IJPT
1735-2657/03/22-25-29
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 2:25-29, 2003

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Mebudipine and Dibudipine: A Review

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Received November 1, 2003; Revised November 22, 2003; Accepted December 6, 2003

This paper is available online at *http://ijpt.iums.ac.ir*

ABSTRACT

Based on QSAR studies two new DHP calcium-channel blockers, mebudipine and dibudipine, were synthesis and evaluated for their pharmacological activity in various tissues. These studies showed that, these compounds, with potency comparable or greater than that of nifedipine could relax the smooth muscles of various vascular tissues. Electrophysiological study showed that they antagonized calcium current in F1 neuronal soma membrane in Helix aspesa cells. Mebudipine has a greater time- and voltage- dependent inhibitory effect, as compared to nifedipine and this property could explain its prominent vaso-selective action. Based on pharmacokinetic studies it is found that these two compounds are extensively metabolized by hepatic cells and this will results in low bioavailability after oral administration. However, these newer 1,4-DHPs address the problem of the short half-life of nifedipine, and are metabolically stable, possess comparable pharmacological activity as nifedipine and are therefore suitable for further development as potential therapeutic alternatives to the existing 1,4-DHP calcium-channel blockers. Based on their vaso-selectivity and longer half-lives and negative chronotropic activity, It is concluded that they have a great potential for further development as a new drug.

Keywords: *Calcium-channel blocking, Dihydropyridines, Nifedipine*

Since their introduction of calcium-channel blockers by Fleckenstein [1], these compounds have found to have special significance in the therapy of hypertension, angina pectoris and other cardiovascular diseases [2]. They can also be effective in non-cardiovascular medicine [3]. Among the classes of calcium-channel Blockers, Dihydropyridine derivatives are widely used because of their potent vasodilating activity and weak cardiodepressant action [1]. Since their introduction in sixties, dihydropyridines have undergone several changes to optimize their efficacy and safety. Four generations of dihydropyridines [4] are now available. The first-generation agents have proven efficacy against hypertension. However, because of their short duration and rapid onset of vasodilator action, these drugs were more likely to be associated with adverse effects. The pharmaceutical industry responded to this problem by designing slow-releasing preparations of the short-acting drugs. These new preparations (second generation) allowed better control of the therapeutics effect and a reduction in some adverse effects. Pharmacodynamic innovation with regard to the dihydropyridines began with the third-generation agents (amlodipine, nitrendipine). These drugs exhibit more stable pharmacokinetics, are less cardioselective and, consequently, well tolerated in patients with heart failure. Highly lipophilic dihydropyridines are now available (lercanidipine. lacidipine) [4]. These fourth-generation agents provide a real degree of therapeutic comfort in terms of stable activity, a reduction in adverse effects and a broad therapeutics spectrum, especially in myocardial ischemia and potentially in heart failure.

This work summarized the work carried out in our laboratory on two new lipophilic dihydropyridines to develop one such drug.

SAR AND SYNTHESIS

Hansch analysis was used by Mahmoudian and Richards [5] to examine QSAR of substituted 4-phenyl DHPs and correlate the substituted parameters with their potency in inhibiting the binding of [^{3}H]nitrendipine to the microsomal fraction of guinea-pig longitudinal muscle. They confirmed the finding of Rodenkirchen et al. (1979) [6] in that the minimum width of substituent at the ortho-position or meta-position of the 4-phenyl ring, correlated well with the activity of DHPs. It was also shown that an optimal drug-receptor interaction is only possible when the ortho-aryl substituent obtains the highest degree of spatial complementarity to the active site of the receptor. A fact which is also supported by quantum chemical study [7].

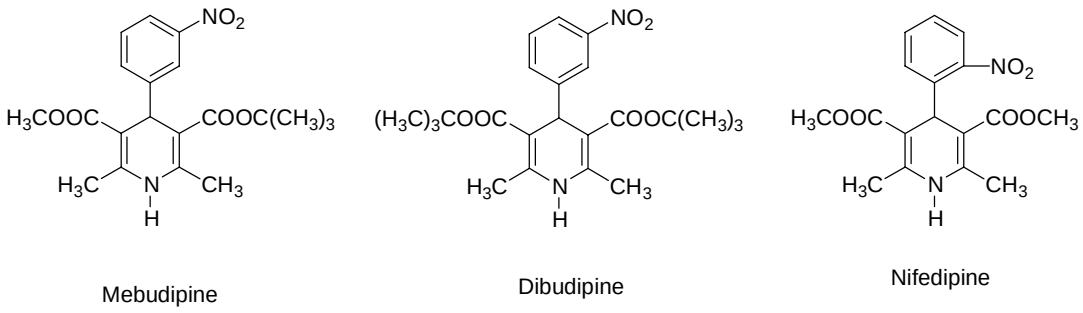

Fig 1. Chemical structure of the 1,4-DHP analogues dibudipine, mebudipine and nifedipine.

