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**Epilepsy - Therapy, Counselling and Problem Patients**

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**Medical Therapy of Epilepsy**

When to start therapy in patients with epilepsy depends on the frequency of seizure activity and on the owner’s attitude concerning medical therapy. Generally, treatment should be started if there are four to six seizures within a six month period, if seizures begin to accumulate, if seizures are prolonged, and/or in cases of status epilepticus, where there is an increased risk of neuronal damage and continued seizure activity. The treatment of epilepsy is not necessarily life-long. Spontaneous remission is possible, and some patients “grow out of” the disease (1). It is therefore a possibility to attempt to wean the animal off therapy in cases where there has been no seizure activity within the preceding year. This must not be done abruptly, but should occur with a gradual dose reduction over a long period of time (six to eight months). A rapid dose reduction should be avoided, because there is an increased risk of seizure relapse, and because, in the case of phenobarbital, the drug is addictive.

Many of the newer antiepileptic drugs are not, unfortunately, effective in the dog and cat, because they are efficiently metabolized in the liver in these animals. The drugs of choice in the long-term therapy of epilepsy are limited to two drugs with long half-lives: phenobarbital and potassium bromide.

Phenobarbital should be given to dogs and cats at a dosage of 3 - 5 mg/kg/day. The total daily dosage is divided and administered twice a day to reduce both fluctuations in the serum concentration and side-effects. The serum concentration of phenobarbital varies greatly between individuals and it is therefore necessary to monitor the serum concentration of phenobarbital in the individual patient. Phenobarbital is metabolized in the liver. A steady state is achieved after about two weeks, and first after that period, can full therapeutic effect be expected. At this point the patient’s serum concentration of phenobarbital can be measured. The therapeutic serum concentration (the level within which the drug is expected to be therapeutically effective) is 65-150 mmol/l (15-45 µg/ml). The dosage of phenobarbital is not adjusted if the animal is seizure free in the presence of a low serum concentration of phenobarbital. The phenobarbital dosage is increased if the animal is not seizure free. The serum concentration of phenobarbital should be measured with every dosage change (but first after two weeks have passed) and if significant alterations in the clinical seizure pattern arise. If the patient is still not seizure free or the seizures are not satisfactorily reduced in lieu of high normal serum concentrations, add-on therapy with bromide is indicated. Up to 50% of dogs whose seizures are not adequately controlled with phenobarbital therapy become satisfactorily controlled or seizure free when phenobarbital therapy combines with bromide. The phenobarbital dosage can often be gradually reduced 25 - 50% in these patients. Due to the extremely long half-life of bromide, complete therapeutic effect is first realized after 100 to 200 days. Ideally, reduction in phenobarbital dosage should be, at the earliest, begun after this time. In practice, however, it may be necessary to begin a phenobarbital dosage reduction at an earlier time due to side effects associated with combination therapy (earliest two months after the start of add-on therapy, when bromide is expected to begin to have some effect). Phenobarbital dosage reduction should be effectuated slowly (over several months). In countries where bromide is not available commercially, it can be prescribed from a pharmacy (bromide 100 mg/ml aqueous solution or bromide 200 mg/ml aqueous solution). When potassium bromide is given as an add-on medication in dogs a dosage of 30 - 40 mg/kg/day should be used (preferably with a late evening meal). Potassium bromide may also be used as a first choice and then the dosage should be 40 - 60 mg/kg/day. The therapeutic range of bromide in dogs is 100-200 mg/dl when potassium bromide is used as an add-on drug and 250-300 mg/dl when used as mono therapy. Excretion occurs by the kidneys and is dependent on concomitant chloride intake. Attention should therefore be given to the dietary influence of the excretion of bromides. A high dietary chloride content shortens the elimination half-life causing decreased therapeutic serum bromide concentrations and thereby loss of therapeutic efficacy (2). Bromide is a first choice for seizure control in canine patients with hepatic dysfunction. Bromide should not be used for the treatment of epilepsy in the cat, as there is little documentation of its effect and side-effects when used in this species. Both phenobarbital and bromide may give side-effects. The most common adverse effects seen with phenobarbital are sedation, ataxia, and polyphagia. Signs of bromide toxicosis include ataxia, depression, stupor, anisocoria, muscle pain, dermatological signs such as rash and nodular pustular skin lesions, and gastrointestinal signs such as anorexia, vomiting and constipation. Necrolytic dermatitis has been described in dogs treated with phenobarbital (3). An increased risk for the development of acute pancreatitis has been reported in connection with the long-term treatment with phenobarbital and bromide (4-5). Bile acid...
levels should be monitored as anticonvulsants can cause hepatotoxicity \(^{4-6}\). As changes in blood parameters are sometimes seen in patients under long-term treatment with phenobarbital, haematology and clinical chemistry profiles should be controlled every half year. Immune-mediated neutropenia and thrombocytopenia have been described with phenobarbital \(^{69}\). In dogs one may then have to wean the patient off of phenobarbital and replace it with bromide. Other changes, but of minimal clinical significance include a rise in alanine aminotransferase and alkaline phosphatase (due to enzyme induction), as well as a reduction of serum total and free thyroxin with normal thyroid-stimulating hormone values and no concurrent clinical signs of hypothyroidism \(^{10-12}\).

