Drug-induced blood cell dyscrasia associated with phenobarbital administration in a dog

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Abstract: A 13-year-old, spayed, female Chihuahua dog was referred for evaluation of fever, lethargy, and dyspnea. Hematologic evaluation revealed severe neutropenia, thrombocytopenia, and mild anemia. The dog had been undergoing phenobarbital therapy for the past 7 weeks because of generalized seizures due to meningoencephalomyelitis of unknown etiology. After ruling out other possible causes of cytopenias, a tentative diagnosis was made of drug-induced blood cell dyscrasia. The neutropenia and thrombocytopenia resolved after discontinuation of phenobarbital (8 days and 15 days after discontinuation, respectively). This is the first case report in Korea to demonstrate blood dyscrasia associated with idiosyncratic adverse effects of phenobarbital.

Keywords: leukopenia, neutropenia, phenobarbital, thrombocytopenia

Phenobarbital (PB) is a long-acting barbiturate that enhances γ-aminobutyric acid-mediated increases in chloride conductance by opening chloride channels [11, 12]. PB is a well-tolerated and effective anticonvulsant for various seizures and certain types of clinical epilepsy in dogs and cats [9, 11, 12].

PB has infrequent complications including hyperactivity, restlessness, excessive sedation, ataxia, polyuria, polydipsia, and polyphagia; these typically occur during the initial phase of therapy [9, 10]. In most dogs, these side effects usually are tolerated after 2 to 4 weeks of therapy [10]. No actual hepatocellular damage during PB treatment has been confirmed; however, PB administration can contribute to the induction of serum liver enzyme activities in dogs [2, 8]. In addition, PB has infrequently been associated with hematologic adverse drug events (ADEs) in dogs, including reversible neutropenia, thrombocytopenia, and anemia [5, 6]. Long term use of PB can also lead to bone marrow necrosis [13].

This case report describes the clinical and laboratory features of PB-related cytopenia and treatment outcomes. To the best of authors’ knowledge, this is the first case report demonstrating blood dyscrasia associated with idiosyncratic ADE of PB in our country (South Korea).

A 13-year-old, spayed female Chihuahua dog, weighing 2.8 kg, was referred to Konkuk University Veterinary Teaching Hospital for evaluation of fever, lethargy, and anorexia. About 9 months previously, the dog had been admitted for evaluation of generalized seizure and diagnosed with meningoencephalomyelitis of unknown etiology (MUE), based on magnetic resonance imaging findings (Fig. 1), and cerebrospinal fluid (CSF) analysis showing mononuclear pleocytosis (208 cells/µL; reference range: 0–5 cells/µL). Further tests including a polymerase chain reaction test for canine distemper virus and CSF culture were negative. Despite the diagnosis of MUE in this dog, the owner was unable to administer any medication due to personal circumstances. Since that visit, the frequency of seizures had increased, so PB (2.5 mg/kg, per orally [po], quarter [q] 12 h, Hana Pharm, Korea) had been prescribed by the referring veterinarian approximately 7 weeks prior to admission to our hospital. Any other drugs except for PB had not been supplied to the dog by the referring veterinarian. Vaccinations and preventive parasiticidal agents had been administered 6 months prior to our initial examination.

A physical examination revealed hyperthermia (40.4°C), delayed capillary refilling time, reduced skin turgor, and low blood pressure (systolic pressure 94 mmHg). A complete blood count (CBC) showed leukopenia (1.3 × 10³/µL; reference range: 6–17 × 10³/µL) with severe neutropenia (367/µL; reference range: 3000–11000/µL), lymphopenia (643/µL; reference range: 1000–4800/µL), and thrombocytopenia (171 × 10³/µL; reference range: 200–500 × 10³/µL) (Table 1). Dohle’s bodies and band cells, with toxic changes, including vacuolation, toxic granules, less condensed chromatin, and blue cytoplasm, were detected in a Diff-Quik-stained blood smear (data not shown). Biochemical analysis revealed elevated serum alkaline phosphatase activity (275 U/L; reference range: 15–
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Hypoalbuminemia (2.8 g/dL; reference range: 2.9–4.2 g/dL), hypoglycemia (57 mg/dL; reference range: 70–118 mg/dL), hypokalemia (3.5 mmol/L; reference range: 3.8–5.0 mmol/L), and an elevated level of C-reactive protein (CRP; above 210 µmol/L; reference range: < 20 µmol/L). Other parameters were within the reference ranges. The serum PB concentration was 12.1 µg/mL (reference range: 15–45 µg/mL). Serological results and microscopy analysis for tick-borne diseases (babesiosis, ehrlichiosis, anaplasmosis, and Rickettsia rickettsii infection) were all negative. Considering sepsis or systemic inflammatory response syndrome (SIRS), a bacterial culture of a blood sample was performed; the test results were also negative. No neoplasms or other risk factors were found on abdominal radiography and ultrasonography. The history and several other test results led to a strong suspicion of PB-induced neutropenia and thrombocytopenia. The anticonvulsant was replaced with potassium bromide (KBr; loading dose of 400 mg/kg divided into four doses over a day; maintenance 40 mg/kg, po, q 24 h; Sigma-Aldrich, USA) and PB was discontinued after our initial exami-

