Chapter 4

Mode of Action of a Combination of Bisoprolol and Amlodipine

Ningling Sun
Department of Cardiovascular & Hypertension Center,
Peking University People's Hospital, Beijing, China

Cardioselective (β_1-adrenoceptor selective) β-blockade reduces blood pressure (BP) in hypertension mainly via reductions in heart rate and cardiac output, and suppression of the renin-angiotensin-aldosterone system. Calcium channel blockers (CCBs) reduce BP by peripheral arteriolar vasodilatation. Bisoprolol, a highly β_1-selective β-blocker, and amlodipine, a long-acting dihydropyridine calcium channel blocker, represent an effective choice of antihypertensive combination therapy due to these complementary antihypertensive mechanisms.

Introduction

Current guidelines for the management of hypertension provide strong support for the use of antihypertensive combination therapy to achieve adequate control of BP in people with hypertension [1, 2]. The guidelines also emphasise the use of combinations using agents from different

classes of antihypertensive drugs, as this approach is likely to provide (at least) additive effects on BP. This chapter will consider the mode of action of two established antihypertensive therapies supported by a substantial evidence base: the selective β_1-adrenoceptor antagonist, bisoprolol, and the dihydropyridine CCB, amlodipine. The early parts of the chapter will focus on the properties of these two agents individually, followed by consideration of how these agents work together in combination.

Therapeutic properties of bisoprolol and amlodipine

Overview of the β-blocker class

Main subtypes of β-blockers

Although there are many β-blockers approved for clinical use, this is a very diverse and heterogeneous class of drugs. Individual members of the class vary in terms of their selectivity for subtypes of the β-adrenoceptor, their potential for acting as partial agonists at the β_1-adrenoceptor (intrinsic sympathomimetic activity [ISA]), actions at other receptors present in the heart and/or vasculature, and their lipophilicity (Table 1) [3–11].

Cardioselective agents without ISA

All β-blockers reduce BP by reducing activation of the sympathetic nervous system and suppression of the renin-angiotensin-aldosterone system [4, 12]. The degree of selectivity for β_1-adrenoceptors and the presence or absence of ISA are important features that distinguish between β-blockers. Cardioselective, or β_1-adrenoceptor selective β-blockers, reduce BP by reducing heart rate and cardiac output, with limited effect on the peripheral vasculature [4, 13]. Non-selective β-blockers, by contrast, increase peripheral resistance by opposing β_2-adrenoceptor-mediated vasodilatation [13, 14].

Bisoprolol, metoprolol, atenolol, and esmolol, have all been described as β_1-selective, without ISA (Table 1). A study in animal tissues *in vitro* reported that nebivolol was highly selective for β_1- versus β_2-adrenoceptors [15], and studies in human myocardium [16, 17] and a study involving administration of a β_1-agonist to human volunteers [18] demonstrated greater β_1- versus β_2-adrenoceptor selectivity for nebivolol versus bisoprolol. However, a head-to-head comparison of this agent and bisoprolol in human myocardium *in vitro* showed that bisoprolol had 16–20-fold greater selectivity for β_1- versus β_2-adrenoceptors, compared with only 3–4-fold selectivity for nebivolol; similar results were obtained using a cultured cell line [19]. The usual dose of bisoprolol (10 mg/day) has been reported to avoid significant blockade of β_2-adrenoceptors, while atenolol blocks about one-quarter of β_2-adrenoceptors at its usual dose of 100 mg/day [20]. Another experimental study demonstrated greater β_1-selectivity for bisoprolol versus atenolol [21]. Studies using cloned human β-adrenoceptors also showed that bisoprolol was more β_1-selective than atenolol or metoprolol. Finally, esmolol is a very short-acting agent used mainly intravenously in the emergency setting for the control of heart rate during supraventricular tachycardia or atrial fibrillation, and is not used clinically for the management of hypertension [22].

The data as a whole confirm that bisoprolol is highly β_1-selective, although, the relative β_1-selectivity of bisoprolol and nebivolol is unclear, and bisoprolol is more β_1-selective than atenolol or metoprolol. There is no clear evidence for additional clinical benefits associated with enhanced nitric oxide release by nebivolol, which occurs secondary to stimulation of β_2- and β_3-adrenoceptors [23].