Our study showed that this spatial complementarity is not restricted to the ortho-position only, but also involves meta and para-positions, The requirements were:

1. A bulky substituent at the ortho-position; activity increased with increase in the minimum width of substituent at ortho-position;
2. A wide but not long substituent at the meta-position; activity increased with increase in minimum width of substituent, but decreased with the increase in length of substituent at the meta-position;
3. A small (preferably H) substituent at the para-position: activity decreased with increase in both the minimum width and length of substituent at the para-position.

This analysis also revealed something about the environment of the binding site, since a positive correlation was observed for the hydrophobicity of substituent at the ortho-position and a negative one for the para-position. This indicated that the environment around ortho-position was lipophilic and that around the para-position was hydrophilic. The border of these two phases would be expected at the meta-position and this was confirmed by the fact that hydrophobicity of the meta-substituent did not have a great influence on the binding of DHPs.

Quantum chemical studies [7] also confirmed these results, and showed that the phenyl ring had a perpendicular orientation with respect to DHP ring and the rigidity of this orientation correlated well with the activity.

The SAR studies led to the synthesis of two new calcium-channel blockers: mebudipine and dibudipine [8] (Fig 1). Mebudipine was synthesis by the reaction of 25.0 g of t-butyl-2-(3-nitrobenzylidene) acetoacetate with 12.5 g. of methyl 3-amino-crotonate in methanol under reflux for 18 h. Similarly, dibudipine is synthesis by the reaction of 20 g of 3-nitro-benzaldehyde and 60.0 g of t-butyl acetoacetate in methanol and in the presence of ammonium solution under reflux for 10 h.

Table 1. The potencies of mebudipine, dibudipine and nifedipine for reduction of contraction force of isolated rat left atrium and relaxing precontracted isolated rat aorta [9].

	Mebudipine	Dibudipine	Nifedipine
pIC_{30}^{atrium}	5.37±0.13[a]	5.49±0.15[a]	6.36±0.11[a]
pIC_{50}^{aorta}	8.61±0.09[a]	7.59±0.12[a]	8.29±0.07[a]
$IC_{30}^{atrium}/IC_{50}^{aorta}$	1738	126	85

[a] Values are means ± S.E.M.

After purification these two compounds were evaluated for their pharmacological activity [8].

PHARMACODYNAMIC PROPERTIES

The pharmacological potencies of these compounds were evaluated by studying their effects on the contractions of various tissues [8-9].

Effects on calcium-induced contractions of isolated guinea-pig ileum

Pre-treatment of the isolated K^+-depolarized guinea-pig ileum with mebudipine, dibudipine and nifedipine resulted in a shift to the right of the calcium dose-response curves and the response percentage ratio for mebudipine (at a fixed concentration of calcium) was significantly smaller than those of dibudipine and nifedipine whereas this parameter did not differ significantly for dibudipine and nifedipine [8].

Effects on rat isolated aorta

Rat aortic rings pre-contracted with 40 mM KCl were relaxed by mebudipine, dibudipine similar to nifidipine. The results indicated the pIC_{50} of mebudipine was greater than that of nifidipine which in turn was greater than that of dibudipine. Therefore the potency of these drugs for relaxing K^+-induced contractions is mebudipine > nifidipine > dibudipine [8].

Table 2. pIC_{50} values of negative chronotropic and inotropic effects of mebudipine and nifedipine on spontaneous beating and electrically-driven (at 2 Hz frequency)left rat atrium [10]

	Mebudipine	Nifedipine	t-test
Negative chronotropism	8.76±0.15[a]	7.77±0.12[a]	$P<0.001$
Negative inotropism	5.77±0.22[a]	6.66±0.03[a]	$P<0.01$
t-test	$P < 0.001$	$P < 0.001$	
$IC_{50}^{inotropism}/IC_{50}^{chronotropism}$	977	15	

[a] Values are means ± S.E.M.

