



**RED LIGHT,
GREEN LIGHT**

PEER REVIEWED



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Which of the following drugs would be appropriate in the management of this patient?

Based on the information provided, how would you grade the following drugs and why?

Turn the page and
compare your results ►

Epileptic Dog with Osteoarthritis

RAMBO, A 7-YEAR-OLD, NEUTERED MALE GOLDEN RETRIEVER, was presented for evaluation of osteoarthritis (OA). The dog had been diagnosed with idiopathic epilepsy 4 years earlier, and his seizures were well controlled with phenobarbital at 5 mg/kg PO twice a day. On physical examination, the dog had difficulty rising and exhibited apparent pain on palpation of the hip joints. Results of a complete blood cell count were normal. Results of a serum chemistry panel, however, disclosed elevated levels of alkaline phosphatase (ALP) at 790 U/L (ie, 6 times normal; reference range, 5-131 U/L) and alanine aminotransferase (ALT) at 180 U/L (ie, 1.5 times normal; reference range, 12-118 U/L), with a decreased total thyroxine (T_4) concentration of less than 0.5 $\mu\text{g/dL}$ (reference range, 0.8-3.5 $\mu\text{g/dL}$). Pelvic radiography revealed degenerative joint disease. The serum phenobarbital level was 28 $\mu\text{g/mL}$ (therapeutic range, 15-45 $\mu\text{g/mL}$).



RED = do not use



YELLOW = proceed with caution



GREEN = safe

Phenobarbital

(continued administration)



Potassium bromide



Levetiracetam



Gabapentin



Carprofen



Tramadol



Polysulfated glycosaminoglycan



Omega-3 fatty acids



S-Adenosyl-methionine



L-Thyroxine



ALP = alkaline phosphatase, ALT = alanine aminotransferase, OA = osteoarthritis, T_4 = thyroxine



Did you answer?

The following represents the best responses based on drug metabolism, pharmacokinetics, species, diagnostic differentials, clinical and laboratory data, and other pertinent findings.

Phenobarbital

(continued administration)

| CORRECT RESPONSE



Differentiating benign hepatic enzyme elevations attributed to enzyme induction from those attributed to mild hepatocyte change linked to drug-induced hepatotoxicity is important when determining whether ongoing phenobarbital treatment is safe. In dogs with benign liver enzyme elevations, the degree of elevated ALP level is typically higher than that of ALT. However, severely elevated ALT levels should prompt caution and further evaluation.¹⁻⁵ Assessment of liver function (ie, albumin level, bile acid assay) may help predict impending hepatic failure.^{5,6} Risk for hepatotoxicity may be greater if the serum drug concentration approaches the maximum therapeutic range⁶; a proposed therapeutic trough of less than 35 µg/mL has been suggested.⁵

As noted in this patient, the ALT level was mildly elevated and the albumin was within normal range. Further evaluation of liver function with a bile acid assay would more completely assess the patient for hepatic dysfunction. If bile acid assay results were normal, phenobarbital therapy could be continued. If the results were abnormal, transition to another antiseizure medication would be recommended.

Potassium bromide

| CORRECT RESPONSE



Potassium bromide can be an effective single-agent antiseizure medication in dogs and is generally well tolerated, with minimal risk for hepatotoxicity.^{1,6} For this patient, transition to potassium bromide or another antiseizure medication should be considered in order to minimize the risk for phenobarbital-induced hepatotoxicity if (1) compromised hepatic function is evident based on results of a bile acid assay or (2) long-term NSAID therapy for OA is planned.

Potassium bromide has a long half-life in dogs and does not reach steady-state blood concentrations for approximately 2 to 3 months. Therefore, if immediate withdrawal of phenobarbital were desired and seizure control were marginal, potassium bromide may not be the best choice as an alternative antiseizure medication.

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Levetiracetam

| CORRECT RESPONSE



Levetiracetam is a well-tolerated antiseizure medication, with evidence of efficacy as adjunctive therapy that lowers seizure frequency in dogs.⁶⁻⁹ Levetiracetam has not been investigated extensively as monotherapy, but it may be effective.¹⁰

For this patient, transition to levetiracetam or another antiseizure medication should be considered in order to decrease the risk for phenobarbital-induced hepatotoxicity if (1) compromised hepatic function is evident based on results of a bile acid assay or (2) long-term NSAID therapy for OA is planned. In contrast to potassium bromide, levetiracetam has a short elimination half-life, so administration would result in steady-state blood concentrations more quickly.⁶⁻⁹ Because of cytochrome P450 enzyme induction by phenobarbital, higher doses of levetiracetam might be needed until the effects of phenobarbital on enzyme induction have subsided,¹¹ which may be 3 to 5 weeks or longer after discontinuation of phenobarbital.^{12,13}