Table 1. Profiles of relevant complete blood counts and serum biochemical data and serum phenobarbital (PB) concentrations in a dog with cytopenia

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Days after admission</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>WBC (× 10³/µL)</td>
<td>1.3</td>
<td>1.17</td>
</tr>
<tr>
<td>RBC (× 10³/µL)</td>
<td>7.23</td>
<td>5.80</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>39.5</td>
<td>37.1</td>
</tr>
<tr>
<td>PLT (× 10³/µL)</td>
<td>171</td>
<td>86</td>
</tr>
<tr>
<td>Nphs counts (/µL)</td>
<td>367</td>
<td>443</td>
</tr>
<tr>
<td>ALB (g/dL)</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>CRP (µmol/L)</td>
<td>&gt; 210</td>
<td>&gt; 210</td>
</tr>
<tr>
<td>sPB (µg/mL)</td>
<td>12.1</td>
<td>–</td>
</tr>
</tbody>
</table>

WBC, white blood cells; RBC, red blood cells; Hct, hematocrit; PLT, platelets; Nphs, neutrophils; ALB, albumin; CRP, C-reactive protein; sPB, serum phenobarbital concentration.

Fig. 1. Magnetic resonance imaging of a dog with generalized seizure. The intracranial lesions are shown in the transverse (A–C) and sagittal images (D–F). Multiple lesions (arrows) are present in the left temporal, parietal and frontal lobes. The lesions are iso-intense on T1-weighted image (A and D), hyper-intense on T2-weighted image (B and E). In the post contrast T1-weighted image, the lesion was not enhanced (C and F).
nation. The dog entered a sterilized intensive care unit filled with oxygen, and treatment was initially treated with antibiotics (30 mg/kg, intravenously [iv], q 8 h, cefotaxime; Wooridul Pharmaceutical, Korea; 5 mg/kg, subcutaneously [sc], q 12 h, enrofloxacin; Bayer, Korea; 15 mg/kg, iv, q 12 h, metronidazole; DAI HAN Pharm, Korea), recombinant human granulocyte colony-stimulating factor (rhG-CSF; 5 µg/kg, sc, Leukokine Inj 300; CJ Healthcare, Korea), and a balanced electrolyte solution (0.9% saline solution containing 30 mEq potassium chloride, 120 mL/kg/day, iv, DAI HAN Pharm) for hemodynamic stability and prevention of a subsequent inflammatory response. A 20% dextrose solution (DAI HAN Pharm) was infused intravenously based on blood glucose level to treat the persistent hypoglycemia. Immunosuppressive medications for MUE treatment were not prescribed at that time to allow observation of the therapeutic response. Blood gases, electrocardiography, and urine production were also monitored in this dog during its hospitalization.

On the second day after admission, the blood pressure was improved (systolic pressure 134 mmHg). However, the hypoglycemia, hyperthermia (39.8°C), and depressed mentation continued. In addition, a CBC revealed significant leukopenia, neutropenia, and thrombocytopenia (white blood cell [WBC] 1.17 × 10³/µL; Neutrophil 443/µL; PLT 86 × 10³/µL). The reticulocyte index value was extremely low. The numbers of band cells with toxic changes and Dohle’s bodies remained unchanged. The dog developed metabolic acidosis with compensatory hyperventilation. Decreased venous pH (7.29; reference range: 7.30–7.45), low levels of bicarbonate (14.3 mEq/L; reference range: 18–26 mEq/L), and low levels of partial pressure of carbon dioxide (29.6 mmHg; reference range: 33–55 mmHg) were identified. Sodium bicarbonate (8.4%; Huons, Korea) was administered for bicarbonate supplementation. Although rhG-CSF had been administered daily for three days, the neutropenia showed no improvement. Antibiotics and other supportive therapies were maintained.

On the fifth day after admission, the electrolyte imbalance, hypoglycemia, metabolic acidosis, fever, and lethargy were resolved. The other hematologic results, including leukopenia, neutropenia, and thrombocytopenia were unchanged. The serum PB level (5.6 µg/mL) decreased.

On the eighth day after admission, the WBC (9.09 × 10³/µL) and neutrophil (6,454/µL) counts were within the reference ranges and no band cells with toxic changes could be identified. The serum PB level (2.6 µg/mL) was lower than on the first day of admission (Table 1). The thrombocytopenia, anemia, and hypoalbuminemia still persisted, but the dog was discharged from the hospital at the owner’s request.

