ANTI-EPILETIC DRUGS

General Principles of Treating Epilepsy, Seizure or Convulsion

1. Try to identify the type of condition and specific classification take good history.
2. Remember that primary epilepsy can not be cured but could be managed.
3. When seizure is in progress and it is prolonged it is therefore life threatening use emergency action (approach) i.e. i.v. administration of drugs.
4. Seizures that are periodic, recurring use preventive oral medication.
5. Oral preventive therapy often must be titrated to the individual patient and reviewed regularly adjusting dose and hence controlling the disease.

Cases of Epilepsy in Veterinary Medicine

- Animals that suffer epilepsy: Canine *spp* (Dogs). Familiar or idiopathic type is common in exotic breeds of dog e.g. pug, Labrador, German shepherds, Golden retrievers etc.
- In cats (Felines): Korat cats due to absence of cerebral gyri (Lissen Cephaly) results in seizures.
- Equines: Benign epilepsy seen in young foal particularly Arabian horses.
- Bovine: Brown Swiss, Swedish Red Cattle, *spp* etc. This familiar listerosis disease.
- Caprine/Goats: Cowdriososis, caused by cowdria ruminatium.
- Gerbils: also suffer from epilepsy.
- Anti-convulsant: These are drugs used to treat convulsive conditions of seizures.
- Antiepileptic drugs: these are drugs used to manage epilepsy or seizures..

Drugs requirement for treatment of epilepsy

Maintenance therapy –

1. Fairly long duration of action.
2. Metabolic tolerance from liver enzyme induction should not enhance drug clearance as to render the therapy impracticable.
3. Good oral absorption and subsequent passage of blood brain barrier.
4. Effectiveness of sub-sedative dose rate.
5. Absence of major side effect.

Status epileptics

1. Effective, centrally acting muscle relaxant properties.
2. Should have rapid or set of action but long duration of action is not important.
3. Available in a formulation suitable form for intravenous or I.m. inj.
4. Minimal effects on cardiovasuclar and Respiratory system.

First-line of Anticonvulsant Drugs.

- Phenobarbital.
- Potassium bromide (KBr)
- Sodium bromide (NaBr)
- Diazepam

Second-line (add on) Anticonvulsant Drugs.

- Clonazepam.
- Clorazepate
- Felbronate
- Gabapentin
- Levetiracetam
- Topiramate
- Valproic acid
- Zonisamide

Drugs Used to treat status Epilepticus

- Diazepam 0.5-1.0mg/kg i.v. bolus can be repeated 2-3 times at interval of 5-10mm
- Phenobarbital 2-4mg i.v. bolus can be repeated 20-30mm interval to dosage of 20mg/kg.
- Pentobarbital 2-15mg/kg i.v. to effect stoppage of motor activity.
- Propofol 1-2mg/kg i.v. to stop motor activity at 0.1-0.6km/kg/min.

Mechanism of action of Drugs used as Anticonvulsant and Anti-epileptic drugs.

Drugs used in seizure reduction act by the following means:

- Block the initiation of electrical discharge from the focal area.
- Or more commonly, prevent the spread of abnormal electrical discharge to adjacent brain areas.

- This is done by blockade of voltage-gated channel (Na^+ or Ca^{2+})
- Enhancement of inhibitory GABA ergic transmission.
- Interfering with excitatory glutamate transmission.

Drugs contraindicated for epilepsy patients.

1. Flourinated quinolones
2. Lidocaine.
3. Methyl xanthines
4. Morphine sulphate
5. Chloramphenicol
6. Metoclopramide

Phenobarbital – Mechanism of action

- Increases the threshold required for seizure discharge and decreases the discharge to surrounding neuron.
- Acts on the GABA eragic releptors.
- It inhibits glutamate activity.

