# Pancreatitis associated with potassium bromide/phenobarbital combination therapy in epileptic dogs

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**Abstract** — In a retrospective study, at least 10% of dogs receiving potassium bromide/phenobarbital combination therapy, compared with 0.3% of dogs receiving phenobarbital monotherapy, had probable pancreatitis. Pancreatitis may be a more frequent and more serious adverse effect of potassium bromide/phenobarbital combination therapy than has been reported previously.

**Résumé — Pancréatite reliée à l'association médicamenteuse bromure de potassium/phénobarbital dans le traitement de chiens épileptiques.** Dans une étude rétrospective, au moins 10 % des ayant reçu l'association médicamenteuse bromure de potassium/phénobarbital étaient atteints d'une pancréatite probable, comparé à 0,3 % des chiens ayant reçu du phénobarbital seul. La pancréatite pourrait être un effet indésirable de l'association médicamenteuse bromure de potassium/phénobarbital plus fréquente et plus grave que ce qui a été rapporté jusqu'ici.

*(Traduit par docteur André Blouin)*

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Potassium bromide (KBr) is gaining popularity as an antiepileptic drug in dogs. Potassium bromide is most commonly used as an addition to phenobarbital therapy in dogs whose seizures are not well controlled with phenobarbital alone. However, because potentially fatal hepatotoxicity can be associated with phenobarbital therapy, KBr has also been recommended as the drug of first choice for canine epilepsy (1,2). Historically, KBr has been considered a safe drug for dogs, with less risk of organ toxicity than has been associated with the use of other antiepileptic drugs. The most commonly reported adverse effects of KBr therapy are polydipsia, polyuria, polyphagia, gastric irritation, sedation, ataxia, and behavioral changes (3–5). Pancreatitis is only occasionally listed in the literature as a potential adverse effect, and the occurrence is reported to be rare (6). To our knowledge, only 2 studies have reported evidence of pancreatic disorders possibly associated with KBr therapy (7,8). The first involved 22 dogs receiving KBr in addition to phenobarbital therapy for poorly controlled epilepsy (7). An unspecified number of dogs in the study had evidence of pancreatic problems, such as pancreatitis, pancreatic atrophy and insufficiency, and pancreatic fibrosis. In the second study, pancreatitis attributed to polyphagia and garbage ingestion developed in 2 of 23 dogs (8.6%) receiving both KBr and phenobarbital (8). In neither study were the pancreatic problems attributed solely to the KBr. One recent study showed epilepsy to be a risk factor for acute fatal pancreatitis, but associations with individual antiepileptic drugs were not made (9).

In a prospective study we are presently conducting on 51 epileptic dogs receiving phenobarbital therapy, KBr was added to the therapeutic regimen for 6 of the dogs at some point during the 1-year study period. Two of the 6 dogs receiving KBr subsequently developed marked elevations of serum amylase and lipase activities and corresponding clinical signs of pancreatitis (cases 1 and 2; Table 1). One of these dogs was euthanized as a consequence of the pancreatitis. A 3rd dog developed acute clinical signs of pancreatitis and died before presentation to the veterinarian. Upon postmortem examination, performed at the Atlantic Veterinary College (AVC), the dog was diagnosed with hemorrhagic necrotizing pancreatitis (case 13; Table 1). Serum biochemical profiles performed prior to the addition of KBr showed normal serum amylase and lipase activities for all 3 dogs.

Because of the apparent high incidence of pancreatitis associated with the addition of KBr to the therapy in our prospective study (3/6 dogs), we did a retrospective survey of submissions to the AVC Diagnostic Laboratory from December 1997 to March 1999 for serum KBr and phenobarbital concentrations. The goal of the survey was to determine what percentage of dogs receiving KBr and/or phenobarbital had biochemical analyses

