MINI REVIEW

PHYSICOCHEMICAL PROPERTIES AND PHARMACOLOGY OF AMLODIPINE BESYLATE: A BRIEF REVIEW

Syed Furqan Ahsan, Marium Fatima Khan*

Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Karachi, Pakistan

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ABSTRACT

Hypertension is one of the well-studied risk factors for cardiovascular diseases and the oldest class of hypertensive drugs is the calcium channel blockers. Amlodipine besylate (ADB) belongs to the dihydropyridine family and is known as an effective initial treatment for hypertension and angina. It has a gradual onset of action and is administered in concomitant diseases with minimal side effects. Its basic mechanism of action is the blockage of calcium ions influx into cardiac muscles and vascular muscles. The physical appearance of ADB is white crystalline with a molecular weight of 567.1. Its 6.9 mg is equivalent to 5 mg of amlodipine (AM) free base. This review focuses on all the basic aspects of ADB which is one of the initial treatment regimens for cardiovascular diseases since last two decades.

Keywords: Amlodipine besylate, calcium channel blocker, cardiovascular diseases.

1. INTRODUCTION

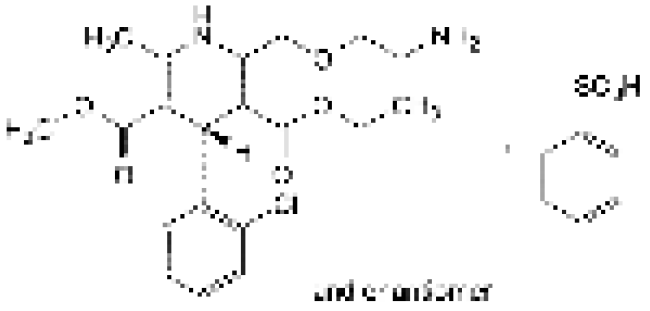
Amlodipine besylate (ADB) is an important second-generation calcium channel blocker that belongs to the dihydropyridine family. It is used for the treatment of hypertension and angina. It is more selective for arterial vascular smooth muscle than for the cardiac tissue. It is approved for the treatment of hypertension and for variant and stable angina and may also be used for dilated cardiomyopathy. ADB has ameliorating effects on the plasma and myocardial catecholamine levels and significantly reduces calcium deposition. It has a negative inotropic effect on the heart that results in a decrease in heart work load[1-5].

ADB possesses unique pharmacological properties that distinguish it from other agents of this class such as more prolonged half-life, high volume of distribution, and gradual elimination. ADB has slow absorption and prolonged effect, which makes it suitable for convenient once-daily administration[6,7]. These properties are attributed to a high degree of ionization (>90% at physiological pH) due to the presence of a basic side chain at the dihydropyridine ring[1]. ADB is an effective free base but in practice, it is administered in the form of racemate as a salt with the acids containing pharmaceutically acceptable anions. These acidic salts are prepared for improving its bioavailability[8].

2. PHYSICOCHEMICAL PROPERTIES

ADB is 3-ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate which is a dihydropyridine derivative with calcium antagonist activity. Some of its basic physicochemical properties are described as follows[1,9-12]:

Structure:



* Corresponding Author Email: marium87@gmail.com

Chemical Formula: $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$

Molecular Mass: 567.1

CAS No.: 111470-99-6

State: 97.0–102.0% (anhydrous substance)

Color: White or almost white powder

Solubility: Slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in 2-propanol.

pK_a: 8.6

Hygroscopicity: Amlodipine (AM) free base is not hygroscopic. The ability of ADB to uptake water strongly depends on the crystalline form of the material. The stable anhydrous form of ADB was stored for almost 2 months at 92% relative humidity and 25 °C without a significant water uptake. Slow transformation of the anhydrous ADB or its monohydrate form to the dihydrate occurs if the material is placed directly in water. However, if water has been gently removed from the monohydrate form leaving the crystal structure intact, the rehydration takes in only a few minutes if stored at 92% relative humidity.

