Chapter 8

Safety and Tolerability of a Single-Tablet Combination of Bisoprolol and Amlodipine

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Bisoprolol and amlodipine have been available for therapeutic use in the management of hypertension for more than three decades and their safety and tolerability profiles are well understood. Clinical evaluations of treatment with bisoprolol/amlodipine combinations, including within randomised trials and using real-world evidence, have revealed tolerability profiles consistent with clinical experience from this long period of therapeutic use with both agents, and add further support for a role for this treatment in the management of hypertension.

Introduction

Bisoprolol and amlodipine have been available for therapeutic use for the management of hypertension for more than 30 years. The safety and tolerability profiles of these drugs, and the patients in whom they

should and should not be used, are well understood (see Chapter 2 of this book for a summary of the place of bisoprolol and amlodipine in current guidelines for the management of hypertension). This chapter reviews the safety and tolerability of these agents, with respect to both clinical evaluations of bisoprolol/amlodipine combination tablets in patients with hypertension, and their individual therapeutic properties as described in the clinical literature.

General tolerability and safety profiles of bisoprolol and amlodipine

Most common side effects

The all-cause side effects for bisoprolol and amlodipine, listed in the European Summary of Product Characteristics (SmPC) for the bisoprolol/amlodipine combination tablet are shown in Table 1. Most of the side effects listed in Table 1 are "uncommon" (occurring in <1% of patients; less frequent side-effects were omitted from the table for conciseness and clarity). Among "common" side-effects of bisoprolol (occurring in at least 1% but <10% of patients), dizziness, headache, and fatigue are described as occurring mainly early in treatment. A similar statement is made for dizziness and fatigue for amlodipine. Other "common" side-effects are gastrointestinal symptoms (both agents), cold/numb extremities (bisoprolol), fatigue/asthenia, symptoms associated with vasodilatation (palpitation, manifestations of peripheral oedema, flushing), dyspnoea, muscle symptoms, and visual disturbances (amlodipine). Oedema is the only "very common" adverse event (occurring in at least 10% of patients treated with a combination of bisoprolol and amlodipine).

It has been suggested that a nocebo effect may apply to some side effects of β-blockers, where patients prescribed one of these drugs are willing to ascribe the presence of some pre-existing symptoms to the new treatment after being briefed by the prescribing physician on the possibility of it occurring [1, 2]. A systematic review found that, of 100 patients reporting stated side effects, a majority of cases were unlikely to be

Table 1 Summary of all-cause 'Uncommon', 'Common', and '*Very common*' side effects of bisoprolol/amlodipine combination tablets from European prescribing documentation.

Body system	Related to bisoprolol	Related to amlodipine
Psychiatric	Depression, sleep disorders	Mood changes (incl. anxiety), depression, insomnia
Nervous system	**Dizziness[a], headache[a]**	Tremor, dysgeusia, syncope, hypoesthesia, paraesthesia, **somnolence, dizziness, headache[a]**
Eye	–	**Visual disturbances, incl. diplopia**
Ear and labyrinth	–	Tinnitus
Cardiac	Atrioventricular conduction disorders, deterioration of existing heart failure, bradycardia	Arrhythmia[b], **palpitation**
Vascular	Hypotension, **cold/numb extremities**	Hypotension, **flushing**
Respiratory, thoracic and mediastinal	Bronchospasm in patients with history of bronchial asthma or COPD	Cough, rhinitis, **dyspnoea**
Gastrointestinal	**GI disturbances, e.g. nausea, vomiting, diarrhoea, constipation**	Vomiting, dry mouth, **GI disturbances, e.g. abdominal pain, nausea, dyspepsia, altered bowel habits**
Skin and subcutaneous tissues	–	Alopecia, purpura, skin discoloration, hyperhydrosis, pruritis, rash, exanthema, urticaria
Musculoskeletal and connective tissue	Muscle weakness, cramps	Arthralgia, myalgia, back pain, **ankle swelling, muscle cramps**
Renal and urinary	–	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast	–	Impotence, gynaecomastia
General/ administration site conditions	Asthenia[a], **fatigue[a]**	Chest pain, pain, malaise, **fatigue, asthenia, *oedema***