Effects on isolated human internal mammary artery

Mebudipine and dibudipine similar to nifidipine relaxed isolated human internal mammary artery rings pre-contracted by KCl (40 mM) [9] (Mirkhani et al., 1999). Since the maximum relaxation induced by each compound differed in each experiment, the EC_{50} values were used to compare their potencies. It was found that the potency of K^+-induced contraction of internal

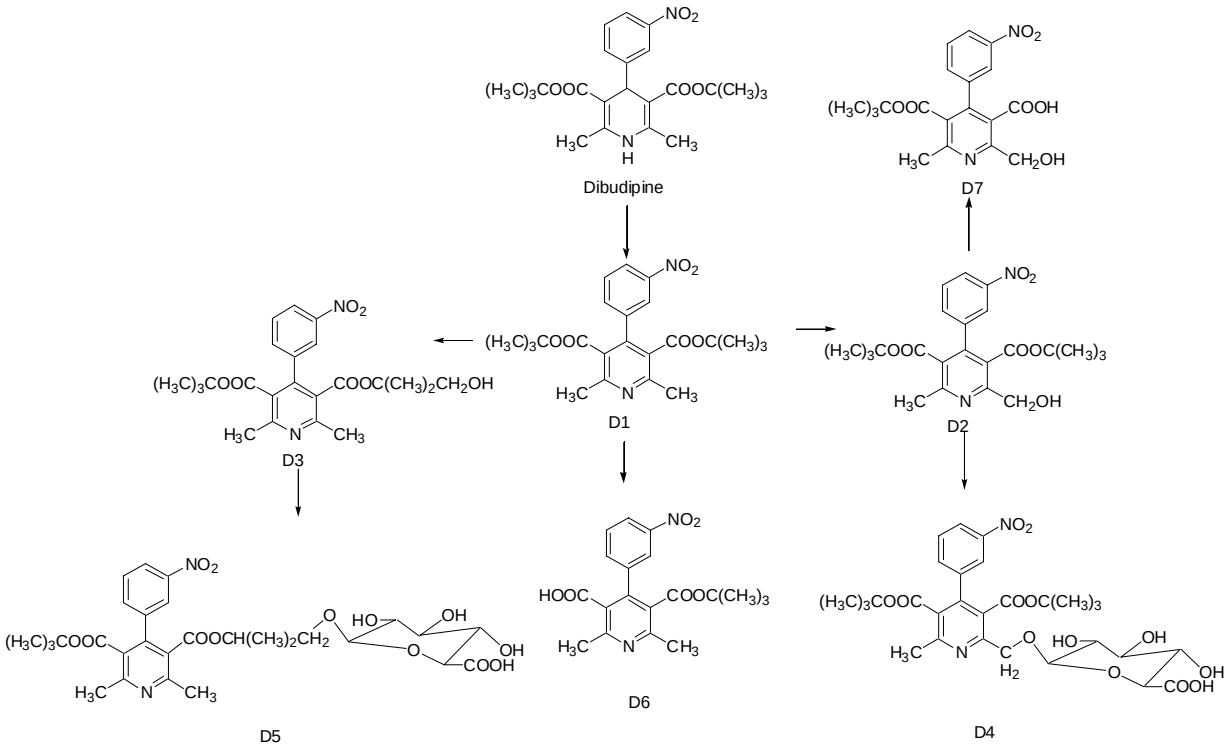

Fig 2. Proposed pathway for the metabolism of dibudipine (100μm) by isolated rat hepatocytes

mammary artery did not differ significantly from that of nifedipine while the potency of mebudipine in eliciting this effect was greater than that of dibudipine [9] (Mirkhani et al., 1999).

Effects on the isolated rat left atrium

Mebudipine and dibudipine similar to the nifedipine dose dependently reduced contraction force of the rat left atrium. The pIC_{30} values of mebudipine and dibudipine were smaller than that of nifedipine. The vaso-select effect of these compounds showed the following order; mebudipine > dibudipine ≈ nifedipine (Table 1 [9]).

The negative inotropic effect of mebudipine and dibudipine were significantly lower than that of nifedipine, (mebudipine compared with nifedipine, $P < 0.0001$; dibudipine compared with nifedipine, $P < 0.005$). pIC_{50} values for relaxing precontracted isolated rat aorta are taken from Mahmoudian et al.[8]. They concluded that in comparison with first generation calcium-channel blockers such as nifedipine; mebudipine and dibudipine showed a significant vaso-selectivity [9].