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**Table 1. Case descriptions of dogs with elevations in serum amylase and/or lipase activities while receiving either potassium bromide/phenobarbital combination therapy, or phenobarbital monotherapy**

| Case | Patient | History | Amylase (300–1400 U/L)[c] | Lipase (30–560 U/L)[c] | Serum KBr (12.5–37.5 mmol/L)[c] | Serum PB (54–190 mol/L)[c] |
|---|---|---|---|---|---|---|
| 1[a] | Springer spaniel (4.5 y, N/M) | Vomiting for 24 h[b] | 6474 | 2965 | 10,4 | 44 |
| 2[a] | Terrier (3.5 y, N/M) | Vomiting for 24 h, lethargic, dehydrated; ingested fatty meal | 9466 | 3384 | 16 | 87 |
| 3[a] | Terrier cross (6 y, S/F) | Vomiting for 24 h; got into garbage 3 d ago | 8009 | 2062 | 24,5 | 81 |
| 4[a] | Miniature poodle (10 y, S/F) | Diarrhea, vomiting, depression | 3821 | 1994 | 26,4 | 84 |
| 5[a] | Poodle cross (9 y, N/M) | Anorexic, lethargic for 2 d; history of pica | 18 108 | 6444 | 3,9 | 142 |
| 6[a] | Staffordshire terrier (2 y, N/M) | Vomiting, shaking[b,d] | 3897 | 986 | 23,8 | 80 |
| 7 | Golden retriever (14 y, F) | No history of illness | 1456 | 510 | 19,4 | 92 |
| 8 | Greyhound (7.5 y, N/M) | No history given | 1655 | 99 | 21,8 | 138 |
| 9 | Welsh springer spaniel (9 y, M) | Routine check-up | 1581 | 178 | 19,4 | 96 |
| 10 | Spaniel cross (5.5 y, N/M) | Ataxic, bumping into walls | 1527 | 220 | 36,8 | 126 |
| 11 | Rhodesian ridgeback (7 y, N/M) | Seizures getting worse; also has Cushing's disease | 1824 | 514 | 18,6 | 85 |
| 12 | Boxer cross (5 y, F) | No history given[d,e] | 1552 | 225 | 12,3 | 101 |
| 13[a] | Shetland sheepdog (3 y, N/M) | Acute onset of vomiting, depression, death; AVC postmortem diagnosis of hemorrhagic necrotic pancreatitis | — | — | 13,1 | 82 |
| A[a] | Border collie (5 y, N/M) | Vomiting for 24 h[f] | 3052 | 2852 | | 49 |
| B[a] | Standard schnauzer (9 y, N/M) | Painful abdomen[b,d] | 2079 | 197 | | 64 |
| C | Dalmation (11 y, N/M) | Painful limb; history of pancreatitis prior to PB[d] | 1877 | 196 | | 39 |
| D | Bulldog (5 y, M) | Weight loss over 3 mo; activity and appetite normal[e] | 1558 | 160 | | 80 |
| E | Labrador retriever (14 y, S/F) | No history of illness | 2279 | 294 | | 49 |
| F | Shetland sheepdog (10 y, N/M) | No history of illness | 2000 | 474 | | 67 |
| G | Labrador retriever (5.5 y, S/F) | Healthy; pre-anesthetic examination: elevated amylase/lipase prior to starting PB | 4021 | 679 | | 72 |
| H | Labrador retriever cross (6 y, N/M) | Vomiting, diarrhea, hepatomegaly, splenomegaly, atypical lymphoid cells noted on CBC; AVC postmortem diagnosis of lymphosarcoma | 1566 | 95 | | 130 |

KBr — potassium bromide; PB — phenobarbital

Cases 1–13 were receiving KBr/PB combination therapy; cases A–H were receiving PB monotherapy. Serum KBr and PB concentrations recorded here were those determined closest to the episode of pancreatitis

[a]Cases with clinical signs consistent with pancreatitis that were used to determine prevalence rates of suspected pancreatitis

