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Effect of Carvedilol in Portal Hypertensive Gastropathy (PHG)

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Abstract

Carvedilol is a potent beta-blocker with mild anti-alpha 1 adrenergic activity, offering therapeutic potential in various medical contexts. Its nonselective beta-blocking action results in decreased heart rate and cardiac output and induces splanchnic vasoconstriction, thereby reducing portal blood inflow and lowering portal pressure. This holds particular significance in addressing conditions like Portal Hypertensive Gastropathy (PHG), which is associated with chronic anaemia in cirrhosis patients. A key therapeutic aim in managing PHG is the reduction of portal pressure.

Introduction

Carvedilol, a formidable nonselective beta-blocker with a modest anti-alpha 1 adrenergic effect (about one-tenth of its beta-blocking potency), was initially developed to combat arterial hypertension and heart failure. In terms of beta-receptor antagonism, it surpasses propranolol by a factor of 2-4. Carvedilol also possesses antioxidant properties. Its nonselective beta-blocking action leads to reduced heart rate, cardiac output, and splanchnic vasoconstriction, culminating in diminished portal blood flow and, consequently, a decline in portal pressure. Additionally, its alpha 1 adrenoceptor blocking feature contributes to a decrease in hepatic vascular tone, further reducing portal pressure. Nonetheless, the vasodilatory aspect of carvedilol can potentially induce arterial hypotension and sodium retention, particularly concerning patients with advanced cirrhosis. Drugs affecting cytochrome P450 2D6 activity, such as quinidine, paroxetine, fluoxetine, and propafenone, can elevate plasma concentrations of R-carvedilol (a stereoisomer with alpha- and beta-adrenergic blocking properties), heightening the risk of hypotension during carvedilol administration. Genetic polymorphisms in cytochrome P450 2DS can also impact this risk. Therefore, it is advisable to initiate carvedilol at low doses (6.25 mg/day) and gradually titrate upwards to a maximum of 25 mg twice

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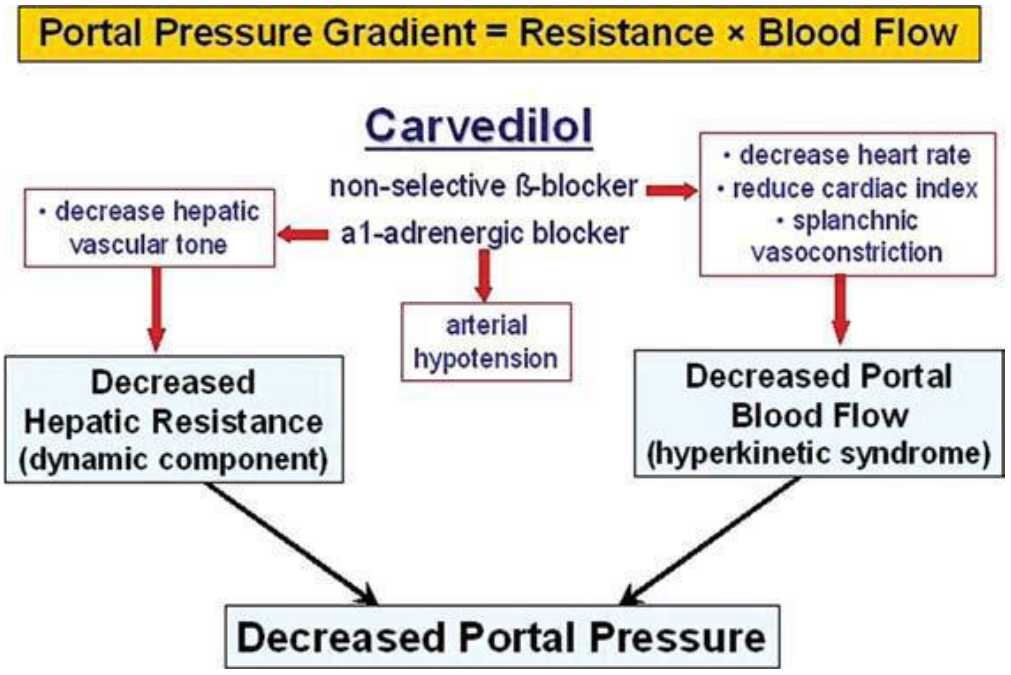
daily (50 mg for patients weighing >85 kg). Titration should occur at intervals of 1-2 weeks, and taking the medication with food can moderate absorption speed and minimize side effects. The dose should not be increased if patients exhibit symptoms or have systolic blood pressure <90 mm Hg or heart rate <50 beats per minute.

