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Role of Propranolol and Gabapentin in Paroxysmal Sympathetic Hyperactivity

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Abstract

Paroxysmal sympathetic hyperactivity (PSH) is a result of acute brain injury that has been well known for many decades. However, the evidence for management of PSH is almost entirely anecdotal in nature. We reviewed case reports or series of pharmacotherapy management of PSH. These studies mentioned treatment options, but few studies exist to guide treatment strategies. For many years, the syndrome was not clearly understood; therefore, the therapy has focused on control of symptoms. In 2014, a Steering Committee came together to develop a conceptual definition and produced a consensus set of diagnostic criteria. Although understanding the diagnostic criteria is very well needed in management of patients with PSH, pharmacologic management is also crucial. Data describing the drug choices, dosing, and duration of therapy are also sparse. Recognition of appropriate medications is important because PSH is associated with morbidity, longer hospitalization, delaying transfer to rehabilitation units, and increasing cost. In this review article, we discussed the common medications used in the treatment of PSH. Treatment should target symptom abortion, prevention of symptoms, and refractory treatment. Symptom-abortive medications are indicated to control discrete breakthrough episodes, using medications such as morphine and short-acting benzodiazepines. Other medications used for prevention of symptoms and refractory treatment include long-acting benzodiazepines, nonselective β-blockers, α2 agonists, opioids, and GABA agonists. The mechanisms by which these agents improve symptoms of PSH remain speculative. However, a combination of medications from different classes seems the most effective approach in managing PSH symptoms. There is wide variability in clinical practice with regard to drug choices, dosing, and duration of therapy. Future research needs to be conducted using the new PSH assessment measure to appropriately apply drug management.

Keywords: Propranolol, Gabapentin, Paroxysmal Sympathetic Hyperactivity.

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1. Introduction

Propranolol is a lipid soluble non-selective β-adrenergic receptor antagonist, or BB; that is, it blocks the action of E and NE at both β1- and β2- adrenergic receptors [1]. Propranolol is able to cross the blood–brain barrier and exert effects in the central nervous system in addition to its peripheral activity [2]. Propranolol is a nonselective beta-blocker that blocks the action of catecholamines (adrenaline and noradrenaline) at both beta-1 and beta-2 adrenergic receptors. By blocking the beta-adrenergic sites, propranolol inhibits sympathetic effects that act through these receptors [3]. Propranolol is highly lipophilic BB that diffuse rapidly through the brain tissue[[3]. Following oral administration, complete absorption of the drug occurs. However, maximum part of the dosage is removed via hepatic extraction, and only 25% of the drug reaches systemic circulation. It is extensively metabolized, and most of its metabolites are excreted in urine. Plasma half-life of propranolol is 3–6h [3].

2. Administration of Propranolol:

Like most medications, BB are metabolized predominately in the liver (both the active and inactive

compounds). Approximately a quarter of the ingested drug reaches systemic circulation due to the first-pass metabolism in the hepatic circulation. The active metabolite of propranolol is 4-hydroxypropranolol, which is formed through hydroxylation using the cytochrome P450 2D6 (CYP2D6) enzyme [3]. Propranolol administration can be either oral or intravenous. With intravenous administration, there should also be continuous electrocardiogram monitoring with a slow infusion. This route of administration primarily occurs in an inpatient setting. The doses of propranolol vary, being primarily dependent on what condition the medication is treating [4].

3. Medical uses of Propranolol:

- HTN.
- Angina pectoris (with the exception of variant angina).
- Myocardial infarction.
- Tachycardia (and other sympathetic nervous system symptoms, such as muscle tremor) associated with various conditions, including anxiety, panic, hyperthyroidism, and lithium therapy.
- Portal hypertension, to lower portal vein pressure.
- Prevention of esophageal variceal bleeding and ascites.
- Anxiety.
- Hypertrophic cardiomyopathy [5].
- Aggressive behavior of patients with brain injuries [6].

4.Adverse Effects of Propranolol:

Common side effects of using propranolol include bradycardia, gastrointestinal issues, abdominal pain, nausea, erectile dysfunction, and wheezing/bronchospasms. Propranolol use can also cause drowsiness, fatigue, and cold extremities. Some extreme side effects to be aware of include allergic reactions, insulin resistance, and hallucinations [7].

