MAOIs, blood pressure, and propranolol

Abstract

Propranolol (predominantly a beta-2 blocker) prevents both the post-dose elevation of blood pressure that some people experience, especially after larger doses of MAOIs, and the **exercise-induced hypotension**. Might they also help the excessive orthostatic hypotension that is manifest, in the absence of exercise, by some patients on MAOI drugs? That last question is yet to be verified by controlled experiments in a larger number of patients.

> **Terms: beta-blockers**, aka β-blockers, β-adrenoceptor antagonists
> [in this text I will use the term beta-blockers because some typefaces do not translate the Greek character, thus, when typeface substitution occurs characters are not rendered correctly]
> **Postural, or orthostatic hypotension**: the significant drop in blood pressure that occurs when going from lying or sitting to the standing position

Introduction

This potential solution to the problem of excessive orthostatic hypotension, which is sufficiently severe to be problematic in a proportion of patients, might be of immediate use and benefit to anyone who is currently experiencing symptoms due to hypotension — it involves taking a therapeutic dose of **propranolol**, discussed below, either as needed, or regularly twice a day. There appear to be parallels with postural tachycardia syndrome (POTS) [1, 2].

> It is remarkable that this phenomenon has been overlooked for so long

Recent information and discussion in my International MAOI Expert Group is informed by other eminent world experts in pharmacology and related fields. This little-known quirk of pharmacology has generated discussion of what may be a long-overlooked and simple solution for **low blood pressure (hypotension)** problems experienced by those taking MAOIs.

The story started with an observation by one of the group members who is an eminent professor of pharmacology and toxicology (Professor Ian Whyte from Newcastle in Australia, who has published many seminal papers). He demonstrated that **propranolol** prevented **post-exercise hypotension** in an individual patient: this phenomenon was consistent and well documented by reliably done, repeated, and clear differences in blood pressure readings. This was mentioned in discussions on the group around the time the COVID epidemic started: that may have played a part in distracting everyone's attention, because it seems to have been forgotten about. I suggested it in one or two patients who sought advice from me over the Internet and although it was clear that propranolol was preventing the **post-dose hypertension**; no one produced enough blood pressure readings to definitively support that it prevented **exercise-induced hypotension**, although several people reported that, subjectively, it had helped.

> An important question, that could be resolved simply, is whether propranolol lessens the sometimes-encountered more severe postural hypotension.
> Step forward 'citizen scientists'!

It may be that, because the main thrust of the discussion was preventing post-dose **hypertension**, the idea they might also prevent **hypotension** just did not stick in anyone's mind. Furthermore, the idea that propranolol might prevent both hypertension and hypotension seems counter-intuitive.

Whatever the explanation of the group's failure to follow up on this idea, something happened recently which made me go back and look at what Professor Whyte had said and recense the discussion and re-present it to the group. That produced comments and ideas which I hope will generate more systematic research. This is a summary of the thinking thus far.

The mechanisms

Beta-blockers are generally regarded as hypotensive agents; however, they produce their effect by slowing the heart rate and by reducing cardiac output, not by reducing resistance to blood-flow (i.e., **systemic vascular resistance [SVR]**).

There are three beta-adrenoceptor subtypes beta-1, beta-2 and beta-3 which are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline.

Beta-1 are in cardiac tissue, and beta-2 are mainly found in the smooth muscle of arterioles regulating blood flow to various tissues and organs, and in bronchioles etc. Skeletal muscle arterioles express particularly high levels of beta-2 vs. alpha-1 adrenoceptors.

Noradrenaline is a weaker agonist than adrenaline at human beta-2 adrenoceptors [3].

Resting vascular tone is alpha-1 mediated, phentolamine (an alpha-1 antagonist) produces orthostatic hypotension, because reflex vasoconstriction is reduced.

Antagonism of beta-1 adrenoceptors in cardiac tissue has negative chronotropic and inotropic effects which decrease blood pressure and oxygen demand, hence improving angina. They prolong the atrial refractory periods and have an antiarrhythmic effect.

