Propranolol: A 50-Year Historical Perspective

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Abstract

Propranolol is a beta-adrenergic receptor antagonist that was developed by the British scientist Sir James Black primarily for the treatment of angina pectoris, more than 50 years ago. It was not long before several other cardiovascular as well as noncardiovascular therapeutic uses of propranolol were discovered. Propranolol soon became a powerful tool for physicians in the treatment of numerous conditions such as hypertension, cardiac arrhythmias, myocardial infarction, migraine, portal hypertension, anxiety, essential tremors, hyperthyroidism, and pheochromocytoma. Owing to its action at multiple receptor sites, propranolol exerts several central and peripheral effects and is therefore useful in various conditions. Right from reduction in postmyocardial mortality to control of anxiety in performers, propranolol plays an important role in a plethora of medical conditions. Interestingly, even today, newer indications of this age-old drug are being discovered. Moreover, propranolol treatment has been found to be cost-effective when compared to other corresponding treatment options for individual indications. In this article, we attempt to recount the journey of propranolol right from its inception to the present day.

Keywords: Anxiety, beta-blocker, myocardial infarction, portal hypertension, propranolol

Introduction

The invention of the beta-adrenergic receptor antagonist, propranolol, by Sir James Black in the 1960s revolutionized the treatment of cardiovascular diseases. For his work, Sir James Black was awarded Nobel Prize in Medicine in 1988.[1,2] His work, to find a way to reduce myocardial oxygen demand in patients with reduced oxygen supply due to arterial disease, began in 1958. Sir James Black has credited the Ahlquist's theory for his work, which led to the development of propranolol.[3-5] Until propranolol was invented, the only drugs available to treat angina were nitrates, which were effective only partially. Soon, it was discovered that propranolol is not only effective in the treatment of angina, but it also has therapeutic effects in other cardiovascular conditions such as hypertension, myocardial infarction, and arrhythmias.[1,2,6-8] Over the years, other applications of propranolol in several noncardiovascular conditions including migraine, essential tremors, anxiety, portal hypertension, hyperthyroidism, and pheochromocytoma have been recognized.[9] Interestingly, many of these indications have, in fact, been discovered serendipitously.[2,10] Propranolol has thus become an important tool for physicians to manage several cardiovascular as well as noncardiovascular conditions. In this article, we will review the journey of propranolol from its inception to the present day.

Mechanism of Action and Pharmacokinetics

Propranolol [Figure 1] 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.[11,12]

Propranolol is highly lipophilic. 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 3–6 h.[11,12] A long-acting preparation of propranolol has also been developed with a half-life of 8–11 h. This sustained-release preparation provides the advantage of once-daily dose with similar efficacy and better patient compliance.[13] Propranolol has a variable bioavailability and its dose needs to be individualized based on response. Dose ranges from 80 mg/day to 320 mg/day.[11]

Therapeutic Uses of Propranolol

The widespread use of propranolol in cardiovascular diseases including ischemic heart disease, arrhythmias, and myocardial infarction has been known for more than 50 years. Here, we will also discuss the role of propranolol in various noncardiovascular conditions with special emphasis on its usage in the management of migraine, essential tremors, anxiety, and portal hypertension.

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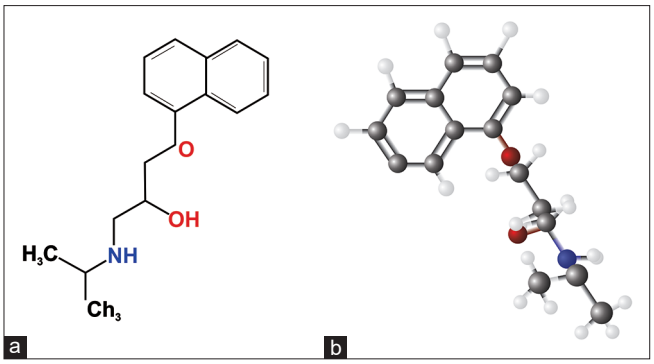

Figure 1: Two-dimensional (a) and three-dimensional (b) representation of molecular structure of propranolol (C16H21NO2)

