[5] The widely discussed mechanisms behind PBIHA in human and veterinary medicine are either peripheral cellular destruction or damage of the bone marrow precursor cells.[10] As none of the patients showed clinically relevant symptoms, neither bone marrow cytology nor histology was performed in our study; therefore, it was not possible to differentiate between these two main causal mechanisms.

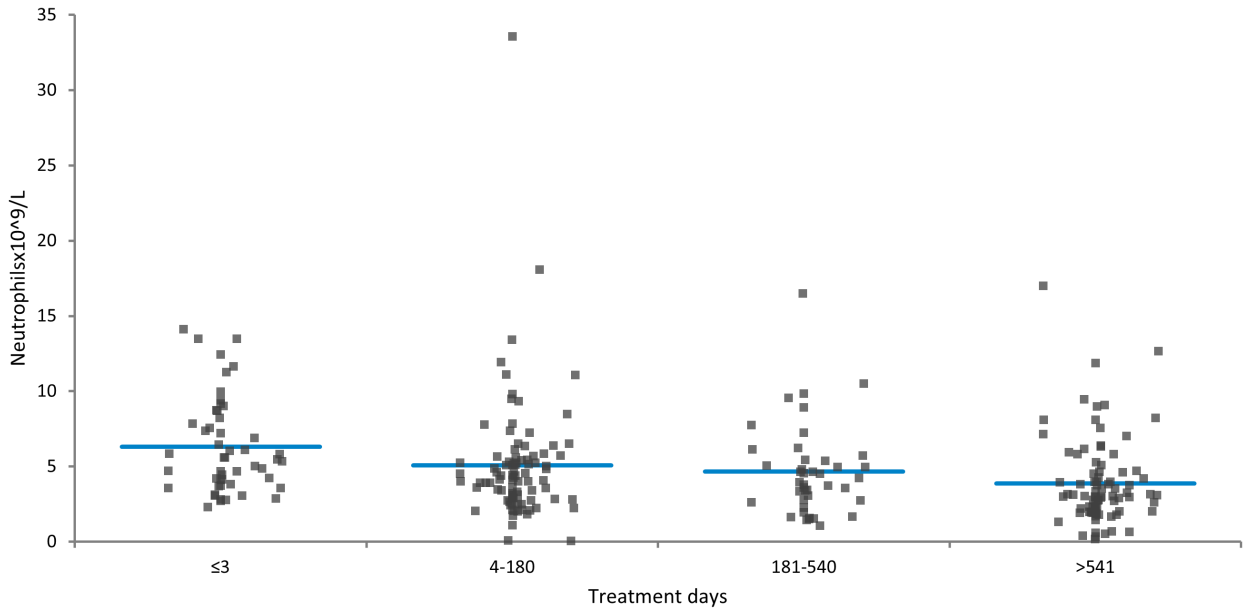

FIGURE 1 Comparison of neutrophil counts among the different treatment groups: a decrease in the number of neutrophils is observed as the days of treatment increase. A statistical difference was found among pre- and post-treatment groups ($p < .005$). The horizontal line represents the median.

The occurrence of neutropenia in cats in our study was >50% and thus more frequent than that reported for PB-treated dogs.[4,5] However, even with bone marrow evaluation, determining the cause of neutropenia is challenging since hematologic changes in patients with PB-induced and immune-mediated neutropenia might be indistinguishable since both cases could present with ineffective neutropoiesis and anemia/thrombocytopenia. Similar results on neutropenia were presented by Scott et al.[11] in dogs. In both studies, neutropenia was the most common cytopenia.[4,11] Severe and life-threatening neutropenia was observed in only two cats during PB treatment. Aside from neurologic symptoms, clinical examinations were unremarkable in both cases; one case also had a pathologic examination available for which no causes for neutropenia were found, which included a severe inflammatory process or infectious disease.

Thrombocyte counts were available only in 29 cats, and in seven cases (24.1%), thrombocytopenia was observed. Since this was a retrospective study, thrombocyte counts were not available for all patients, and several results were excluded due to the presence of platelet aggregates, a common cause of pseudothrombocytopenia in cats.[12] Mild thrombocytopenia was reported in dogs under PB therapy, and the frequency was about 18 percent in a small clinical cohort.[4]

Anemia was present in 21.7% of cats and was mild or moderate during PB treatment. No influence of the serum PB concentration or the duration of treatment was found on the decreased hematocrit values. In all patients except five, the hematocrit recovered during the therapy. Since the anemia was non-regenerative, decreased or ineffective erythrocyte production could have played a role in its development.[13] PB-induced anemia was found to be rare in previous studies.[8,14] In our study, patients with persistent anemia were suspected of having chronic kidney disease and anemia of inflammation based on clinical signs, which included hyperproteinemia. Therefore, we could not determine if chronic kidney disease or anemia versus the effects of PB administration were responsible for the anemia.