Disposition & Pharmacokinetics

- It is a weak acid (pka 7.3) absorbed orally.
- It reaches peak plasma concentration 4-6hours after.
- It ahs half life of 1.27 + 0.21hrs.
- It is bounded to serum protein in dogs.
- The drug is metabolized via microsomel enzymes by oxidative hydroxylation.
- It eliminated in the blood via conjugation of the hydroxyphenobarbital with glucoronide.
- It is eliminated renally.

Preparations:

Oral or injectable preparations

Oral tables contain 0.25, 0.50 or 1grain (15, 30 and 65mg) respectively.

Clinical Use

- It is the widest used anti epileptic drug because it has wide spectrum of activity in different convulsive seizures.
- Clinically, it is used with a loading dose of 12mg/kg i.v.
- It could be given four to six equal hourly doses.
- It could be given in combination with i.v. diazepam to prolong the control of seizures the phenoherbital should be administered 1/m this is to avoid respiratory and cardiovascular depression.

Dosage and Frequency:

Dog – 2-4mg/kg P.O. BID (twice daily) up to 10mg/kg BID.

Given to achieve therapeutic concentrations of 20mg/ml.

Side Effects:

1. It might affect behavior of animal, polyphagia, polydispsia, polyuria.
2. Bone marrow dyscrasias – It can cause allergic reactions in dogs, Panyctopenia, neutropenia.
3. Thyroid – It affects the thyroid gland to cause hypothyrodism.
4. Hepatotoxicity may occur (serum alkaline phosphotase, Alanine amino transminases etc might increase.
5. Acute toxicosis might affect respiratory centres depressing respiration.

Treatment of Acute Phenobarbital Toxicosis.

1. Dogs could tolerate marked overdose (Concetration of 150mg/ml)
2. Artificial respiration oxygen should be provided doxapram and analeptics should be provided to stimulate the respiratory centre.
3. Alkalinization of urine accelerates renal excretion of Phenobarbital.

Bromide (Na, K and NH_4) – Mechanism of Action

- It is not fully understood in earlier years. But it is believed that there is replacement of the negatively charged chloride with bromide the neuron becomes hyperpolarized (RMP becomes more negative in elation to the threshold potential).
- It is also said that the mechanism o faction is related to the plasma concentration.

Pharmacokinetics

- It has a half life of 21-24days.

- It steady state cannot be achieved if or approximately 3-6 months.
- Distribution is to exracellular fluid, but yet penetrates the CNS.
- It is reabsorbed by the kidney slowly thus, due to its marked Reabsorption
- Increase in dietary salt would increase the rate of elimination of the drug.
- Faster elimination takes place in cats than dogs.
- T ½ = 10 days in cats.
- Steady stage in 6 weeks.

Side Effects:

Adverse reactions to bromide tend to be dose dependent.

- Mix recently adverse dry effect in cats include bronchial asthma.
- Experience show the toxicity is related to its anticonvulsant effect which include ataxia, grogginess, hyperactivity.
- Sedative effect may take 3 months to manage.
- Prutitic skin – lesions may occur (glucocorticoid may be used to control prutitus) caused by bromide.
- Like other anti-convulsants, it tends to increase the appetite of dogs.
- Hypertonicity due to effect of the slat might cause gastric irritation and vomiting.

Note: NaCl can be used to treat acute bromide toxicity.

Chemical Properties

1. Diazepam is dissolved in organic solvents e.g. propylene glycol because it is insoluble in water.
2. Viscid solution with a pH of 6.6-6.9.
3. Dilution with water or saline causes cloudiness, but does not alter the potency of the drug.
4. I.M. or I.V. injection. May be associated with signs such as pain.

Pharmacokinetics and fate

Distribution –

Extensive binding (96-98%) to plasma proteins.

In dogs, it has elimination half life of 77min.

Elimination is larger in geriatric patients.

Metabolism –

Oxidation by hepatic microsomal enzymes. Metabolitos excreted in urine as glucuronide conjugates.

