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POLYTHERAPY – MECHANISM OF ACTION

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Benzodiazepine: enhance the inhibitory action of the amino acid neurotransmitter gamma-aminobutyric acid (GABA)-A, which suppress neuronal excitability. The GABA-A receptor is a ligand-gated chloride-selective ion channel. The intracellular influx of the negative charge Cl^- suppresses neuronal excitability. When these receptors are activated, there's a rise in intracellular chloride levels, resulting in cell membrane hyperpolarization and decreased excitation.

Phenobarbital: similar to benzodiazepine acts on GABA-A receptors subunits and extends the amount of time the chloride ion channel is open.

Levetiractem: The exact mechanism through which levetiracetam exerts its anti-epileptic effects is unclear, but is thought to be unique amongst other anti-epileptic medications. Current knowledge suggests that levetiracetam's binding to synaptic vesicle protein 2A (SV2A) is a key driver of its action. SV2A is a membrane-bound protein that is found on synaptic vesicles and is ubiquitous throughout the CNS[4] - it appears to play a role in vesicle exocytosis[11,15] and in the modulation of synaptic transmission by increasing the available amount of secretory vesicles available for neurotransmission.[7] Stimulation of pre-synaptic SV2A by levetiracetam may inhibit neurotransmitter release,[6] but this action does not appear to affect normal neurotransmission. This has led to the suggestion that levetiracetam exclusively modulates the function of SV2A only under pathophysiological conditions.[4] Levetiracetam and related analogues showed a correlation between affinity for SV2A and anti-epileptic potency, further suggesting that action at this site contributes to the anti-epileptic activity of the drug.[11,15]

Levetiracetam has also been shown to indirectly affect GABAergic neurotransmission (despite having no direct effect on GABAergic or glutamatergic receptors) and modulate ionic currents.[7] Similarly, levetiracetam has been shown in vitro to inhibit N-type calcium channels.[8] How, or even if, these actions are implicated in its anti-epileptic action have yet to be elucidated

Ketamine: non-competitively antagonize NMDA $Ca2^+$ channel pores, and binds to NMDA receptors phencyclidine (PCP) binding sites, collectively inducing significant **NMDA receptor inhibitor.** As a consequence, the sensory association areas of the cortex, as well as part of the limbic system and thalamus, are directly depressed by ketamine.

In Status Epilepticus overexpression of NMDA receptors occur, which promote glutamate-induced excitation, these changes lead to calcium accumulation within the cells and trigger apoptosis.

Glutamate receptor (NMDA) antagonists (e.g. ketamine) may be beneficial particularly in refractory stages of SE and they may even help preventing resistance, if administered at early stages.

Overexpression and activation of NMDA receptors may also contribute toward calcineurin-induced internalization of the $GABA_A$ receptors γ-subunits, leading further BDZs resistance. Therefore, NMDA receptors inhibitors may also have another benefit by means of enhancing BDZs potency.

Dexmedetomidine: is an alpha2-adrenoreceptor agonist that acts by decreasing excitatory neurotransmitters via suppression of sympathetic nervous stimulation and nor-epinephrine release, mainly in the region of amygdala, hippocampus, and cerebral or cortex. In addition, dexmedetomidine has neuroprotective properties by decreasing cerebral metabolic and oxygen demands, decreasing brain edema via vasoconstriction and contributing to maintain normal mean arterial pressure.

According to a case report of 3 dogs with Idiopathic Epilepsy that were presented with super-refractory SE, the combination of ketamine-dexmedetomidine IV CRI and mild hypothermia (36.7-37.7 C) resulted in termination of super-refractory SE.

Propofol: acts on $GABA_A$ receptor (non-BDZ site; agonist) and also may interact with gyicine (agonist) and NMDA (antagonist) receptors as well as calcium channels.

Phenobarbitone and sodium thiopentone: act on $GABA_A$ receptors (non-BDZ site; agonists) and also have a neuroprotective effect by decreasing intracellular Na^+ and Ca^+, glutamate release and cerebral oxygen consumption, while also scavenging oxygen free radicals. Phenobarbitone is most commonly used, but it should be closely monitored because an overdose can be fatal. Overall, the panel recommends the use of barbiturates IV CRI in animals with SE ONLY if previous treatment with dexmedetomidine, ketamine or propofol IV CRI fails to terminate SE.

Inhalant anesthetic: acts on $GABA_A$ receptors (non-BZD site; agonist) decrease thalamic neuronal membrane excitability and neurotransmitter release and increase cerebrospinal blood flow while minimizing oxygen cerebral consumption. They are reserved at a last pharmacological option in refractory SE.

What if the Combined Measures with First-, Second- and Third- line treatments as well as supportive care still fail to terminate seizure activities?

- Other pharmacological interventions including but not limited to IV magnesium and allopregnalone can be considered in dogs and cats.

Allopregnanolone (ALLO): The basis through which ALLO able to terminate BZD-refractory SE is not completely understood but has been hypothesized to relate to the ability of ALLO to act as a positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors (Rogawski et al., 2013). BZD acts exclusively on synaptic $GABA_A$ receptors, which as noted above are internalized as SE progresses and become progressively unavailable (Rogawski et al., 2013). It is noteworthy that ALLO also acts on BZD-insensitive $GABA_A$ receptors that increase in abundance at synapses as SE continues (Kapur 2000). The

actions of ALLO on both synaptic BZD-insensitive and extrasynaptic $GABA_A$ receptors provide a novel mechanism of action to that of BZDs (Belelli et al., 2002; Carver and Reddy 2013).

When these pharmacological interventions fail, non-pharmacological interventions (ie, neurostimulation in dogs and cats) can be considered.