UV maxima: Amlodipine free base (methanol): 210 nm (ε = 1 $9\times10^4 M^{-1}cm^{-1}$), 237 nm ($\varepsilon = 2.0\times10^4$ M^{-1} cm^{-1}), 360 nm ($\varepsilon = 6.8\times10^3$ M^{-1} cm^{-1}); ADB (1.1 N HCl): 213 nm ($\varepsilon = 2.4\times10^4$ M^{-1} cm^{-1}), 238 nm ($\varepsilon = 1.9\times10^4$ M^{-1} cm^{-1}), 360 nm ($\varepsilon = 6.6\times10^3$ M^{-1} cm^{-1}).

3. MECHANISM OF ACTION

ADB is a dihydropyridine calcium antagonist that prevents the transmembrane influx of calcium ions into the vascular smooth and cardiac muscle. It attaches to both dihydropyridine and non-dihydropyridine binding sites. The contractile manners of cardiac and vascular smooth muscle are dependent on the movement of extracellular calcium ions into these cells through specific ion channels. ADB inhibits calcium ion influx across cell membranes selectively, with a superior effect on vascular smooth muscle cells than on cardiac muscle cells[12].

4. PHARMACOKINETICS

4.1. Absorption

ADB is well absorbed after oral administration with peak blood concentrations occurring after 6–12 h. The bioavailability often varies but is usually about 60–65% with plasma protein binding of around 97.5% [1,11,13,14]. Absorption of ADB from a capsule is equivalent to that from a solution, suggesting that the slow transfer of ADB into the blood is a property of the drug and not of the dosage form. The absorption of ADB is not affected by food[11,15].

4.2. Distribution

The apparent volume of distribution, observed in healthy volunteers following administration of 10 mg intravenous dose was reported to be 21.4±4.4 lit/kg. The large volume of distribution indicates that the drug distributes extensively into tissue compartments. ADB is about 97% bounded to plasma proteins. (–)-(S)-ADB has the higher binding capability to human serum albumin and plasma as compared to (+)-(R)-enantiomer[1,16,17].

4.3. Metabolism

ADB is extensively but slowly metabolized in the

liver. The metabolites are mostly excreted in the urine along with <10% of a dose as unchanged drug. It is usually not eliminated through dialysis[11,13,14]. The initial metabolic aromatization of the dihydropyridine ring is followed by further metabolism involving side-chain oxidation and hydrolysis of the side-chain ester groups[1,11,18,19].

4.4. Excretion

ADB has a prolonged half-life of 35–50 h, which is the longest among all other calcium channel blockers. When radioactively labeled ADB was administered intravenously, 62% of the dose was recovered in the human urine and the remainder in the feces. Only about 5–10% of the dose was excreted unchanged in the human urine. A similar excretion pattern was observed after oral administration[1].

5. USES AND ADMINISTRATION

ADB is a dihydropyridine calcium-channel blocker with actions similar to those of nifedipine. It is used in the management of hypertension and angina pectoris. AM is given orally as besylate salt but doses are usually expressed in terms of the base. ADB 6.9 mg is equivalent to about 5 mg of AM. The camsilate, maleate and mesilate salts and (*S*)-isomer of ADB are also used. In hypertension, the usual initial dose is 5 mg once daily. The dose can be increased to 10 mg once daily, if necessary. Similar doses are given in the treatment of stable angina and Prinzmetal's angina. Lower initial doses may be used in elderly patients and those with hepatic impairments[11,20,21].

5.1. Administration in Children

ADB has been used to reduce blood pressure in children and adolescents with hypertension. Various studies have shown a significant reduction in the blood pressure after using a once-daily dose of about 20–340 μg/kg in age groups between 13 months to 20 years. Based on the findings of those studies, higher doses or twice daily dosing of ADB were suggested in younger children as compared to older ones[11,22-26].

5.2. Administration in Hepatic Impairment

The clearance of ADB is reduced in patients with hepatic impairment; therefore, lower doses should be administered with an initial dose of 2.5 mg once daily[11].

6. ADVERSE EFFECTS

6.1. Heart Failure

Calcium-channel blockers are normally avoided in patients with heart failure but ADB has not been found to have any adverse effects on morbidity or mortality in patients with severe heart failure. Therefore, it may be a suitable treatment option for angina pectoris or hypertension in such patients. However, a study on hypertensive patients found that ADB was less effective than the diuretic chlorthalidone in the prevention of heart failure[27].