Cardiovascular indications

Even today, more than half a century after they were first introduced, beta-blockers are still the most commonly used class of drugs for managing cardiovascular diseases. Although propranolol was first developed to manage angina pectoris, soon its use in other cardiovascular conditions such as hypertension, cardiac arrhythmias, and myocardial infarction was recognized.[6-8,14] The Beta-Blocker Heart Attack Trial was a landmark trial in the history of propranolol. It was a multicenter, randomized, double-blind, placebo-controlled trial (N = 3837), which was designed to evaluate whether administration of propranolol postmyocardial infarction led to reduction in mortality. Results were encouraging with statistically significant reductions in total mortality (9.8% vs. 7.2%, $P < 0.005$), cardiovascular mortality (8.9% vs. 6.6%, $P < 0.01$), mortality due to arteriosclerotic heart disease (8.5% vs. 6.2%, $P < 0.01$), and sudden death (4.6% vs. 3.3%, $P < 0.05$). Safety profile was found to be acceptable. The results also showed that propranolol has an antiarrhythmic effect which may, at least in part, be responsible for the observed reduction in sudden cardiac death. The positive results of this study led to widespread use of propranolol for reduction in morbidity and mortality associated with myocardial infarction.[8,15]

Many new generation cardioselective beta-blockers are now available. Nevertheless, propranolol continues to be used in specific conditions. Propranolol has been found to be as beneficial as the third-generation beta-blocker, carvedilol, on left ventricular volume and function after primary coronary stenting in acute myocardial infarction. Propranolol, being cost-effective, can be preferred over carvedilol for this indication.[16]

Barton *et al.* assessed the efficacy and safety of high-dose propranolol for the management of supraventricular tachyarrhythmias (SVTs) in infants (N = 287). SVTs were successfully managed in 67.3% of the study population through entire inpatient stay, and 87.7% of those discharged on propranolol were recurrence-free at follow-up.[17] Several other studies also support the efficacy of propranolol in treating SVT in infants.[18,19] Apart from propranolol, digoxin has also been used to treat SVT in this patient population. The evidence related to comparative efficacy/safety of propranolol and digoxin has been conflicting. Bolin *et al*. conducted a large retrospective database study including 2657 neonates and found that while digoxin and propranolol were the most commonly prescribed drugs for SVT in infants, the use of digoxin decreased to 23% and propranolol increased to 77% of all the antiarrhythmic medications prescribed between 2004 and 2015. They also found that odds for mortality in the propranolol arm were 0.32 times than that for the digoxin arm (confidence interval [CI]: 0.17–0.59; $P < 0.001$). Moreover, hospital costs in the propranolol group were significantly lesser than that in the digoxin group ($P = 0.003$). Thus, it can be safely said that propranolol is superior to digoxin in the management of SVT in infants.[20] Furthermore, propranolol has also shown promising results in heart failure caused by pediatric hypertrophic cardiomyopathy and is considered as treatment of choice in this condition.[21]

It is well established that platelets play a vital role in the pathogenesis of cardiovascular diseases. Whether beta-blockers that are mainly prescribed by virtue of their beneficial effects on heart rate, blood pressure, and myocardial oxygen demand also have a direct effect on platelet aggregation was evaluated by Bonten *et al.* in a meta-analysis including 31 studies. They found that beta-blockers significantly decreased platelet aggregation (standardized mean difference − 0.54, 95% CI: −0.85–−0.24, $P < 0.0001$). In addition, this effect was more pronounced in nonselective lipophilic beta-blockers such as propranolol.[22]

Propranolol has been extensively used for the management of essential hypertension. Although the exact mechanism of its antihypertensive effect is not known, propranolol is known to work through several mechanisms including peripheral vasodilation, central sympathetic blockage, cardiac output reduction, and renin–angiotensin–aldosterone–sympathetic axis inhibition.[11] Further, the anxiolytic effect of propranolol is also well known.[23] Based on all these factors, presently, propranolol is being considered for the treatment of resistant arterial hypertension. A randomized, double-blind, placebo-controlled trial (APROPRIATE study, N = 200) is currently ongoing to evaluate the effect of propranolol, when added to a multidrug regimen, in resistant hypertension.[24]