It is important to give the owner a realistic description of expected side-effects, emphasizing that they appear with greater intensity at the start of the treatment, only to subside after two to four weeks. Otherwise, the owner may get the false impression that the animal’s quality of life will be permanently impaired by the antiepileptic treatment and, therefore, as a result, choose to have the animal euthanized. Combination therapy results in more side-effects than monotherapy.

A big problem in the treatment of patients with epilepsy is dealing with the not so small group of epilepsy patients that are refractory to treatment with phenobarbital and/or bromide. In recent years, it has been shown that in some dogs not responding well to therapy with Phenobarbital and potassium bromide, a reduction in seizure activity may be achieved with a combination of these two drugs with the human antiepileptic drugs gabapentine, levetiracetam, or zonisamide \(^{19-20}\). Primidone (Mysoline\(^{69}\)) has been used in dogs with epilepsy and is an effective drug. The anticonvulsant effect can be attributed to the 85% of the drug that is metabolised to phenobarbital in the liver. Primidone has a greater hepatotoxic potential than phenobarbital and it is more expensive. Phenobarbital is therefore the preferred product.

Diazepam is an especially effective anticonvulsant in the acute treatment of epilepsy (the drug of choice in the initial treatment of status epilepticus), but is not useful in the long-term treatment of epilepsy. Dogs develop tolerance to the drug within a few days and long-term treatment in cats can lead to liver damage \(^{60}\). In patients suffering from symptomatic epilepsy due to an active pathological condition in the brain, anticonvulsant treatment should be combined with treatment targeted directly towards the primary CNS disease.

**Monitoring epilepsy patients**

An epilepsy patient should be called in at least twice a year to a clinical control of the patient’s epilepsy status. The owner should bring in an overview of seizures in that period (keep a seizure calendar), so that treatment efficacy can be evaluated. The serum concentration of Phenobarbital/potassium bromide should be measured when there is an increase in seizure frequency, when there is a resumption of seizure activity after a seizure-free period, and after adjustments made in drug dosages. If there is treatment failure, the following reasons should be considered:

- Incorrect diagnosis, incorrect choice of antiepileptic drug, incorrect dosage of the antiepileptic drug, failure to monitor drug levels, owner non-compliance, presence of a systemic disease causing increased metabolizing or excreting of the antiepileptic drug, the patient has gained weight (drug dosage needs to be adjusted), the animal has developed a tolerance to the drug or monotherapy is insufficient.

It is crucial for the success of the treatment that the following points are discussed with the owner:

- Not all patients achieve a seizure-free existence (but often a satisfactory reduction in seizure activity)
- For some animals it is not possible to achieve a satisfactory therapeutic effect consistent with a good quality of life
- The animal’s disease can be a mental strain on the family
- Prepare the owner for the side-effects of the drug
- Control appointments are necessary
- Stress can provoke seizures
- Clustering of seizures is potentially dangerous - a veterinarian must be contacted immediately
- Spontaneous remission is possible

**References**

7. Dayrell-Hart B, Steinberg SA, van Winkle TJ, Farnbak GC.