Gabapentin

| CORRECT RESPONSE



In some human studies,¹⁴⁻¹⁶ gabapentin has been shown to have analgesic properties, and although these properties have not been definitively documented in dogs, this drug may have analgesic effects.¹⁷ Gabapentin is also used as adjunctive medication for the control of partial seizures in humans and may have a role as adjunctive therapy for the control of seizures in dogs.^{7,18} Gabapentin is primarily eliminated by the kidneys. Although the liver also metabolizes gabapentin in dogs, there are no known reports of gabapentin-induced hepatotoxicity in dogs.^{7,19}

Carprofen

| CORRECT RESPONSE



NSAIDs can be effective treatment of OA and, in many dogs, may be well tolerated.²⁰⁻²² Of note, however, idiosyncratic hepatotoxicity attributed to carprofen therapy has been reported.²³ Other adverse effects associated with administration of an NSAID include dose-dependent GI and renal toxicities.²⁴

ALP = alkaline phosphatase,
ALT = alanine aminotransferase,
GI = gastrointestinal, NSAID = nonsteroidal
antiinflammatory drug, OA = osteoarthritis

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**Polysulfated
glycosaminoglycan
injections have been
shown to decrease
inflammatory
mediators and
improve signs of
lameness in dogs.^{30,31}**

GI = gastrointestinal, NSAID = nonsteroidal antiinflammatory drug, OA = osteoarthritis, PSGAG = polysulfated glycosaminoglycan, SAME = S-adenosyl-methionine, T₄ = thyroxine, TSH = thyroid-stimulating hormone

Carprofen

(continued from page 17)

If bile acid assay results in this dog were normal, carprofen therapy theoretically could be considered for treatment of this patient's OA. However, although there is no documentation that concurrent use of phenobarbital and an NSAID may result in greater likelihood of hepatotoxicity in dogs, drug-induced hepatotoxicity in humans is more common when 2 or more hepatotoxic drugs are administered concurrently.²⁵ If bile acid assay results were abnormal, NSAID therapy would not be recommended because of the increased risk for GI and renal toxicities.²⁰

The best carprofen options for this patient would be either (1) regular use of other medications for OA, with carprofen used only as needed or not at all, or (2) transition to an alternative antiseizure medication, with administration of carprofen for treatment of OA after phenobarbital has been discontinued and the effects of phenobarbital enzyme induction have subsided.¹¹⁻¹³ Regular monitoring of liver enzymes and function while the patient is being treated with carprofen would be recommended.²⁰

Tramadol

| CORRECT RESPONSE

There is some evidence that oral tramadol may be an effective analgesic in dogs with OA.²¹ The opioid-like metabolite of tramadol is only produced in small amounts in dogs; thus, analgesic effects may occur from other metabolites that inhibit the reuptake of serotonin and norepinephrine. Tramadol is generally well tolerated by dogs,^{21,26-28} but it reportedly can result in seizures in humans, although it is unclear whether seizures only occur with overdosing or also occur with therapeutic dosing.²⁹ Therefore, in dogs with concurrent epilepsy, tramadol should be used only with careful clinical monitoring.

Polysulfated glycosaminoglycan

| CORRECT RESPONSE

Polysulfated glycosaminoglycan (PSGAG) injections have been shown to decrease inflammatory mediators and improve signs of lameness in dogs.^{30,31} PSGAG is a safe, well-tolerated medication, and there would be no contraindications in this patient. PSGAG is a heparin analog, so caution should be taken when used concurrently with an NSAID.³¹ PSGAG injections have resulted in prolonged clotting times and buccal mucosal bleeding times in dogs,³² but clinically significant hemorrhage in dogs has not been documented.³⁰ In one study in birds,³³ severe hemorrhage was evident after injections of PSGAG.

Omega-3 fatty acids

CORRECT RESPONSE

Omega-3 fatty acids have been shown to be beneficial in humans with OA, are thought to be beneficial in dogs as adjunctive therapy for OA,^{34,35} and would not be contraindicated in this patient. Omega-3 fatty acids are generally well tolerated, although adverse effects potentially include decreased platelet function (which might be exacerbated by concurrent NSAID therapy), GI signs, and altered immune function.³⁶

S-Adenosyl-methionine

CORRECT RESPONSE

S-Adenosyl-methionine (SAmE) is an antioxidant supplement that increases glutathione levels and provides other cytoprotective effects for patients with a compromised hepatobiliary system.³⁷⁻³⁹ In addition, there is evidence that SAmE can be beneficial therapy for OA in humans.⁴⁰ If this patient's liver function were compromised, administration of this supplement may provide cytoprotective effects and serve as beneficial OA therapy.⁴¹

L-Thyroxine

CORRECT RESPONSE

Phenobarbital can alter thyroid hormone testing in dogs.^{12,42-44} Decreased levels of total and free T₄ and eventual increased levels of thyroid-stimulating hormone (TSH) have been reported with phenobarbital use, but concurrent clinical hypothyroidism does not seem to develop.⁴⁴ This patient had no clinical signs of hypothyroidism and was suspected to be euthyroid; because his low T₄ level is attributed to phenobarbital therapy, L-thyroxine supplementation would not be recommended.

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