Cardioselective agents with ISA

Xamoterol, acebutolol, celiprolol and nevibolol are β_1-selective agents with ISA (Table 1). ISA tends to limit reductions in heart rate and cardiac output during β-blockade and can limit adverse metabolic effects associated with a pack of cardioselectivity (see below) [24]. However, the presence of ISA appears to blunt the beneficial outcomes seen in several studies with cardioselective β-blockers in patients with heart failure [23].

Table 1 Overview of the mechanistic properties of the β-blocker class [3–11].

	β_1-selective?	ISA?	Other clinically significant actions?	Lipophilicity?
Bisoprolol	**Yes**	**No**	**–**	**Moderate**
Metoprolol	Yes	No	–	High
Atenolol	Yes	No	–	Low
Esmolol	Yes	No	Short-acting	Low
Xamoterol	Yes	Yes	–	Low
Acebutolol	Yes	Yes	β_2 agonist	Moderate
Celiprolol	Yes	Yes	β_2 agonist α_1 antagonist	Low
Nevibolol	Yes	Yes	Activates NO synthesis[a]	Moderate
Propranolol	No	No	–	High
Sotalol	No	No	Class III antiarrhythmic	Low
Timolol	No	No	–	High
Carvedilol	No	No	α_1 antagonist	Moderate
Pindolol	No	No	β_2 agonist	Moderate
Oxprenolol	No	No	–	High
Labetolol	No	No	α_1 antagonist	Low
Bucindolol	No	Mild	α_1 antagonist	High

ISA: intrinsic sympathomimetic activity; NO: nitric oxide.
[a]Via activation of β_2-and β_3-adrenoceptors.
Compiled from information presented in references [3–11].

Non-cardioselective agents

Blockade of β_2-adrenoceptors by non- (or less) cardioselective β-blockers is more likely than by cardioselective agents to induce potentially serious side effects such as bronchospasm, compared with non- (or less) cardioselective agents [25]. As an example, current European prescribing information states that bisoprolol (highly β_1-selective) must be used with caution in patients with bronchial asthma or obstructive airways diseases, while propranolol (non-selective) is formally contraindicated in patients with a history of bronchial asthma or bronchospasm. The use of a cardioselective agent may reduce the risk of other side effects commonly attributed to β-blockade, such as cold extremities, metabolic disturbances and erectile dysfunction in men [8].

Lipophilicity/hydrophilicity

The lipophilicity of a β-blocker determines its ability to cross the blood-brain barrier, and consequently the possibility for it to exert an effect in the central nervous system (CNS). However, the lipophilicity of a β-blocker per se does not predict the extent to which its therapeutic actions will be mediated by an effect in the CNS, as has been described for hydrophilic β-blockers such as atenolol [3].

Therapeutic properties of amlodipine

Overview of the CCB class

CCBs are also a heterogeneous class of drugs [26–28]. There are three classes of CCBs: most agents in use are dihydropyridines (including amlodipine), while the phenylalkylamine and benzothiazepine classes are each represented by a single agent in current clinical use (verapamil and diltiazem, respectively). All CCBs block the L-type calcium channel, although verapamil and diltiazem interact with the channel at different sites than dihydropyridine CCBs. Blockade of these channels reduces the influx of calcium into smooth muscle cells that is required to maintain contractility. The net result of this action in the vascular system is vasodilatation. All CCBs reduce BP by inducing peripheral arteriolar vasodilatation, with the dihydropyridines more potent in this regard [29]. Dihydropyridines have little potential for reducing cardiac contractility in clinical use, although this may occur during treatment with the other CCB classes, especially verapamil [27].

The duration of action of CCBs (Table 2) varies widely from nifedipine (plasma elimination half-life 2–5 h) to amlodipine (plasma elimination half-life 30–50 h) [26–28]. A number of agents employ sustained release tablets to prolong their action and reduce the number of tablet intakes/day, while amlodipine is administered once daily without the need for use of a sustained release preparation. The long duration of action of amlodipine has clinical significance, in that superior control of BP

Table 2 Overview of calcium channel blockers [26–28].