GI: gastrointestinal; incl.: including.
[a]Especially at the beginning of treatment.
[b]Including bradycardia, ventricular tachycardia, atrial fibrillation.
Uncommon = prevalence in ≥0.1% and <1% of patients; Common = prevalence in ≥1% and <10% of patients; Very common = prevalence in ≥10% of patients.
Less common side effects: Rare = ≥0.01% and <0.1% of patients; Very rare = ≥0.001% and <0.01% of patients. These side effects are not shown here for conciseness – see the full Summary of Product Characteristics for more details.
Data source: Summary of Product Characteristics for Concor AMLO tablets (Merck Healthcare KGaA, Darmstadt, Germany).

associated with β-blockade, e.g. for dizziness, 81% of cases (95% confidence interval [CI], 73 to 89%) were likely to have developed it on placebo, for diarrhoea 82% (95% CI, 70 to 95%), and for hyperglycaemia 83% (95% CI, 68 to 98%) [3]. Six commonly cited side effects of β-blockers were less common with β-blockers compared to placebo. Bradycardia (33% of cases [95% CI, 21 to 44%]) and intermittent claudication (41% [95% CI, 2 to 81%]) were more clearly associated with β-blockade, though it should be noted that this analysis was not limited to cardioselective β_1-adrenoceptor blockers. Some of the more common side effects of these agents are considered in more detail below:

Peripheral oedema is a well-known side-effect of calcium channel blockers, including dihydropyridines such as amlodipine [4]. Oedema is the only side effect of bisoprolol/amlodipine combination tablets that is listed as "very common" in Table 1. A meta-analysis of 22 trials, including 7,226 patients, showed that the risk of peripheral oedema with amlodipine was 2.9-fold higher versus placebo ($p<0.0001$); however, further analysis suggested that 37% of these events were unrelated to amlodipine treatment [5]. The incidence of oedema on amlodipine was dose related, with a 2.0-fold increase versus placebo at a dose of 2.5–5 mg, compared with a 3.1-fold increase at a dose of 10 mg ($p<0.0001$ for each). Bisoprolol is not associated with peripheral oedema.

Headache is a common symptom of bisoprolol and amlodipine that is described as occurring more frequently at the beginning of treatment and tends to disappear on continued treatment (Table 1). Headache of varying aetiology is a common symptom of hypertension and may be driven in part by activation of the renin-angiotensin-aldosterone system [6, 7]. A systematic review in this area described a reduction in the frequency of headache with several antihypertensive drug classes, with β-blockers being most effective in this regard [8]. Indeed, β-blockers, including bisoprolol, may reduce the frequency of headache of different aetiologies [9–11]. Channel blockers were ineffective on headache frequency in the meta-analysis described above [5]. However, another recent meta-analysis stratified patients by the dose of amlodipine [2]. The incidence of headache was not increased for amlodipine 10 mg versus placebo in the meta-analysis described above (risk ratio: 0.92

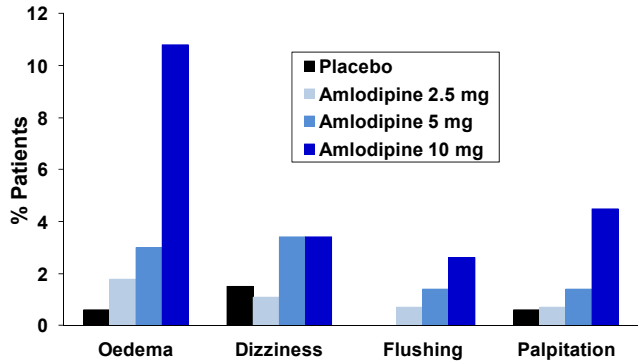
[95% CI, 0.74 to 1.15]), and was reduced versus placebo at a dose of 2.5–5 mg (risk ratio: 0.52 (95% CI, 0.40 to 0.69) [2].