Stimulation of beta-2 receptors has vaso-dilatory effects

Intrinsic sympathomimetic activity (ISA), an old term, is now understood and is due to **partial agonist activity at beta-2 adrenoceptors** — thus producing a lesser response than the endogenous ligands (adrenaline, noradrenaline) and other full beta-agonists.

Physiology

The effect of beta-blockers may vary according to the existence or absence of a pathological, or drug-induced, condition, such as essential hypertension, the effects of MAOIs, and according to the basal state of the system. This is particularly relevant to dilation and constriction of arterioles.

Normally, with exercise, and other stimuli, arterioles supplying muscular tissue dilate under the influence of **adrenaline-induced beta-2 stimulation,** facilitating increased blood flow — this lowers SVR and BP. The effect of drugs that are **predominantly beta-2 blockers** (propranolol is the only one generally available for clinical use) is to block that vaso-dilation of the arterioles, thus preventing the lowering of SVR and BP.

The threshold concentration for activation of beta-2 receptors is lower than that for alpha-receptors, thus in physiological states adrenaline predominantly stimulates beta-2 receptors. Both types of receptors are activated at high concentrations of adrenaline. Therefore, alpha-mediated vasoconstriction becomes a factor only at higher concentrations of adrenaline.

The adrenal gland is effectively a post-ganglionic nerve ending which releases adrenaline upon stimulation. Circulating adrenaline is the primary catecholamine active during exercise — it is responsible for the beta-2-mediated vasodilation in skeletal muscle. In **unmedicated subjects** a failure of alpha-mediated vasoconstriction is a potent cause of orthostatic hypotension (e.g. POTS), the physiological response to which is a reflex

tachycardia, which maintains blood flow to critical organs. **But, in the presence of beta-1 blockade, this reflex tachycardia response will be blunted with consequent exacerbation of hypotension** (because beta-1 receptor stimulation mediates increased heart rate and contractility). Drugs like metoprolol and atenolol, which are predominately beta-1 blockers, would be relatively, or absolutely, contraindicated because of the inhibition of compensatory reflex tachycardia.

MAOIs and BP

In the presence of alpha-adrenoceptor blockade/dysfunction, which is theorised to be the most likely reason for the orthostatic hypotension in patients on MAOIs*, the vaso-constriction does not occur, and vaso-dilation strongly predominates.

> Systemic vascular resistance and BP fall due to activation of beta-2 adrenoceptors in arterioles

An alpha-adrenoceptor antagonist, or relative alpha-blockade due to false neurotransmitters*, will cause the vasodilation in muscle to have more pronounced effect, SVR is decreased, no reflex tachycardia occurs and therefore BP decreases to a relatively greater degree. Thus, in the presence of significant alpha-adrenoceptor antagonist activity (direct or indirect), unopposed beta-2 adrenoceptor activity when adrenaline is released during exercise produces a greater fall in blood pressure.

> *Because MAOIs are thought to lead to an increase of octopamine and similar compounds, which are taken up into sympathetic nerve terminals and act as false neurotransmitters, thereby reducing the effect of noradrenaline. This also effectively reduces stimulation at alpha receptors, thus lowering BP — when adrenaline levels increase, this effect becomes more pronounced, 'adrenaline reversal'.

Adrenaline reversal

When elevated concentrations of adrenaline are present, either during exercise, or in other situations, then an exaggerated response, '**adrenaline reversal' occurs**. This term describes a reversal of the BP effect of large doses of adrenaline, from a pressor response (mediated by alpha receptors) to a **depressor response** (mediated by beta-2 receptors). NB phenylephrine and noradrenaline lack sufficient beta-2 effects to cause this reversal.

As summmarised by Katzung et al. [4]:

> In conclusion, the alpha blockers phentolamine and phenoxybenzamine in acute experiments decrease the blood pressure more than does complete interruption of the sympathetic tone. This seems mainly due to the reflex increase in adrenaline output that in turn stimulates beta2 receptors and thus further decreases vascular resistance and hence blood pressure (and of course increases the heart frequency). **The hypotensive effect can effectively be reversed by beta blockers with beta2-receptor blocking properties.**

A variety of physical and psychological stimuli produce increases in adrenaline concentrations and such stimuli may therefore be relevant to this mechanism of hypotension — **examples are, stress, anxiety, excitement, noise, cold, heat, and pain.** It is thus possible they may influence the propensity to excessive hypotension.