	DHP?	Cardiac contractility	Heart rate	Peripheral vasodilatation	Plasma half-life (h)[a]
Amlodipine	**Yes**	**–**	**–**	**+++**	**30–50**
Felodipine	Yes	–	–	+++	11–16
Lacidipine	Yes	–	–	+++	13–19
Lercanidipine	Yes	–	–	+++	8–10
Nicardipine	Yes	–	–	+++	2–4
Nifedipine	Yes	–	–[b]	+++	2–5
Nimodipine	Yes	–	–	+++	1–2
Isradipine	Yes	–	–	+++	8
Verapamil	No[c]	↓↓	↓↓	++	3–7
Diltiazem	No[d]	↓	↓	++	3–6

DHP: dihydropyridine; h: hour.
[a]For immediate-release formulations.
[b]Short-acting agents such as nifedipine may cause reflex tachycardia, but this is mitigated by the use of prolonged-release formulations; higher doses of all agents may increase heart rate.
[c]Phenylalkylamine.
[d]Benzothiazepine.
'–' indicates little or no effect.
'++' and '↓' indicate moderate effect.
'+++' and '↓↓' indicate strong effect.
Compiled from information presented in references [26–28] and the Summaries of Product Characteristics at www.medicines.org.uk/emc (June 2022).

throughout the 24-hour dosing interval has been reported for amlodipine versus agents with a shorter duration of action administered once daily [30]. In addition, the long duration of action of amlodipine provides a sustained antihypertensive effect even in the common setting of one or two missed doses, in contrast to a shorter-acting antihypertensive agent [31]. Short-acting CCBs administered without a sustained-release formulation may induce reflex tachycardia [27].

Verapamil (especially) and diltiazem reduce heart rate via an action on the atrioventricular node and verapamil can be useful in controlling the ventricular rate during episodes of supraventricular tachycardia or atrial fibrillation when administered intravenously. For this reason, these agents are contraindicated in patients with second- or third-degree atrioventricular block, or severe bradycardia. Dihydropyridine CCBs do not have a clinically significant action at the atrioventricular node.

Amlodipine and bisoprolol together: implications for clinical practice

Current European guidelines for the management of arterial hypertension give strong support to the use of two-drug combinations of antihypertensive agents from the time of diagnosis of hypertension [1]. Use of combination therapies with distinct modes of action facilitates additive effects on BP. Indeed, a large meta-analysis of studies evaluating antihypertensive combination therapies of different classes found that the effects of two-drug combinations on BP were close to that predicted from adding together the expected effects of each agent had they been used as monotherapy [32].

Several factors identify amlodipine and bisoprolol as suitable for co-administration in a combination tablet:

Proven efficacy in the management of hypertension: Both bisoprolol and amlodipine have been used in the management of hypertension for about 30 years, and are indicated for this purpose. Both agents are also indicated for the management of angina. Numerous clinical studies have confirmed the efficacy of these agents in these conditions (reviewed elsewhere [8, 33, 34]). The efficacy of bisoprolol and amlodipine in combination is described in Chapter 6.

Complementary mechanisms of BP reduction: Bisoprolol is a non-vasodilatory β-blocker, while amlodipine is a CCB that induces peripheral vasodilation. A study in 78 patients with hypertension showed that markers of sympathetic nervous activation were elevated in about 70% of patients. Bisoprolol and a CCB, verapamil, reduced different markers of sympathetic activity, consistent with an action involving distinct, but complementary, mechanisms [35]. Therefore, β-blockade and calcium channel blockade fulfil the key criterion for inclusion within a combination of being from distinct pharmacological classes.

Once-daily dosing: Once-daily dosing is required for the management of hypertension, to limit the complexity of the treatment regimen. The elimination half-life of amlodipine is 30–50 h, as described above, and that of bisoprolol is 9–12 h, and the antihypertensive effect of each agent is maintained over the 24-hour dosing interval [36]. Both

of these drugs are therefore suitable for once-daily dosing, and are used once daily in the routine management of hypertension (and angina pectoris). Chapter 5 describes pharmacokinetic studies with the bisoprolol-amlodipine combination tablet in more detail.

Conclusions

Rational partners for antihypertensive combination therapy should act via complementary mechanisms. Cardioselective (β_1-adrenoceptor selective) β-blockade reduces BP mainly via actions on the heart (reductions in heart rate and cardiac output) and via suppression of the renin-angiotensin-aldosterone system and sympathetic nervous activity. CCBs are peripheral arteriolar vasodilators. Together, these are potent mechanisms for controlling hypertension, and bisoprolol, a highly β_1-selective β-blocker, and amlodipine, a long-acting dihydropyridine CCB, represent an effective choice of antihypertensive combination therapy.

References

1 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.