6.2. Porphyria

Although there have been reports of the successful use of ADB in patients with porphyria, some studies have reported the occurrence of acute exacerbation in such patients[28-30].

6.3. Miscellaneous Adverse Effects

A number of other adverse events occurring in response to the regular use of ADB in 1091 patients with hypertension have been reported. Around 12% (128) patients stopped the intake of the drug due to the appearance of adverse effects. The most common reported adverse effects include ankle edema, flushing, headache, skin rash, and fatigue[31].

7. INTERACTION OF ADB

7.1. Interaction with Excipients

ADB is reported to interact with lactose in pharmaceutical formulations. A study on the stability of ADB in solid dosage form revealed that the mixtures of lactose, magnesium stearate and water induce some instability. The major degradation product was found to be amlodipine besylate glycosyl. Therefore, use of lactose-free ADB formulation is recommended for the safety, quality, efficacy, and low cost of the product[32].

7.2. Interaction with Food

The absolute bioavailability of AM upon oral administration is usually unaffected by food.

However, grapefruit juice can alter the oral pharmacokinetics of AM due to irreversible inactivation of the intestinal CYP3A4 enzyme as well as by inhibiting P-glycoprotein. This results in the subsequent reduction of the intestinal and/or hepatic efflux transport[1].

7.3. Interaction with Combination Drugs

The evaluation of pharmacokinetic interactions between ADB, valsartan and hydrochlorothiazide revealed no clinically relevant interactions. Similarly, combination of ADB and olmesartan medoxomil is also known to have no impact on the pharmacokinetic profiles of individual drugs. Concomitant use of ADB and atorvastatin in patients with hypertension and dyslipidemia has shown to be well tolerated without any adverse pharmacodynamic interaction. The use of triple combination i.e. ADB + Olmesartan Medoxomil + hydrochlorothiazide has also demonstrated to be safe[1].

8. CONCLUSION

ADB is considered a more selective drug for arterial vascular smooth muscle than for the cardiac muscles. ADB is marketed in the form of racemate as a salt with acids which helps in improving its bioavailability. Lactose-free ADB formulation is recommended for the efficacy, stability of the product, as it reportedly produces some instability with ADB and magnesium stearate in a solid form. ADB has no negative effect with other antihypertensive drugs. However, in this review, it is discussed that its intestinal and hepatic efflux transport is decreased due to the intake of grapefruit juice. Large randomized controlled trials performed for cardiovascular effects gave good evidence for ADB's good efficacy and safety. ADB should be considered a first-line antihypertensive agent because it has such better pharmacokinetic advantages over other calcium antagonists in the long-term cardiovascular diseases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Ananchenko G, Novakovic J, Lewis J. Amlodipine Besylate, In: Brittain HG (Ed.), Profiles of Drug Substances, Excipients, and Related Methodology, Elsevier, Inc., Canada, 2012; pp. 31-77.
2. Civantos B, Aleixandre A. Blood pressure and alpha-vascular reactivity in hypertensive rats treated with amlodipine and dietary Ca. Eur J Pharmacol. 2004;489:101-110.
3. European Pharmacopoeia. Monograph on Amlodipine besylate, 3rd ed., Council of Europe, Strasbourg, UK, 2001; pp. 431-432.
4. Kadioglu Y, Ozturk M. Spectrofluorimetric determination of amlodipine in human plasma without derivatization. Braz J Pharm Sci. 2012;48:719-725.
5. Reynolds JEF. Martindale-The Extra Pharmacopoeia, 31st ed., The Royal Pharmaceutical Society, London, UK, 1996; pp. 819-820.
6. Cutler SJ. Cardiovascular agents, In: Beale JM, Block JA (Eds.), Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 12th ed., Lippincott-Williams & Wilkins, Baltimore, MD, USA, 2011; p. 626.
7. Omar MA. Assay of amlodipine besylate in tablets and human biological fluids by square wave adsorptive cathodic stripping voltammetry. Int Res J Pure Amp Appl Chem. 2013;3: 133-146.
8. Szabo L, Chis V, Pirnau A, Leopold N, Cozar O, Orosz S. Spectroscopic and theoretical study of amlodipine besylate. J Mol Struct. 2009;924:385-392.
9. British Pharmacopoeia. Monograph on Amlodipine besylate, Her Majesty's Stationary Office, London, UK, 2016; Electronic version.
10. Moffat AC, Osselton MD, Widdop B. Clarke's Analysis of Drugs and Poisons, 4th ed., Pharmaceutical Press, London, UK, 2011; pp. 889-890.
11. Sweetman S. Martindale: The Complete Drug Reference. Pharmaceutical Press, London, UK, 2009.
12. Naikwade J. Evaluation of fast dissolving tablets