5.Contraindications of Propranolol:

Prescribers should exercise extreme caution when prescribing BBs to patients with diabetes. This is because this class of medication can mask the symptoms of hypoglycemia, which includes flushing, tachycardia, sweating, and dizziness. Furthermore, since the main effect of propranolol is to decrease heart rate, it is contraindicated in those who have bradycardia (less than 60 beats per minute) [8]. Propranolol is also contraindicated in those with any lung pathologies, such as COPD, asthma, or emphysema [3]. Since propranolol is metabolized by hepatic enzymes and excreted through the renal system, prescribers should proceed with caution when prescribing it to a patient with known hepatic or renal impairments. Furthermore, dosages may need to be adjusted to avoid toxicity resulting from the inability to metabolize or clear the medication from the body properly [9].

6.Monitoring of Propranolol:

Propranolol is generally well tolerated drug, with most of its common side effects are usually mild and can be managed conservatively without requiring discontinuation of medication [3]. Whenever a patient receives propranolol therapy, it is beneficial to routinely monitor their BP, pulse, and respiratory rate. It is especially important in those with coronary artery disease, COPD, or any other condition that β-blockade might negatively affect. Regular monitoring is possible at home with portable BP and pulse monitors or routinely scheduled visits to primary care physicians [4].

7. Toxicity of Propranolol:

Ingestion of greater than 1 g of propranolol in 24 hours can potentially be lethal and lead to profound bradycardia, bradyarrhythmia, hypotension, bronchospasm. When suspecting a BB overdose, a patient should always receive glucagon immediately. Glucagon has shown to be very effective in reversing BB overdose, increasing heart rate, and myocardial contractility [9].

8. Role of Propranolol in PSH:

Propranolol, a medication commonly prescribed for PSH, it has anti-inflammatory, neuroprotective, and glucose regulation mechanisms that combine to improve outcomes for persons with TBI and developing PSH, it is associated with improvements in GCS scores for those patients, also, reduced acute care hospital length of stay and mortality rate [10]. TBI is correlated with increased sympathetic activity on the expense of parasympathetic system due to loss of cortical control after brain injury [11]. Propranolol as a highly lipophilic non selective BB has cardioprotective and neuroprotective effect. At cardiac level, it reduces heart rate, perfusion volume, and mean arterial pressure, this in turn, reduces oxygen consumption and lowers the risk of myocardial infarction. At the nervous level, it reduces cerebral perfusion, thereby reducing glucose and oxygen consumption. These effects lower the basal metabolic rate by tempering the effects of catecholamines [12], so, early usage of propranolol after TBI controls hemodynamics and blood sugar with decreased catecholamine levels correlated with the improvement of GCS [11]. Propranolol is the best BB to limit secondary injury and decrease mortality in patients with TBI [13]. Propranolol was the drug of choice and was shown to reduce the LOS and mortality rate in moderate-to-severe TBI patients with PSH. No other BBs in single administration were able to demonstrate the similar efficacy, probably owing to their pharmacodynamics (i.e., propranolol has lipophilic properties that allow penetration of the blood-brain barrier) [14]. Although bradycardia and hypotensive events occur early after TBI, low-dose intravenous propranolol does not increase their number or severity. Early use of propranolol after TBI appears to be safe and may be associated with decreased ICU and hospital LOS [15]. Retrospective studies have shown that BBs, specifically propranolol, significantly decrease mortality of TBI through mechanisms not yet fully elucidated but are thought to counterbalance a hyperadrenergic state resulting from a TBI [16]. In vivo models of TBI demonstrate increased cerebral perfusion, decreased cerebral hypoxia, reduced cerebral edema, and improved neurologic recovery with propranolol administration [17]. Early administration of propranolol after TBI was associated with improved survival [18], and will continue to be the standard prophylactic pharmacotherapeutic method as it limits the risk of sympathetic storming in high-risk patients with TBI [19]. A prospective randomized controlled trial has supported the routine administration of BB therapy as part of a standardized neurointensive care protocol [20].

9.1. Dosage in PSH:

40 mg every 12 hrs. orally [21].

9.2. Gabapentin

Medical uses of Gabapentin:

Gabapentin is an anticonvulsive medication that was first discovered in the 1970s. The medication received approval from the US Food and Drug Administration (FDA) in 1993 and has been available in generic form in the USA since 2004. It has the potential of an anticonvulsive medication and can be used as an adjunct to more potent anticonvulsants [22] .

Also, it proves beneficial in managing certain types of neural pain and psychiatric disorders [22]:

- Neuropathic pain-postherpetic neuralgia.
- Partial seizures.
- Anxiety and depression.
- Movement disorders like restless leg syndrome, tremors.
- Alcohol withdrawal.