In our study, cats who received combination therapy had lower hematocrits than those who received monotherapy. However, in studies by Pakozdy et al. an influence of PB dose, serum level, or treatment duration on hematologic changes was not found in dogs.[4,5] LEV has been used in animals as a second choice in cases of PB intolerance and has been successfully used in both monotherapy and combination therapy with only mild side effects.[1] Conversely, LEV has been shown to have a greater effect on hematocrit in people.[15] In two case reports, cats with severe pancytopenia and other severe side effects from PB administration were successfully switched to LEV, with a resolution of symptoms within a few weeks.[8,14] However, a study by Marsh et al showed that despite relatively low PB serum levels in three cats who had received both LEV and PB, the cats had unexpected side effects.[7] In our study, we did not observe an overdosing with LEV administration. Nevertheless, the effect of PB on hematocrit in these patients is questionable since most cats recovered after a few months without the need to discontinue treatment.

We observed an influence on the length of PB treatment and the severity of leukopenia and neutropenia. In our study, the time to onset of severe leukopenia and neutropenia was between 25 and 114 days. Compared with other studies, the onset of cytopenias is approximately 2–12 weeks in cats and 1–107 months in dogs after the start of the PB treatment.[4,5,7,8,14] In most studies, the time of resolution of cytopenias after discontinuing PB therapy was about 4–10 weeks in cats and 2–3 weeks in dogs. However, the resolution of anemia was longer than that of neutropenia in dogs.[5,8,11,14]

An unexpected finding was observed in patients administered PB within the therapeutic range; they had lower leukocyte counts, and one patient even had severe leukopenia. However, due to the low number of patients in our study, more studies are needed to confirm these results.

It should be emphasized that despite the high proportion of cats with cytopenias in our study, none showed obvious clinical illness associated with the hematologic abnormalities. In dogs with severe PB-induced leukopenia, pneumonia was described as a clinical consequence, but any kind of infection can also be expected.[4]

It should be stated that our study has several limitations. First, the cause–effect relationship between PB and hematologic cytopenias is unclear. Evaluating adverse drug-related reactions can be challenging, as the cause–effect relationship is usually difficult to confirm due to underlying diseases, combination therapies, and possible drug-independent medical conditions. To confirm the hypothesis that PB treatment leads to the occurrence of cytopenias, including anemia, leukopenia, and thrombocytopenia, treatment discontinuation would be needed to see whether recovery from the cytopenias would occur or, if recurrences would occur after re-exposure to PB. Scott et al demonstrated recovery of the bone marrow cells in dogs treated with PB. The median neutrophil response time was 14 days; thrombocytopenia was 10 days; and anemia was 29 days. It can be expected that most PB-induced cytopenias resolve with PB withdrawal/tapering alone, but the influence of additional medication, such as steroids and/or antibiotics, should be considered. Knowledge about response times upon PB withdrawal/tapering could be helpful for patient management.[11] However, this approach is theoretical, as the withdrawal of antiepileptic drugs can have serious consequences. Therefore, a risk–benefit analysis leads most clinicians to continue the treatment in well-controlled epileptic cases. A re-challenge with the suspected drug after remission of hematologic changes is unethical and, from a clinical point of view, practically impossible. The second limitation of our study is that bone marrow examinations were not carried out. As such, we could not differentiate between peripheral cellular destruction and bone marrow suppression. Moreover, concurrent bone marrow disease could not be completely ruled out. The high percentage of patients with an unknown FeLV/FIV status in our study should not be underestimated, especially since both are known causes of neutropenia; however, a recent study performed at our laboratory showed a low incidence of these diseases in patients presenting at our hospital (<4.3%).[16] If we had not included these cases, it would have meant a significant loss of patients in this retrospective study.

5 | CONCLUSIONS

We found hematologic cytopenias in 76.8% of PB-treated cats with a lack of clinical illness even when all cell lines were decreased. In the case of neutrophils, changes were more relevant; we saw severe or life-threatening neutropenia in only a few patients. Our findings emphasize that PBIHA is frequent in cats but that changes are usually mild to moderate, and treatment change should only be considered in exceptional cases. Nevertheless, patients with severe neutropenia should be evaluated more closely, with an emphasis on possible secondary infections.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflict of interest.

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