2 Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115. https://doi.org/10.1161/hyp.0000000000000065.

3 Drayer DE. Lipophilicity, hydrophilicity, and the central nervous system side effects of beta blockers. Pharmacotherapy. 1987;7:87–91. https://doi.org/10.1002/j.1875-9114.1987.tb04029.x.

4 Poirier L, Tobe SW. Contemporary use of β-blockers: clinical relevance of subclassification. Can J Cardiol. 2014;30:S9–s15. https://doi.org/10.1016/j.cjca.2013.12.001.

5 Kendall MJ, John VA. Oxprenolol: clinical pharmacology, pharmacokinetics, and pharmacodynamics. Am J Cardiol. 1983;52:27d–33d. https://doi.org/10.1016/0002-9149(83)90639-2.

6 Smart NA, Kwok N, Holland DJ, Jayasighe R, Giallauria F. Bucindolol: a pharmacogenomic perspective on its use in chronic heart failure. Clin Med Insights Cardiol. 2011;5:55–66. https://doi.org/10.4137/cmc.S4309.

7 Pathak A, Mrabeti S. β-blockade for patients with hypertension, ischemic heart disease or heart failure: where are we now? Vasc Health Risk Manag. 2021;17:337–48. https://doi.org/10.2147/vhrm.S285907.

8 AlHabeeb W, Mrabeti S, Abdelsalam AAI. Therapeutic properties of highly selective β-blockers with or without additional vasodilator properties: focus on bisoprolol and nebivolol in patients with cardiovascular disease. Cardiovasc Drugs Ther. 2021. https://doi.org/10.1007/s10557-021-07205-y.

9 Nawarskas JJ, Cheng-Lai A, Frishman WH. Celiprolol: a unique selective adrenoceptor modulator. Cardiol Rev. 2017;25:247–53. https://doi.org/10.1097/crd.0000000000000159.

10 MacNeil DJ. The side effect profile of class III antiarrhythmic drugs: focus on d,l-sotalol. Am J Cardiol. 1997;80:90g–8g. https://doi.org/10.1016/s0002-9149(97)00718-2.

11 Oliver E, Mayor F, Jr., D'Ocon P. Beta-blockers: historical perspective and mechanisms of action. Rev Esp Cardiol (Engl Ed). 2019;72:853–62. https://doi.org/10.1016/j.rec.2019.04.006.

12 Blumenfeld JD, Sealey JE, Mann SJ, Bragat A, Marion R, Pecker MS, et al. Beta-adrenergic receptor blockade as a therapeutic approach for suppressing the renin-angiotensin-aldosterone system in normotensive and hypertensive subjects. Am J Hypertens. 1999;12:451–9. https://doi.org/10.1016/s0895-7061(99)00005-9.

13 Kelbaek H, Godtrfedsen J. Effects of acute cardioselective and non-selective beta-adrenergic blockade on left-ventricular volumes and vascular resistance at rest and during exercise. Scand J Clin Lab Invest. 1991;51:161–6.

14 Wollam GL, Cody RJ, Jr., Tarazi RC, Bravo EL. Acute hemodynamic effects and cardioselectivity of acebutolol, practolol, and propranolol. Clin Pharmacol Ther. 1979;25:813–20. https://doi.org/10.1002/cpt1979256813.

15 Van de Water A, Janssens W, Van Neuten J, Xhonneux R, De Cree J, Verhaegen H, et al. Pharmacological and hemodynamic profile of nebivolol, a chemically novel, potent, and selective beta 1-adrenergic antagonist. J Cardiovasc Pharmacol. 1988;11:552–63. https://doi.org/10.1097/00005344-198805000-00007.

16 Brixius K, Bundkirchen A, Bölck B, Mehlhorn U, Schwinger RH. Nebivolol, bucindolol, metoprolol and carvedilol are devoid of intrinsic sympathomimetic activity in human myocardium. Br J Pharmacol. 2001;133:1330–8. https://doi.org/10.1038/sj.bjp.0704188.

17 Bundkirchen A, Brixius K, Bölck B, Nguyen Q, Schwinger RH. Beta 1-adrenoceptor selectivity of nebivolol and bisoprolol. A comparison of [3H]CGP 12.177 and [125I]iodocyanopindolol binding studies. Eur J Pharmacol. 2003;460:19–26. https://doi.org/10.1016/s0014-2999(02)02875-3.