The dog was reevaluated at seven and fifteen days after discharge. The owner was satisfied with the improved appetite and activity of the dog. Fifteen days after discontinuing PB, a CBC revealed leukocytosis and thrombocytosis. The hematocrit value (37%) and serum albumin level (2.7 g/dL) was improved, but still low. The CRP value (60 µmol/L) was also improved.

Twenty-three days after discontinuing PB, the dog had completely recovered clinically. All affected blood parameters were within reference ranges, and the serum PB level (1.6 µg/mL) was lower than before. As the dog recovered, all medications were discontinued, except the anticonvulsant drug KBr (40 mg/kg, po, q 24 h). Finally, prednisolone (1 mg/kg, po, q 12 h, Yuhan, Korea) and cyclosporine A (25 mg/dog, po, q 24 h; Novartis, Switzerland) were added to the treatment to manage the MUE. To date, no blood abnormalities have appeared in the dog that has been well managed and shown no clinical signs.

In the present case, SIRS was diagnosed using the proposed criteria for the diagnosis of SIRS [4]; the dog showed two out of four parameters in SIRS criteria including hypothermia or hyperthermia, leukocytosis or leukenia, tachycardia, and tachypnea. Alterations supporting the diagnosis were also found in other biochemical results including hypoalbuminemia, hypoglycemia, a left shift with toxic changes, and elevated CRP. Although the cause of SIRS was not fully identified, PB administrations are thought to be the cause of subsequent modulation of systemic immunity or cytokine-mediated inflammation as well as destruction of neutrophils, platelets, and erythrocytes.

PB is considered a safe anticonvulsant and is frequently used in dogs and cats. Nevertheless, it occasionally causes life-threatening hematologic disorders [5, 6].

Previous reports have demonstrated that PB intoxication, accompanied by high PB levels, can induce pancytopenia [6]. However, PB can induce severe blood dyscrasia even at low dosages, as in the present case, where the PB level was even lower than the reference range (15–45 µg/mL).

The ADEs affecting the hematologic system have been categorized as type A (dose-dependent responses) or type B (idiiosyncratic reactions unrelated to pharmacologic effects) reactions [3, 7, 14]. The representative drugs causing type A ADEs are chemotherapeutic agents and oxidants [14]. A case with a dose-related type A ADE is expected to improve with dose reduction [3]. Although type A ADEs can affect the quality of life, they are usually reversible and rarely require withdrawal of medicine [15]. Some drugs, in classes such as estrogenic compounds, nonsteroidal anti-inflammatory drugs, antibiotics, antithyroid drugs, anticonvulsants, antiparasitics, and cardiac drugs, can produce idiosyncratic type B ADEs [14]. These type B ADEs differ from type A ADEs with respect to their pathogenesis, which occurs unpredictably and is apparently unrelated to well-known pharmacologic mechanisms in type B ADEs [15].

The mechanism by which PB induces leukenia, thrombocytopenia, and anemia as ADE of PB treatment has not been fully explained [6]. A previous report that evaluated the bone marrow of dogs with PB-induced pancytopenia showed the occurrence of myeloid hyperplasia [5]. The study revealed that the PB-induced blood dyscrasia could be caused by destruction of mature granulocytes [5, 14]. Another study
suggested that bone marrow necrosis caused by PB exposure could also result in leukopenia, thrombocytopenia, and/or anemia [13]. In the present case, no bone marrow specimens were evaluated. In humans, drug-induced cytopenia is defined when it is discovered during administration of the drug and resolves within one month after discontinuation of the medication [1]. Thus, based on the clinical diagnosis and treatment progress, PB induced blood dyscrasia was conclusive in the present case.

In the present case, PB administration produced hematologic ADEs, which are unrelated to a PB’s pharmacologic effects, at a serum PB concentration even lower than the reference range. Considering dose-independence, unpredictability, and irrelevance of PB’s pharmacologic effects, the ADE in this case was classified as an idiosyncratic type B ADE of anticonvulsants. Although the pathogenesis of PB in this case has not been fully identified, peripheral destruction of mature blood cells is suspected as the mechanism of toxicity based on time to recovery (8 days after discontinuation); Destruction of mature granulocytes usually resolves 1 weeks after discontinuation of treatment, while bone marrow necrosis or myelofibrosis usually recovers 3 to 8 weeks after stopping treatment [14].

Despite its rare occurrence, PB-induced blood dyscrasia is a life-threatening ADE of clinical significance because of the near impossibility of predicting and preventing its adverse reactions. However, this critical ADE could be minimized by careful monitoring of clinical responses and laboratory parameters. The present case report is the first to introduce blood dyscrasia as an idiosyncratic ADE associated with PB in our country.

References