Somnolence after diazepam may persist due to active metabolite and enterphepatic recirculation.

Cimetidine H2 receptor antagonist interfere with metabolism of diazepam this prolong the effects of diazepam.

Mechanism of Action –

It increases the availability of inhibitory neuro-transmitters (glycine). This result to anti-axiety effect of skeletal muscles and relaxation.

It facilitates the inhibitory neurotransmitter GABA (Gamma Amino Butyric Acid) this result to sedative effect.

Pharmacologic Effects

Central nervous system

1. Anti convulsant effect
2. It has very little effect of tranquilizing effect in dogs, cats or horses when administered alone.
3. Effect in sick patient varies from mild to profound sedation
4. Low dose of diazepam can be used to stimulate appetite in some inappetance patient.

Respiratory System

1. Minimal in healthy patient when given done
2. When combined with other drugs anesthetic agent this result to respiratory depression.

Cardiovascular System

1. When given, in low or moderate doses it brings about minimal change in cardial output and arterial pressure. In large doses, it causes decreased mean arterial pressure.
2. Heart rate sometime in decreased.

Diazepam is a benzodiazepines

The Clinical Use

Dosage:- 0.5 – 2mg/kg in dogs, 0.25 – 2.0mg/kg in cats Po BID-TID

Route of administration: 1m or 1v orally (Tid)

1. Benzodiazepines are rarely used alone in healthy patient.
2. Diazepam has aesthetic use

- It may be injected immediately before, or mixed with, Ketamine in healthy or sick dogs, cats, horses or small ruminants. ‘
- It is used as pre medication agent.

Diazepam Toxicity

It could be reversed by flumazenil which bind competitively, reversibly and specifically to the same receptor sites in C.N.S. So flumazenil could be used in case of toxicity of the drug due to overdose.

Clonazepam and other Benzodiazepines (Clonazepam, Lorazepam, Clorazepate)

This is also a benzodiazepine used for management of epilepsy. Clorazepate and Clonazepam are used for chronic treatment in man where as diazepam and lorazepam are drugs of choice in the acute treatment of status epilepticus. Clonazepam suppresses seizure spread from the epiletogenic focus and is effective in absence and myoclonic seizures. Clorazepate is effective in partial. Seizures when use in conjuction with other drug e.g. Phenobarbital.

Pharmacokinetics of Clonazepam

- The drug is dose- dependent (Zero order)
- ($t\ ^{1}/_{2}$) Half life is ranging from 1-6h.
- Bioavailability with oral dosing depends on the physical state and formulations containing macronized drug. It is possible to maintain plasma concentration within arrange which should be clinically effective wiht4 oral dosing three times daily.

Clinical Use

It is used in emergency treatment of status epilepticus

Dosage and Frequency

0.1-0.5mg/kg, P.O. BID-TID

Side Effects

- Diarrhea may sometime occur
- Withdrawal signs if the drug is stopped abruptly

FELBAMATE

Mechanism of Action

- Inhibition of excitatory signals or inhibition of sodium influx
- Potentiation of GABA receptors mediated Chloride.

Pharmacokinetics

- Felbemate is wells absorbed after oral administration
- In young days or pediatric animals bioavailability is as little as 30% of that in adult dogs.
- Drug is metabolized via hepatic metabolism to metabolites that are inactive

t $^{1}/_{2}$ is 4-8hrs in adult dogs

t $^{1}/_{2}$ is puppies or pediatric patients 2.5hrs

Dosage

Ranges from 15mg/kg divided twice daily to 30mg/kg

Peak concentration of the drug is achieve in dogs when given 60mg/kg

Side effects

***** Sedation * Polyuria, Polyphagia, Polydipsia

* Aplastic anaemia due to bone marrow depression

Clinical Use

- The drug is very safe
- It has bread mechanism of anti-convulsant activity
- It is very useful in monotherapy
- It is proved to be efficiencies for treatment of generalized seizures.
- In dogs in combination with Phenobarbital can be used to control refraction epilepsy.