18 Nuttall SL, Routledge HC, Kendall MJ. A comparison of the beta1-selectivity of three beta1-selective beta-blockers. J Clin Pharm Ther. 2003;28:179–86. https://doi.org/10.1046/j.1365-2710.2003.00477.x.

19 Maack C, Tyroller S, Schnabel P, Cremers B, Dabew E, Südkamp M, et al. Characterization of beta(1)-selectivity, adrenoceptor-G(s)-protein interaction and inverse agonism of nebivolol in human myocardium. Br J Pharmacol. 2001;132:1817–26. https://doi.org/10.1038/sj.bjp.0703992.

20 Brodde OE. The pharmacology of bisoprolol. Rev Contemp Pharmacother. 1997;8:21–33.

21 Baker JG. The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and beta3 adrenoceptors. Br J Pharmacol. 2005;144:317–22. https://doi.org/10.1038/sj.bjp.0706048.

22 Garnock-Jones KP. Esmolol: a review of its use in the short-term treatment of tachyarrhythmias and the short-term control of tachycardia and hypertension. Drugs. 2012;72:109–32. https://doi.org/10.2165/11208210-000000000-00000.

23 Cruickshank JM. Are we misunderstanding beta-blockers. Int J Cardiol. 2007;120:10–27. https://doi.org/10.1016/j.ijcard.2007.01.069.

24 Jaillon P. Relevance of intrinsic sympathomimetic activity for beta blockers. Am J Cardiol. 1990;66:21c–3c. https://doi.org/10.1016/0002-9149(90)90758-s.

25 Kubota Y, Asai K, Furuse E, Nakamura S, Murai K, Tsukada YT, et al. Impact of β-blocker selectivity on long-term outcomes in congestive heart failure patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:515–23. https://doi.org/10.2147/copd.S79942.

26 Elliott WJ, Ram CV. Calcium channel blockers. J Clin Hypertens (Greenwich). 2011;13:687–9. https://doi.org/10.1111/j.1751-7176.2011.00513.x.
27 Sica DA. Pharmacotherapy review: calcium channel blockers. J Clin Hypertens (Greenwich). 2006;8:53–6. https://doi.org/10.1111/j.1524-6175.2005.04140.x.
28 Horowitz BZ. What are the pharmacokinetics of calcium channel blockers (CCBs)? 2021. MedScape. Available from: https://www.medscape.com/answers/2184611-167308/what-are-the-pharmacokinetics-of-calcium-channel-blockers-ccbs. Accessed June 2022.
29 Godfraind T. Discovery and development of calcium channel blockers. Front Pharmacol. 2017;8:286. https://doi.org/10.3389/fphar.2017.00286.
30 Eguchi K, Kario K, Hoshide Y, Hoshide S, Ishikawa J, Morinari M, et al. Comparison of valsartan and amlodipine on ambulatory and morning blood pressure in hypertensive patients. Am J Hypertens. 2004;17:112–7. https://doi.org/10.1016/j.amjhyper.2003.09.008.
31 de Leeuw PW, Fagard R, Kroon AA. The effects of missed doses of amlodipine and losartan on blood pressure in older hypertensive patients. Hypertens Res. 2017;40:568–72. https://doi.org/10.1038/hr.2016.190.
32 Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122:290–300. https://doi.org/10.1016/j.amjmed.2008.09.038.
33 Kaplan NM. Amlodipine in the treatment of hypertension. Postgrad Med J. 1991;67 Suppl 5:S15–9.
34 Jeffers BW, Robbins J, Bhambri R, Wajsbrot D. A systematic review on the efficacy of amlodipine in the treatment of patients with hypertension with concomitant diabetes mellitus and/or renal dysfunction, when compared with other classes of antihypertensive medication. Am J Ther. 2015;22:322–41. https://doi.org/10.1097/mjt.0000000000000202.
35 Sun N, Hong T, Zhang R, Yang X. The effects of verapamil SR and bisoprolol on reducing the sympathetic nervous system's activity. Hypertens Res. 2000;23:537–40. https://doi.org/10.1291/hypres.23.537.
36 Davidov ME, Singh SP, Vlachakis ND, Blumenthal JB, Simon JS, Bryzinski BS, et al. Bisoprolol, a once-a-day beta-blocking agent for patients with mild to moderate hypertension. Clin Cardiol. 1994;17:263–8. https://doi.org/10.1002/clc.4960170509.