Dizziness is another common side effect associated with antihypertensive therapy, as well as many other causes [12]. A review of spontaneous reports of adverse events to a pharmacovigilance database found associations with dizziness for all antihypertensive classes except β-blockers [13]. However, this side effect is known to occur with bisoprolol and amlodipine, typically early in therapy (Table 1). It is important to identify and intervene to correct more severe presentations of dizziness, as this is associated much more strongly with serious adverse outcomes such as falls in older, vulnerable individuals [9]. As a highly selective β_1-adrenoceptor blocker, bisoprolol does not cause marked peripheral vasodilatation [14, 15]. In one retrospective study in patients with heart failure, for whom it was not possible to increase the dose of a vasodilating β-blocker (carvedilol), all 13 patients with dizziness as a limiting factor, and 9/15 patients with hypotension as a limiting factor, could be safely switched to bisoprolol [16].

Dose-relationship of side effects

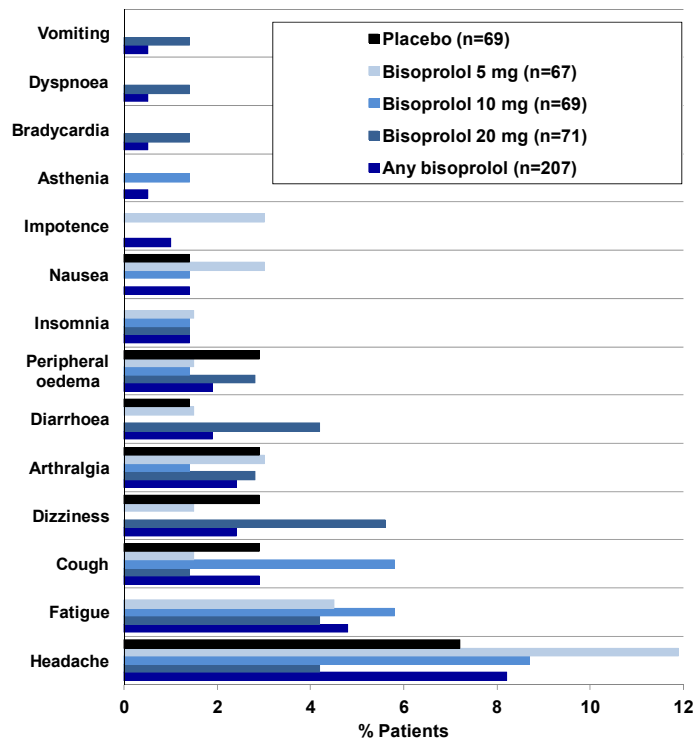
Figure 1 shows the incidence of dose-related side effects with amlodipine from clinical trials that compared amlodipine directly with placebo using the United States (US) label of a marketed formulation of this drug (N=1,750 and N=1,250, respectively) [17]. The incidence of oedema and palpitation rose steeply at a dose of amlodipine 10 mg, while the incidence of the other side effects remained relatively low. A systematic review of the tolerability of different doses of bisoprolol within the permitted dosage range in Europe is not available. The side effects of bisoprolol were not clearly dose related in a randomised comparison of bisoprolol 5–20 mg versus placebo (Figure 2) [18]. This is especially the case for bisoprolol dosages of 5–10 mg, which is the range of bisoprolol doses used in the bisoprolol/amlodipine combination tablets, and 10 mg is the usual maximum dose of bisoprolol. The data for bisoprolol 20 mg is shown here for completeness, and to help highlight any dose-relationship of side effects that may have been present.

Figure 1 Dose-relationship of side effects of amlodipine [14].



Drawn from data presented in the US label of a marketed formulation. These were the only side effects considered to be dose-related in this analysis.

Figure 2 Dose relationship of side effects of bisoprolol [15].



Drawn from data presented in reference [15].