Noncardiovascular indications

Migraine

Migraine is one of the most common causes of primary headaches. It is a debilitating disease that is characterized by episodes of unilateral throbbing headache associated with symptoms such as nausea, vomiting, photophobia, and phonophobia.[25] Management mainly aims to reduce frequency, duration, and severity of migraine attacks; increase responsiveness of acute attacks to abortive therapy; and improve quality of life. First-line drugs for migraine prophylaxis include divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, and timolol.[26,27]

Rabkin *et al.* accidentally found the therapeutic effect of propranolol for migraine while they were studying its use

in the management of angina pectoris.[2] Since then, several studies have been conducted wherein propranolol was found to be safe and effective in managing migraine headaches.[28-31] Holroyd *et al.* conducted a meta-analysis to evaluate results from 53 such studies ($N = 2403$) that assessed the effect of propranolol on migraine headaches. Reduction in migraine activity was 44% (when daily headache recordings were used to assess efficacy) and 65% (when less conservative measures such as clinical ratings of improvement and global patient reports were used to assess efficacy) for propranolol and only 14% for placebo.[32] A Cochrane review conducted by Linde and Rossnagel evaluated 58 clinical trials assessing efficacy and safety of propranolol compared to placebo and other drugs (including other beta-blockers, calcium antagonists, and several other drugs) in adults with migraine. The results showed propranolol to be more effective than placebo and as effective and safe as other drugs.[33]

Recently, He *et al*. conducted a network meta-analysis to compare various migraine prophylactic medications. A network meta-analysis is a relatively new concept in which multiple treatments are compared by direct comparisons of interventions within randomized controlled trials, and indirect comparisons are also made across studies based on a common comparator. The medications compared by He *et al*. included topiramate, gabapentin, propranolol, amitriptyline, divalproex, and valproate. Of these six medications studied, propranolol, topiramate, and divalproex demonstrated significantly less average migraine headache days compared to placebo (topiramate: −1.20, 95% CI: −1.83–−0.70; propranolol: −0.98, 95% CI: −1.86–−0.07; divalproex: −1.28, 95% CI: −2.44–−0.27). Moreover, patients with topiramate or propranolol also exhibited significantly reduced headache frequency compared to placebo (topiramate: −1.17, 95% CI: −1.98–−0.35; propranolol: −1.37, 95% CI: −2.49–−0.29). Further, propranolol was found to be safer and more tolerable when compared to topiramate (propranolol vs. topiramate, all adverse events: odds ratio (OR): 0.57, 95% CI: 0.36–0.90; withdrawal: OR: 0.66, 95% CI: 0.44–0.99; withdrawal due to adverse events: OR: 0.58, 95% CI: 0.37–0.91) and divalproex (divalproex vs. propranolol, all-cause withdrawal, OR: 2.09, 95% CI: 1.11–4.52). Thus, considering all the parameters together, propranolol was the most beneficial treatment for migraine.[34]

Propranolol has also been shown to be effective in pediatric migraine. In a Cochrane review of controlled trials to assess the agents used for migraine treatment in children, of the several drugs studied, propranolol (propranolol vs. placebo: OR: 27.6, 95% CI: 6.58–115.77, $P < 0.001$) was one of the two drugs that were found to be effective.[35] In a randomized double-blind trial which compared propranolol with sodium valproate for migraine prophylaxis in pediatric patients, while both drugs were found to be equally effective in all other parameters, the reduction in baseline headache frequency was better with propranolol ($P = 0.044$).[36] Hence, the beneficial effect of propranolol in reducing headache frequency as seen in the network meta-analysis described above seems to be also relevant in pediatric population.

Essential tremors

Essential tremors are involuntary, rhythmic, and oscillatory movements that occur when the limb is held in a fixed posture against gravity or during active movement but are absent at rest (except in advanced cases). When severe, they can affect daily activities such as writing, eating, and dressing and may lead to psychosocial impairment with poor quality of life.[37] Pharmacotherapy is recommended when tremors start to affect activities of daily living. Propranolol and primidone (anticonvulsant medication) are the first-line medications used, and propranolol is the only drug approved by the United States Food and Drug Administration (FDA) for the treatment of essential tremors.[38] Efficacy of propranolol in the treatment of essential tremors was first reported in the early 1970s. The exact mechanism of propranolol in essential tremors is not yet clear. However, it is believed that the blockade of peripheral noncardiac beta-2 receptors located in muscle spindles accounts for antitremor effects.[38] Evidence-based guidelines by the American Academy of Neurology published in 2011 recommend propranolol and primidone as the first line of treatment (Level A, established as effective) for essential tremors.[39] It has been observed that about 50%–70% of the patients respond to propranolol and 50% respond to primidone, when compared to placebo. In addition, the dropout rate with propranolol is <20% while that for primidone is 20%–30%.[38] Thus, propranolol appears to have an advantage over primidone. Moreover, because of limited availability of primidone in India, propranolol turns out to be the first choice.[40]