Recommendation when using the drug

- Complete blood count and liver should be monitored

GABAPENTIN

Mechanism of Action

- Promoting the release of GABA, although the actual mechanism of release is not known.

Pharmacokinetics

- It is well absorbed after oral administration absorption appears to be dose dependent.
- The antiepileptic effects last longer them- anticipated this is based on the half life it reaches steady state in 24hours to 48 hours.

- The drug is eliminated entirely by renal elimination. This avoids hepatoxicity and drug interaction.

Dosage and Administration

10-30mg/kg orally every shows (Tid) 60mg/kg (Tid)

Doses are usually higher doses

Side Effects in dogs

Mild dizziness, nausea and vomiting have occurred in humans.

ZONISAMIDE (ZeoNisamide).

Mechanism of Action

- Blockage of both voltage-aged sodium channels and T-tyic calcium current
- It also acts by enhancement of GABA receptor

Pharmacokinetics

- Orally active and well distributed throughout the body
- It has a long life (50-60hrs) when administered without enzyme inducers.
- If it is given with enzyme inducers it shortens its half life to 25-30hrs.

The parent compound (thirty percent). Its N-acetyl metabolite (twenty percent), and its glucuronide (fifty percent) are excreted in the urine.

Adverse Effect

***** Typical C.N.S adverse effect

* May cause kidney stone

* Loss of appetite

* Sedation

Clinical Use

***** For focal and generalized seizures

Dosage: 4-8mg/kg day or 10mg/kg BID

LEVETIRACETAM (lee vet ye RA Se tam).

Mechanism of Action

Its mechanism of anticonvulsant action is unknown

Pharmacokinetics

- The drug is well absorbed orally

- Excretion is urinary with most of the drug 66-70 being unchanged
- These is no hepatic metabolism
- It has a remarkable force pharmacokinetic drug interaction for this reason is a good choice for adjunctive therapy.

The Side Effects

- Salvation, restlessness, vomiting and ataxia at dosages as high as >400mg/kg.

Dosages and Frequency

In drugs 20mg/kg P.O. TID,; 500-400

$t\ ^{1}/_{2}$ = 4-10hrs

Steady State of drugs

2-3 days

PHENYTOIN (diphenyl hydration)

Is no longer recommended for use in dogs, cats or foals due to undesirable pharmacokinetics properties. In dog too rapid metabolism in dogs, this reduces its effectiveness.

In Cats too slow metabolism in cats, this increases the risk of toxicity (Salivation, Vomiting, Weight loss).

In foals it has erratic plasma concentration it is carefully given at 15-40mg/kg, P.O.TID.

Dosage: It can be given I.V 5.10mg/kg, with subsequent administration at 1-5mg/kg, I.V, I,m or P.O every 2-4hrs for 12hrs.

Mechanism of Action

- Blocks voltage-gated sodium, channels by selectively binding to channels in the in active state and slowing its rate of recovery.
- It also blocks voltage- dependent-calcium channels and interferes with the monoaminergic neurotransmitters.

TOPIRAMATE (toe peera mate Pronounced)

(its effectiveness is not yet know)

Mechanism of Action

- Blocks voltage dependent, use-dependent sodium channels
- Shown to increase the frequency of chloride channel opening by binding to the GABA receptors.

- Prevents phosphorylation of variety of proteins, including anti- epileptic targets.
- Calcium current (Possess High- Voltage) (L Type) are reduced.

Pharmacokinetics

- Well absorbed orally
- Oral bioavailability of 100%
- Peak concentration occurs in about two hours
- 30% of each dose is metabolized.

$t^{1}/_{2}$ 20-25hrs

Adverse Effects

- C.N.S and git disturbances
- Impaired concentration
- Dizziness
- Ataxia
- Nervousness
- Confusion
- Nausea, Weight loss