[b]Mild hemolysis of serum sample

[c]AVC Diagnostic Laboratory reference range

[d]Moderate lipemia of serum sample

[e]Moderate hemolysis of serum sample

[f]Marked lipemia of serum sample

and clinical histories supportive of pancreatitis. Sixty-eight dogs were identified as receiving KBr or KBr/phenobarbital combination therapy. One dog was receiving KBr monotherapy, and 64 dogs were receiving both KBr and phenobarbital. Information concerning inclusion of phenobarbital in the therapeutic regimen was unavailable for 3 dogs receiving KBr. Of the 68 dogs receiving KBr or KBr/phenobarbital combination, 18 (26%) had serum biochemical profiles, including serum amylase and lipase activities, performed at the AVC Diagnostic Laboratory during the same 16 mo (and after the start of KBr therapy). Twelve dogs had increased serum amylase and/or lipase activities (cases 1–12; Table 1), with 6 of the 12 having a history supportive of a diagnosis of clinical pancreatitis. Clinical signs considered supportive of a diagnosis of pancreatitis included vomiting, diarrhea, anorexia, and abdominal pain. One additional dog receiving KBr and phenobarbital had a clinical history and AVC postmortem diagnosis of acute pancreatitis (case 13). The remaining 6 dogs with elevations in serum amylase and/or lipase activities had only mild elevations of amylase, with either no history on the laboratory submission form or a history that was not suggestive of clinical pancreatitis. If only those dogs with available biochemical analyses or postmortem diagnosis were used as the denominator in our calculations, 37% (7/19) of dogs receiving KBr had evidence of suspected pancreatitis. Even if serum biochemical analyses had been available and found to be normal for all of the remaining KBr-treated dogs, the prevalence of suspected pancreatitis associated with KBr therapy would still have been a minimum of 7/68 (10%). All 7 dogs with suspected pancreatitis were receiving both KBr and phenobarbital, and all had serum KBr and phenobarbital concentrations within or below the typically recommended therapeutic ranges (KBr, 12.5 to 37.5 mmol/L; phenobarbital, 54 to 190 μmol/L).

The retrospective survey identified 698 dogs receiving phenobarbital monotherapy. Eighty-eight (13%) of these had serum biochemical profiles, including amylase and lipase activities, performed during the same 16-month period (and after the start of phenobarbital therapy). Eight dogs had increased serum amylase and/or lipase activities (cases A-H; Table 1). Two of the 8 dogs had histories supportive of clinical pancreatitis. Both of these dogs had very lipemic serum samples, which may cause falsely increased serum amylase and lipase activities. Five of the remaining dogs with increases in amylase and/or lipase activities had only mild elevations in amylase and histories not suggestive of pancreatitis. The 6th dog had more marked increases in serum amylase and lipase activities but was healthy on physical examination performed at the time of blood collection, with no history of illness. This dog also had a history of increased serum amylase and lipase activities prior to phenobarbital therapy. If only those dogs with biochemical analyses available were used as the denominator in our calculations, 2% (2/88) of dogs receiving phenobarbital monotherapy had evidence of possible pancreatitis. If biochemical analyses had been available and were normal for all other dogs receiving phenobarbital monotherapy, the prevalence of suspected pancreatitis in dogs receiving phenobarbital monotherapy would have been 2/698 (0.3%). An odds ratio based only on those dogs with biochemical analyses available showed that the risk of pancreatitis was 29 times greater in dogs receiving KBr/phenobarbital combination therapy than in dogs receiving phenobarbital monotherapy (95% confidence interval (CI): 6.9 to 118.8). If the odds ratio was based on all dogs (least-case scenario), the risk would be 37 times greater in dogs receiving KBr/phenobarbital combination therapy (95% CI: 10.5 to 130.5).

A number of factors need to be considered when interpreting the results of the retrospective study presented here. First, pancreatitis was confirmed by postmortem examination in only 1 dog. A definitive diagnosis could not be made for the other dogs with suspected pancreatitis. The clinical signs of pancreatitis are nonspecific and can be seen with other conditions. Similarly, elevations in serum amylase and lipase activities are not specific for pancreatitis. Azotemia, renal disease, and other gastrointestinal conditions may also cause elevations of these enzymes. None of the dogs with suspected pancreatitis in our study had biochemical evidence of azotemia or renal disease, and many had inflammatory hemograms that supported the possibility of pancreatitis. Also, not all dogs with pancreatitis have increased serum amylase and lipase activities. Second, we could only estimate the prevalence of pancreatitis in this study. Serum biochemical analyses were not available for all dogs. Many veterinary clinics now perform their biochemical analyses in-house, so some cases of pancreatitis in both groups of dogs (dogs receiving KBr/phenobarbital combination and dogs receiving phenobarbital monotherapy) may not have been identified by our study. Also, digestive upset and vomiting are frequently seen with KBr therapy. Often, biochemical analyses are not performed at the time of presentation for vomiting, because the signs are attributed to gastric irritation from the KBr. Therefore, some cases of self-resolving or mild pancreatitis may be missed. Third, information concerning drug dosages, duration of treatment, and severity of seizure activity was not available for many of the dogs in this study. All of these factors may play a role in the risk of pancreatitis. This information was available for 3 of the 7 KBr-treated dogs that developed pancreatitis. All 3 had been receiving phenobarbital for ≤ 2 y (2 y, 1 y, 10 mo, respectively), and KBr for ≤ 1 y (1 y, 8 mo, 1 mo, respectively). All 3 had seizures that were poorly controlled with phenobarbital alone. Phenobarbital and KBr dosages were within typical maintenance ranges.