Anxiety

The International Classification of Disease-10 by the World Health Organization classifies anxiety into four categories as follows: phobic anxiety disorder (agoraphobia with/without panic disorder, social phobias, and specific phobia); other anxiety disorder (panic disorder, generalized anxiety disorder [GAD], mixed anxiety, and depressive disorder); obsessive-compulsive disorder; and reaction to severe stress and adjustment disorders (acute stress reaction, posttraumatic stress disorder [PTSD], and adjustment disorders).[23] Management of anxiety disorders includes a combination of cognitive behavioral therapy and pharmacotherapy. Commonly used therapeutic agents for anxiety disorders include selective serotonin reuptake inhibitors, venlafaxine, tricyclic antidepressants, and benzodiazepines.[23] The autonomic hyperactivity and hyperarousal associated with anxiety disorders respond well to propranolol. Propranolol is used to suppress the physical symptoms associated with GAD that are caused by noradrenergic stimulation such as tachycardia, palpitations, sweating, and tremors. Propranolol can also be prescribed to be taken before a public performance situation such as delivering a lecture or singing in a concert.[23,41] Propranolol has been effectively used to treat perioperative anxiety. In a randomized, double-blind study, anxiety and

depression scores were significantly lower in the propranolol group ($P < 0.0001$) when compared to the placebo group.[42] Another study compared the efficacy and safety of propranolol in patients receiving two different doses of propranolol (20 mg and 40 mg) with those not receiving any anxiolytic medication. Anxiolysis scores improved significantly in propranolol groups compared with control group ($P < 0.05$).[43]

Propranolol was first used for anxiety in the 1960s.[10] In the initial years, its use in psychiatry was thought to be limited only to anxiety. However, this seems to be changing in the recent years. Studies have shown that propranolol can alter the way memories are stored in the brain and can have an amnestic effect on unpleasant memories.[44,45] This finding has led to a number of studies evaluating propranolol in PTSD. A study by Vaiva *et al*. reported that PTSD symptoms were reduced in patients with trauma exposure receiving propranolol as compared to those not receiving the drug ($P = 0.037$).[46] As per Mahabir *et al*., propranolol not only alleviates the unpleasant memories related to a traumatic event but also seems to improve cognitive function in these patients.[47]

Portal hypertension

Portal hypertension is the increase in portal venous pressure and is defined as hepatic venous pressure gradient (HVPG) of more than 5 mmHg. Only a HVPG of 10 mmHg or more leads to complications such as development of varices, decompensation of cirrhosis, and hepatocellular carcinoma and is therefore considered clinically significant.[48] The gastrointestinal varices that are caused by portal hypertension may cause variceal hemorrhage, and the main aim of management is to prevent hemorrhage. Treatment options include nonselective beta-blockers such as propranolol and endoscopic variceal ligation (EVL). The mechanism of action of propranolol in portal hypertension is through both beta-1 and beta-2 receptors. Beta-1 blockade causes decrease in cardiac output, thus decreasing portal blood flow. On the other hand, beta-2 blockade decreases portal blood flow by splanchnic vasoconstriction via unopposed alpha-adrenergic activity.[49,50]

Studies comparing propranolol and EVL have found both these measures to be equally effective.[51,52] However, EVL is a fairly invasive procedure and is associated with consequent risks. Propranolol is easy to administer, is cost-effective, and is not associated with any procedural risks.[50,52,53] It is, therefore, considered as the first line of treatment. Moreover, propranolol is also believed to have a role in preventing spontaneous bacterial peritonitis which seems to be responsible for variceal bleeding in cirrhotic patients. This beneficial effect of propranolol is due to reduction in bacterial translocation by increasing intestinal transit and decreasing the splanchnic blood flow, thus reducing mucosal edema and congestion.[54]