Contraindications and precautions when prescribing bisoprolol/amlodipine combination tablets

Contraindications and precautions relating to the therapeutic use of bisoprolol/amlodipine combination tablets are summarised in Table 2. Contraindications for bisoprolol relate mainly to exacerbation of acute or decompensated heart failure, bradycardia or intracardiac conduction block, or use in severe bronchial asthma. Contraindications to amlodipine mostly reflect concern over exacerbation of heart failure and also situations where blood pressure (BP) may become dangerously low (hypotension, shock, and aortic stenosis).

Precautions for the use of these agents reflect similar potential concerns (uncontrolled heart failure for both, and atrioventricular conduction block for bisoprolol). Additionally, bisoprolol should be used with caution where there is a high risk of hypoglycaemia, as sympathetic activation is an important part of the counter regulatory response to low blood glucose [19]. Other precautions include situations where any level of β_2-adrenoceptor blockade would be harmful (peripheral artery occlusive disease and obstructive airways disease). With regard to the latter, the use of bisoprolol is supported for patients with less severe obstructive airways disease where there is a compelling indication for its use (e.g. angina, post-myocardial infarction, or heart failure), as bisoprolol's highly selective β_1-adrenoceptor blockade would not be expected to constrict the bronchi (a β_2-adrenoceptor-mediated effect) at usual therapeutic doses [12]. Consistent with these observations, a network meta-analysis of 14 randomised trials and 23 observational studies found that among seven β-blockers evaluated, only propranolol (a non-cardioselective β-blocker) reduced forced expiratory volume in 1 second significantly, while bisoprolol, atenolol, labetalol, celiprolol, metoprolol, and carvedilol did not [20].

Table 2 Contraindications and precautions relating to the use of bisoprolol/amlodipine combination tablets from European prescribing information.

	Related to the bisoprolol component	Related to the amlodipine component
Contraindications	Acute HF Episodes of decompensated HF requiring inotropic therapy Sick sinus syndrome Sinoatrial block Symptomatic bradycardia Symptomatic hypotension Severe bronchial asthma Severe peripheral occlusive disease (incl. severe forms of Raynaud's syndrome) Untreated pheochromocytoma Metabolic acidosis	Severe hypotension Shock (incl. cardiogenic shock) Left ventricular outflow obstruction (e.g. high grade aortic stenosis) Haemodynamically unstable HF
Warnings and precautions		
Patients with heart failure	Use with caution in hypertension angina associated with HF	Use with caution (pulmonary oedema has been observed with amlodipine in patients with severe HF).
Patients with IHD	Do not withdraw therapy abruptly Use with caution in Prinzmetal's angina	–
Hepatic impairment	–	Use with caution (elimination is prolonged but dose adjustments have not been established in these patients)
Renal impairment	–	--
Elderly	–	Use caution when increasing the dose
Diabetes	Use with caution where glucose levels fluctuate severely (may mask symptoms of hypoglycaemia)	–
Obstructive airway diseases	Avoid unless compelling indication (then use with caution)	–
Other areas requiring cautious use	1st degree AV block Peripheral occlusive artery disease Psoriasis Hyperthyroidism (may mask symptoms) Concomitant allergen desensitisation Potential for interactions with other drugs in the peri-operative period (promotion of bradycardia or reflexes to compensate for blood loss)	–

AV: atrioventricular; HF: heart failure; IHD: ischaemic heart disease.
Hypersensitivity to any component of the tablet is also a contraindication; omitted from the table for conciseness.
Contents of the table are paraphrased: please see the full Summary of Product Characteristics before prescribing.
Data source: Summary of Product Characteristics for Concor AMLO tablets (Merck Healthcare KGaA, Darmstadt, Germany).

Tolerability and safety in clinical evaluations of bisoprolol/amlodipine combination tablets

Three randomised trials and three observational studies have provided data on the tolerability and safety of bisoprolol/amlodipine combination tablets (Table 3) [21–26]. One of these studies compared a free combination of bisoprolol and amlodipine with placebo and amlodipine in patients with BP sub-optimally controlled on amlodipine monotherapy [22]. As the bisoprolol and amlodipine components of the combination tablet have been shown to be bioequivalent with commercial formulations of these agents, the tolerability findings are directly comparable with the findings of studies that evaluated bisoprolol/amlodipine combination tablets.