An important question is whether the risk of pancreatitis is associated with KBr in general, or only with KBr in combination with phenobarbital. All of the KBr-treated dogs with suspected pancreatitis in our retrospective study were also receiving phenobarbital. This was also the case with the 2 previously mentioned studies that reported pancreatic abnormalities in KBr-treated dogs (7,8). It is possible that KBr monotherapy does not carry the same risk. Only 1 dog in our study was known to be receiving KBr monotherapy, so assessment of the risk of pancreatitis associated with KBr monotherapy was not possible.

In our prospective study of 51 epileptic dogs, no dog receiving phenobarbital died from phenobarbital-associated hepatotoxicity (Gaskill, unpublished data). However, 2 of the 6 dogs receiving KBr in combination with phenobarbital died due to pancreatitis. This suggests that the risk of fatal pancreatitis associated with KBr/phenobarbital combination therapy may be as or more serious than the risk of fatal hepatotoxicity associated with phenobarbital therapy, at least during the 1st year of therapy.

We conclude that KBr therapy, in combination with phenobarbital, is associated with an increased risk of pancreatitis in epileptic dogs. The prevalence of suspected pancreatitis associated with KBr/phenobarbital combination therapy in our retrospective survey was at least 10%, compared with 0.3% with phenobarbital monotherapy. Because KBr is often very effective in controlling seizures in dogs that have not been well controlled with phenobarbital alone, this drug has an important place in antiepileptic therapy. However, before KBr replaces phenobarbital as the drug of choice for treatment of canine epilepsy, studies are needed to further investigate the association between KBr and pancreatitis, and to determine if the risk of pancreatitis is increased with KBr monotherapy. Additionally, owners of dogs receiving KBr and phenobarbital should be informed of the potential risk of pancreatitis.

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## Answers to Quiz Corner/Les réponses du test éclair

1. e — Contact dermatitis is a T-cell-mediated type IV hypersensitivity reaction.
   *e — La dermatite de contact est une réaction d'hypersensibilité de type IV médiée par les lymphocytes T.*

2. b — The point of maximum intensity is over the pulmonic valve, and the ECG shows marked right heart enlargement. Also, English bulldogs are predisposed to pulmonic stenosis.
   *b — Le pic d'intensité maximale se situe à la valve du tronc pulmonaire et l'électrocardiogramme montre une hypertrophie du cœur droit. En outre, les Bulldogs anglais ont une prédisposition à la sténose pulmonaire.*

3. d — Parasitism, neoplasia, and granulomatous enteritis are the most important differential diagnoses. Of these, parasitism is the only treatable disease, so treatment for parasitism is a reasonable option before completing laboratory examination.
   *d — Le parasitisme, la néoplasie et l'entérite granulomateuse sont les diagnostics différentiels les plus importants. De ceux-ci, le parasitisme est la seule maladie qui peut être traitée, de sorte que le traitement contre le parasitisme représente une option raisonnable avant de compléter l'examen de laboratoire.*

4. a — After 3 d of age, calves are usually no longer susceptible to enterotoxigenic *E. coli* infection.
   *a — Après l'âge de trois jours, les veaux ne sont plus habituellement sensibles aux infections à* E. coli *entérotoxinogène.*

5. b — A single lesion at C5-T2 would account for both sets of neurologic signs.
   *b — Une lésion unique au niveau de C5-T2 pourrait expliquer l'ensemble des signes neurologiques.*

6. c — In kids of this age, the cornual branch of the lacrimal and infratrochlear nerves must be blocked for dehorning.
   *c — Chez les jeunes chèvres de cet âge, le rameau cornual des nerfs lacrymal et infratrochléaire doit être anesthésié pour l'écornage.*

7. b — Such high levels of progesterone indicate pregnancy.
   *b — Un tel taux élevé de progestérone indique une gestation.*

8. b — *Pasteurella* is a common cause of respiratory disease in rabbits.
   *b —* Pasteurella *est une cause courante de maladie respiratoire chez le lapin.*

9. a — Toxoplasmosis is unlikely to cause jaundice.
   *a — Il est peu probable que la toxoplasmose puisse causer de l'ictère.*

10. b — Only lead and zinc affect the hemogram in a similar manner.
    *b — Seulement le plomb et le zinc affectent l'hémogramme de cette façon.*