It is relevant to note that in the postural orthostatic tachycardia syndrome (POTS) propranolol improves symptoms **including orthostatic hypotension** — the symptoms described include, dizziness, **light-headedness, headache, brain fog, fatigue,** blurred vision, nausea, palpitations, tremulousness, and weakness [1, 2, 5].

> The non-pharmacological treatment of POTS includes recommending a salt intake of 10–12 g per day. Atomoxetine has been found to be more effective than midodrine

Available beta-blockers

There are more than a dozen different beta-blockers in clinical use worldwide and they should not be regarded as a homogenous group, their differing pharmacological properties are described here [6, 7].

> The only drug with the correct receptor profile for this purpose is propranolol, and it has an appropriately short half-life

No drugs currently on the market are specific beta-2 antagonists.

Propranolol blocks beta-2 and beta-1 receptors, it is somewhat beta-2 selective [8]. The half-life is ~4 hours [3], and the peak concentration is 1 to 2 hours after ingestion on an empty stomach.

The main currently available beta-blocker with significant partial agonist (ISA) activity is pindolol.

Metoprolol, and atenolol show moderately high selectivity for the beta-1 vs. beta-2 receptor [3] and are **therefore not suitable in this context**.

Other non-selective beta-2-adrenergic receptor antagonists are, Nadolol, Timolol, and Pindolol. Nadolol is not widely available, timolol is only available as eye drops, and pindolol has significant partial agonist [ISA] activity which may make it unsuitable.

Although usual starting doses of propranolol are 40–80 mg/day, in divided doses, **for this indication it may be better to start with 10 or 20 mg.**

Incidentally, the evidence that beta-blockers help anxiety disorders is equivocal, although they are useful for tremor related to performance anxiety in people like musicians — they have been banned in competitive sports, e.g., for rifle shooters [9].

Uses and contra-indications

Clinically beta-blockers are commonly used for hypertension, ischaemic heart disease, heart failure, anxiety, tremor, migraine, and glaucoma.

Side effects include bradycardia, gastrointestinal issues, abdominal pain, nausea, erectile dysfunction, asthma & bronchospasm, and cold extremities. Propranolol can also cause or exacerbate, in those who already have a depressive illness, the symptoms of drowsiness, fatigue, and bad dreams — there is little evidence it precipitates depression *de novo*.

As well as causing cold hands and feet beta-blockers can precipitate Raynaud's phenomenon. Reduction of renal blood-flow may have adverse consequences.

Whether propranolol, as a PRN medication or for short-term use, is absolutely contraindicated in patients with asthma or COPD is an open question which requires a balance to be made between advantages and disadvantages. Its use, especially short-term or as needed use, may be warranted [10-17].

Conclusion

The effect of propranolol on the post-dose hypertension and exercise-induced hypotension appears paradoxical: that 'adrenaline-reversal' paradox is explained above in the context of the administration of MAOIs. Propranolol prevents both the hypertension and the hypotension. The question yet to be answered is whether — contrary to expectation — propranolol might also ameliorate the more severe orthostatic hypotension that occurs in a small proportion of patients, which is sometimes of a problematic degree. In this context, hypotension is caused by adrenaline, mediated by beta-2 receptor activation, that can be brought about by various stimuli, including anxiety. Thus, propranolol may have a wider application than thus-far appreciated.

When hypotension is mediated by beta-2 activation, brought about by stimuli other than exercise, e.g., anxiety, then propranolol may ameliorate it

Most patients on MAOIs get a significant, but not problematic, orthostatic drop in blood pressure. Only a small proportion of patients get excessive hypotension, perhaps because they are sensitive to the effects of adrenaline for some reason, perhaps because of pre-existing autonomic dystrophy (e.g. POTS), or because they have higher adrenaline concentrations. There seems to be a dichotomy between the typical modest drop of BP, versus the problematic drop in BP shown by a lesser proportion of patients — it may be that this group benefits from propranolol.

Straightforward clinical observations, that can be made by patients themselves, and clinicians, should settle this important and relevant issue now that it has, for the first time, been clearly described and explained.

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