The incidence of side effects was low in these studies. The more common side effects reported included those typical of a β-blocker and vasodilatory calcium channel blocker, (e.g. bradycardia, headache, and oedema), as described above. The low incidence of side effects in these studies likely reflects the prior treatment received by the populations of most of the trials with bisoprolol and/or amlodipine.

Conclusions

Bisoprolol and amlodipine have been effective and well tolerated therapeutic options within the management of hypertension for decades. Their side effect profiles, contraindications, and precautions for use are well known and understood. Clinical evaluations of treatment with bisoprolol/amlodipine combinations have revealed tolerability profiles consistent with clinical experience from this long period of therapeutic use with both agents. Moreover, this evidence was from both randomised, controlled trials (the 'gold standard' for clinical evidence) and from real-world evaluations (that add valuable information on the therapeutic profile of a drug in routine clinical practice, away from the often restrictive inclusion and exclusion criteria of randomised trials [27]). These studies confirm that patients can be switched safely to the bisoprolol/amlodipine combination tablets from either monotherapy with either

Table 3 Overview of safety and tolerability findings reported in clinical evaluations of bisoprolol plus amlodipine combinations.

	Prior therapy	Any AE (%)	Most common AE	Serious AE (%)	Discont. for AE (%)	Deaths
Randomised trials						
21	Bisoprolol 5 mg or amlodipine 5 mg	74.5[a]	**B + A combination tablets[a]:** Sinus bradycardia (27.5%)[b] Other bradycardia (14.5%)[b] Peripheral oedema (8.5%)[b]	1.5	3	2 deaths[c]
22	Amlodipine 5 mg QD	B+A[d]: 12.7 Placebo[d]: 11.8	**B + A free combination[a,e]:** Oedema (2.2%) Headache (1.6%) **Placebo**: No individual AE occurred in >2 patients	B+A[d]: 6.6 Plac[d]: 3.2	B+A[d]: 6.6 Plac[d]: 3.20	No deaths
23	None	Not reported	No significant impact on laboratory parameters	Not reported	Not reported	Not reported
Observational studies						
24	Bisoprolol + amlodipine (free combination)	Not reported (total of 101 AE)	**B + A combination tablets[f]:** Swelling (0.2%) Joint swelling (0.1%) Bradycardia (0.04%) Dizziness (0.04%) Headache (0.04%)	0.1	0.1	1 death[c]
25	Not reported	Not reported	**B + A combination tablets[e,f]:** Oedema (7.5%)[e] Headache (3.8%)[e] Fatigue (2.8%)[e] Leg cramps (2.8%)	0	0	No deaths
26	Amlodipine, ramipril or atenolol	Not reported	**B + A combination tablets[e,f]:** Oedema (8%) Headache (4%) Fatigue (3%) Leg cramps (3%)	0	0	No death

A: amlodipine; AE: adverse event; B: bisoprolol; discont.: discontinued; QD: daily.
[a]There was no active comparator in this trial, patients were randomised to combination tablets incorporating different dosage strengths of amlodipine and bisoprolol (see Chapter 6 for more details).
[b]Treatment-related AE.
[c]Unrelated to treatment.
[d]Patients uncontrolled on amlodipine 5 mg were randomised to additional placebo or additional amlodipine
[e]Occurring in at least 3 patients.
[f]Observational study with no comparator group.

agent (for increased efficacy, see Chapter 6 of this book) or from pre-existing free combinations of bisoprolol and amlodipine (to simplify regimens to support good adherence to therapy, see Chapter 7), depending on the local label. The data on the tolerability profile of bisoprolol/amlodipine combination therapy summarised in this Chapter adds further support for the role of this treatment in the management of hypertension.

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