of amlodipine besylate by using co-processed superdisintegrants. Br J Pharm Res. 2013;3: 865-879.
13. Kang D, Verotta D, Schwartz JB. Population analyses of amlodipine in patients living in the community and patients living in nursing homes. Clin Pharmacol Ther. 2006;79:114-124.
14. Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. Clin Pharmacokinet. 1992;22:22-31.
15. Faulkner JK, Hayden ML, Chasseaud LF, Taylor T. Absorption of amlodipine unaffected by food. Solid dose equivalent to solution dose. Arzneimittel Forsch. 1989;39:799-801.
16. Faulkner JK, McGibney D, Chasseaud LF, Perry JL, Taylor IW. The pharmacokinetics of amlodipine in healthy volunteers after single intravenous and oral doses and after 14 repeated oral doses given once daily. Br J Clin Pharmacol. 1986;22:21-25.
17. Abernethy DR. The pharmacokinetic profile of amlodipine. Am Heart J. 1989;118:1100-1103.
18. Beresford AP, McGibney D, Humphrey MJ, Macrae PV, Stopher DA. Metabolism and kinetics of amlodipine in man. Xenobiotica Fate Foreign Compd Biol Syst. 1988;18:245-254.
19. Beresford AP, Macrae PV, Alker D, Kobylecki RJ. Biotransformation of amlodipine. Identification and synthesis of metabolites found in rat, dog and human urine/confirmation of structures by gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry. Arzneimittel Forsch. 1989;39: 201-209.
20. Haria M, Wagstaff AJ. Amlodipine. A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. Drugs. 1995;50:560-586.
21. Murdoch D, Heel RC. Amlodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. Drugs. 1991;41:478-505.
22. Flynn JT, Smoyer WE, Bunchman TE. Treatment of hypertensive children with amlodipine. Am J Hypertens. 2000;13:1061-1066.
23. Flynn JT, Newburger JW, Daniels SR, Sanders SP, Portman RJ, Hogg RJ, Saul JP, PATH-1 Investigators. A randomized, placebo-controlled trial of amlodipine in children with hypertension. J Pediatr. 2004;145:353-359.
24. Flynn JT, Nahata MC, Mahan JD, Portman RJ, PATH-2 Investigators. Population pharmacokinetics of amlodipine in hypertensive children and adolescents. J Clin Pharmacol. 2006;46:905-916.
25. Pfammatter JP, Clericetti-Affolter C, Truttmann AC, Busch K, Laux-End R, Bianchetti MG. Amlodipine once-daily in systemic hypertension. Eur J Pediatr. 1998;157:618-621.
26. Tallian KB, Nahata MC, Turman MA, Mahan JD, Hayes JR, Mentser MI. Efficacy of amlodipine in pediatric patients with hypertension. Pediatr Nephrol Berl Ger. 1999;13:304-310.
27. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med. 1996;335:1107-1114.
28. Cinemre H, Korkmaz U, Alcelik A, Onder E, Gungor A. Safety of amlodipine use in patients with acute intermittent porphyria. Br J Clin Pharmacol. 2007;64:246-247.
29. Gorchein A. Drug treatment of hypertension in acute intermittent porphyria: doxazosin and amlodipine. Br J Clin Pharmacol. 1997;43: 339-340.
30. Kepple A, Cernek PK. Amlodipine-induced acute intermittent porphyria exacerbation. Ann Pharmacother. 1997;31:253.
31. Benson E, Webster J. The tolerability of amlodipine in hypertensive patients. Br J Clin Pharmacol.1995;39:578-579.
32. Abdoh A, Al-Omari MM, Badwan AA, Jaber AM. Amlodipine besylate-excipients interaction in solid dosage form. Pharm Dev Technol. 2004;9:15-24.