10. Mechanism of Action of Gabapentin:

The exact mechanism of action with the GABA receptors is unknown; however, researchers know that gabapentin freely passes the blood-brain barrier and acts on neurotransmitters. Gabapentin has a cyclohexyl group to the structure of neurotransmitter GABA as a chemical structure. Even though it has a similar structure to GABA, it does not bind to GABA receptors and does not influence the synthesis or uptake of GABA [23]. Gabapentin works by showing a high affinity for binding sites throughout the brain correspondent to the presence of the voltage-gated calcium channels, especially alpha-2-delta-1, which seems to inhibit the release of excitatory neurotransmitters in the presynaptic area which participate in epileptogenesis. Even though there is no evidence for direct action at the serotonin, D, benzodiazepine, or histamine receptors, research has shown gabapentin to increase total-blood levels of serotonin in healthy control subjects [24]. The elimination half-life of gabapentin is 5 to 7 hours, and it takes two days for the body to eliminate gabapentin from its system. One benefit of gabapentin use is its mild side-effect profile. The most common side effects are fatigue, dizziness, and headache [23].

11. Administration of Gabapentin:

Gabapentin is highly lipophilic but not bound to plasma proteins, showing linear pharmacokinetics, and not demonstrating any significant protein binding or liver metabolization. It has an oral bioavailability of greater than 90%, independent of dose. Generally, patients achieve steady-state plasma levels within 24 to 48 hours [25]. There is no clinically significant effect in administration with food nor on the extent of absorption or elimination. The elimination half-life of the drug is approximately 6.5 hours. Gabapentin readily crosses the blood-brain barrier. It is primarily excreted renally, with no active metabolites. Dosage adjustment is necessary for patients with renal impairment. Pregabalin does not induce or inhibit CYP enzymes. Also, none of the CYP enzyme inhibitors alter its pharmacokinetics as a consequence [26].

12. Adverse Effects of Gabapentin:

Serious Reactions like:

- Suicidality, depression.
- Anaphylaxis.
- Angioedema.
- Rhabdomyolysis.
- Withdrawal seizure or withdrawal symptoms if discontinued abruptly.

More Common Reactions as:

- Ataxia, tremor, amnesia.
- Dizziness, fatigue, diarrhea, constipation, nausea, and vomiting.
- Fever, headache, and back pain.
- Nystagmus, diplopia.
- Peripheral edema.
- Asthenia
- Weight gain.
- Abnormal thinking.
- Impotence [22] .

13. Monitoring of Gabapentin:

It is necessary to check baseline creatinine levels before and during the treatment, inform patients and screen for depression, behavioral changes, and suicidality [23].

14. Toxicity of Gabapentin:

Gabapentin is considered by the CDC as a substitute for opiates for chronic pain. However, there are growing concerns about its potential for misuse. Gabapentin does not have a high risk of an overdose but can increase the euphoria caused by opioids and reduce drug withdrawals. Furthermore, gabapentin can bypass the blocking effects of addiction treatment medications, and unfortunately, does not show up in urine drug tests [26].

15. Drug-Drug interactions of Gabapentin:

Reports of respiratory depression and sedation, occasionally fatal, have emerged with the coadministration of gabapentin and opioids like morphine, hydrocodone, oxycodone, and buprenorphine [21].

16. Role of Gabapentin in PSH:

Reports have shown the efficiency of daily use of gabapentin on PSH [27], as, Gabapentin has been reported to be a well-tolerated, safe, and efficacious drug [27]. Gabapentin is neuroprotective after TBI, it is proposed to be used to reduce sympathetic hyperactivity, and to reduce secondary brain damage as it binds to alpha subunit of calcium channel and prevents the release of excitatory neurotransmitter [28]. It has emerged as one of the first line agents for pain management [29]. It modulates allodynia and neuropathic pain [30], with improvement in the quality of life in patients with neuropathic pain [28], as authors in a theoretical model suggested that the neuropathic pain is acting as a driver for dysautonomia and this should be considered as pathophysiological mechanism of PSH and thus treatment for PSH should be based on it [31]. According to previous studies, gabapentin is more useful in seizure attacks and spasticity of TBI patients [32]. Although clonidine has been used a general drug for PSH, gabapentin is a better treatment for PSH than clonidine in terms of its action mechanisms and tolerability [33].

Dose of Gabapentin: 100 mg every 8 hrs. orally [34].

17. Conclusions

The mechanisms by which drugs improve symptoms of PSH remain speculative. However, a combination of medications from different classes seems the most effective approach in managing PSH symptoms. There is wide variability in clinical practice with regard to drug choices, dosing, and duration of therapy. Future research needs to be conducted using the new PSH assessment measure to appropriately apply drug management.

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