Mechanism of action of Carvedilol

Carvedilol's impact on portal pressure primarily hinges on its potency as a nonselective beta-blocker. By decreasing heart rate and cardiac index via beta-1 adrenergic receptor blockade and inducing splanchnic vasoconstriction through beta-2 adrenergic receptor blockade, it achieves a reduction in portal blood flow and subsequent portal pressure decrease, akin to the mechanisms of action of propranolol and nadolol. Additionally, its mild anti-alpha 1 adrenergic activity reduces hepatic vascular tone, intensifying the drop in portal pressure. However, this anti-alpha 1 adrenergic activity can induce arterial hypotension.



Drug-Related Adverse Events

Carvedilol shares similarities in side effects with propranolol and nadolol, except for an elevated risk of hypotension and edema. During titration, close monitoring for drug-related adverse events, such as edema, dizziness, bradycardia, hypotension, nausea, and blurred vision, is essential. Dose increments should be avoided if patients develop symptoms or exhibit systolic blood pressure <90 mm Hg or heart rate <50 bpm. Weight should be regularly monitored, as sodium retention initially manifests as weight gain, possibly necessitating diuretic therapy or dose adjustments for patients already taking diuretics. While reversible deterioration of renal function due to hypotension is a risk for patients with hypotension, this has not been reported in cirrhosis patients. Side effects are typically

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more frequent at the outset of therapy and often respond well to dose reduction or eventually resolve with continued treatment. In heart failure studies, carvedilol had to be discontinued due to intolerance or side effects in 5% of patients. Like all nonselective beta-blockers, carvedilol is contraindicated in patients with significant bradycardia, sick sinus syndrome, and partial or complete heart block unless a pacemaker is in place. Therefore, an electrocardiogram is mandatory before commencing therapy. Patients with asthma should avoid carvedilol. Caution is necessary in treating patients with insulin-dependent diabetes, as carvedilol may mask hypoglycemia symptoms.

Portal Hypertensive Gastropathy

Portal hypertension is a nearly inevitable complication of cirrhosis and underlies various complications, including oesophageal and gastric varices, variceal bleeding, portal hypertensive gastropathy (PHG), and more. Reversing portal hypertension is of paramount interest, as it would prevent PH-related complications, clinical decompensation, and mortality. PHG contributes to 8% of nonvariceal upper gastrointestinal bleeding in liver disease patients. The gold standard for assessing portal pressure involves hepatic vein access via a femoral catheter to measure wedged and free pressures, yielding the hepatic venous pressure gradient (HVPG). Elevated HVPG, exceeding a normal range of 1–3 mm Hg to >12 mm Hg, is associated with ascites development and an increased risk of variceal rupture, with severe PH defined as HVPG >15 mm Hg. Treatment approaches for PHG include medications and endoscopic management.

Conclusion on Effect of Carvedilol on PHG

Carvedilol, a newer nonselective beta-antagonist with concurrent alpha 1 antagonist receptor properties, plays a pivotal role in heart failure and hypertension management. It boasts a beta-blocking potency 2–4 times greater than propranolol. Carvedilol achieves portal pressure reduction by lowering heart rate, cardiac output, and inducing splanchnic vasoconstriction, thereby diminishing portal blood inflow and portal pressure. Additionally, its alpha 1 adrenoceptor blocking effect decreases hepatic vascular tone and resistance, further contributing to portal pressure reduction. Nevertheless, the vasodilatory nature of carvedilol carries a risk of arterial hypotension and sodium retention, especially in advanced, decompensated cirrhosis. Some studies suggest that relatively low doses of carvedilol (12.5 mg/day or 6.25 mg bid) provide effective portal pressure reduction with lower hypotension risk, which may be relevant when treating decompensated cirrhosis patients. PHG, a contributor to chronic GI haemorrhage in cirrhosis patients, underscores the importance of reducing portal pressure as a primary treatment objective. Nonselective beta-blockers represent the most thoroughly studied agents for sustaining portal pressure reduction and should be continued on a long-term basis to prevent bleeding recurrence.

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