Management is also based on the type of varices. In patients with small varices but high risk of bleeding, propranolol is recommended as EVL may be technically difficult in these patients. Patients with medium to large varices can be treated with either propranolol or EVL.[50,51] The combination of propranolol and EVL is used in the prevention of recurrent variceal hemorrhage.[49]

A study by Heebøll *et al.* found a positive association between a high native HVPG and a reduction in HVPG following propranolol treatment, thus demonstrating that treatment with propranolol is also effective in patients with advanced portal hypertension.[55] A recent study by Kim *et al.* compared the effectiveness of candesartan and propranolol combination therapy with propranolol monotherapy in reducing portal hypertension in patients with cirrhosis. The study reported no significant difference in pressure reduction between the combined therapy and monotherapy ($P = 0.674$). Therefore, addition of candesartan to propranolol in treating patients with portal hypertension is not recommended.[56] It has been suggested in past that the use of beta-blockers in cirrhotic patients with decompensation may not be associated with favorable outcome. However, a recent study that retrospectively evaluated a large cohort of 2419 patients with cirrhosis and portal hypertension found that all-cause mortality was lower in patients taking nonselective beta-blockers (propranolol, nadolol, and carvedilol) than in those not on beta-blockers.[57]

Other indications

Hyperthyroidism

In hyperthyroidism, there is an increased level of thyroid hormones in the circulation which leads to tachycardia, palpitations, tremors, and anxiety. Propranolol has been widely used to treat these beta-adrenoreceptor effects in hyperthyroidism. In addition to relieving the troublesome symptoms of hyperthyroidism, propranolol is known to have an additional advantage of decreasing the peripheral conversion of thyroxine to triiodothyronine, which is a biologically active hormone.[58] Any thyrotoxic patient being planned for surgery must be clinically and biochemically euthyroid. Propranolol is a beta-blocker which is most commonly used for this purpose and has been found to be safe and effective.[59,60]

Pheochromocytoma

The primary treatment option for pheochromocytoma, which is a catecholamine-secreting tumor of the adrenal gland, is surgical resection. However, surgery is usually associated with high risk due to serious cardiovascular complications caused by release of huge amounts of catecholamines during surgical manipulation of the tumor. Pretreatment with a combination of an alpha-adrenergic blocker such as phenoxybenzamine and beta-blocker propranolol helps in preventing such complications.[61,62]

Recent advances

The first report of the use of propranolol in infantile hemangioma was published in 2008.[63] Further studies have reported propranolol to be safe and effective for this indication.[64-66] Recently, propranolol has also shown promise in certain other conditions. A small study ($N = 17$) showed that in substance-dependent subjects, drug-related memory reactivation under propranolol reduced craving.[67] In another study, propranolol was associated with less cancer-related

psychological distress in patients newly diagnosed with cancer.[68] Furthermore, potential benefits of perioperative propranolol in decreasing perioperative tumor growth have been suggested.[69] All these indications need to be explored further, thus warranting additional studies.

Safety of Propranolol

Propranolol is generally well tolerated. Common adverse events include gastrointestinal disturbances, bradycardia, hypotension, bronchospasm, exertional dyspnea, hypoglycemia, dizziness, fatigue, and insomnia. These are usually mild and can be managed conservatively without requiring discontinuation of medication. Further, propranolol has demonstrated safety for use in pediatric patients.[11,17,36,38,70]

Summary and Future Directions

In summary, propranolol was first developed to treat cardiovascular diseases but soon became the clinician's armamentarium to manage a wide range of other conditions. Propranolol is very effective in managing symptoms caused by sympathetic hyperactivity associated with anxiety disorders, hyperthyroidism, and pheochromocytoma. Further, it is used for preparing patients for surgery in hyperthyroidism and pheochromocytoma. Beta-adrenergic blockade by propranolol also helps in reversing the hemodynamic abnormalities in portal hypertension and is widely used for primary and secondary prophylaxis of variceal bleeding. Propranolol is the only drug approved by the FDA for the treatment of essential tremors. In addition, propranolol is cost-effective compared to other available treatment options. Although propranolol has now been around for more than 50 years and has been proven to be safe and effective in a myriad of conditions, it appears that its potential is yet to be completely explored.

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Conflicts of interest

There are no conflicts of interest.

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