In a similar study, Mirkhani et al. [10] showed that mebudipine had a greater time- and voltage- dependent inhibitory effect, compared to nifedipine and this property could explain its prominent vaso-selective action. In comparison with nifedipine, mebudipine showed a greater negative chronotropic effect, but lower negative inotropic effect (Table 2) [10].

With regards to the above findings, it is suggested that mebudipine might have a selective and protective calcium-channel blocking effect in ischemic regions (ischemia-selectivity), and the potential to be used in cardiovascular diseases without causing harmful effects such as reflex tachycardia and heat failure which have sometimes been seen with the older agents.

Effects on the calcium current

Faizi et al. [11] studied the effect of mebudipine and dibudipine in comparison with nifedipine on Ca^{2+} spikes of F1 neuronal soma membrane in Helix aspesa using current–clamp method.

It had been shown that 55% of Ca^{2+} currents in Helix neurons are carried by L type channels, which were selectively blocked by DHPs [12]. They showed that both compounds reversibly reduced the peak amplitude of action potential and after-hyperpolarization and markedly decreased the duration of Ca^{2+} spikes. The most potent of these DHPs was found to be mebudipine. However, neither of these two new DHPs nor nifedipine changed the resting membrane potential in a significant way.

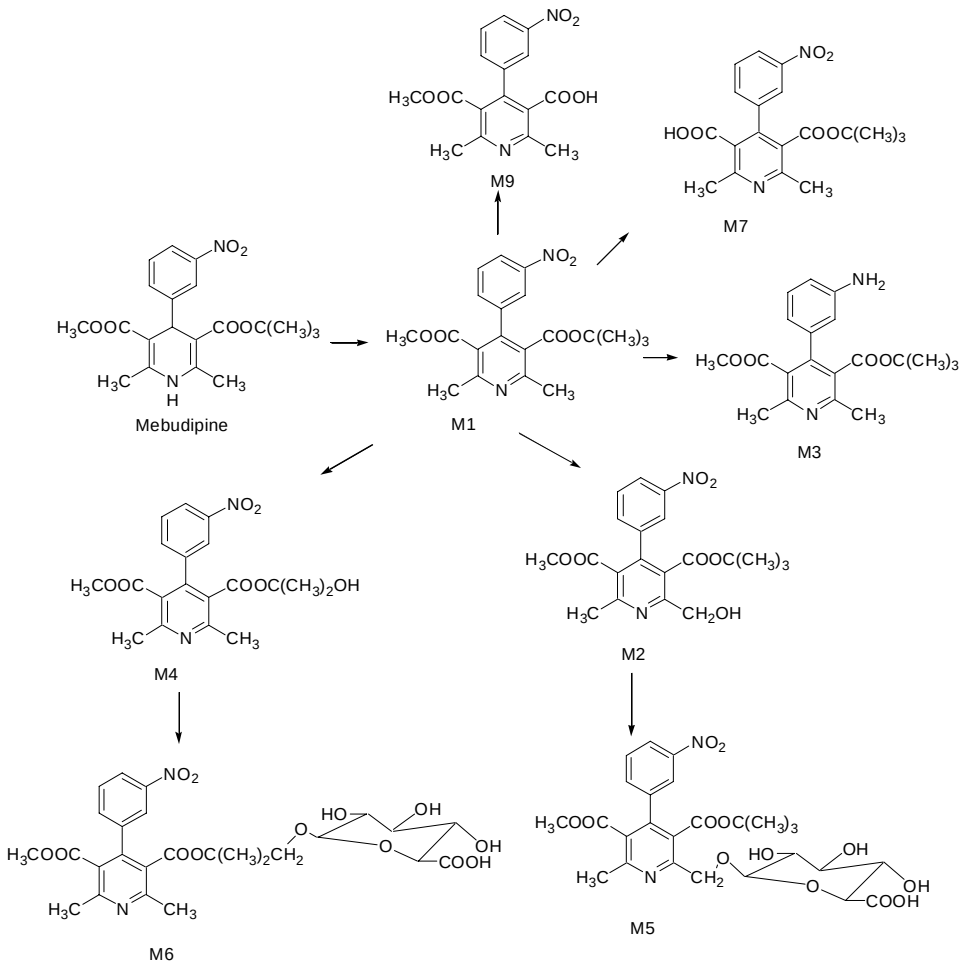

Fig 3. Proposed pathway for the metabolism of mebudipine (100μm) by isolated rat hepatocytes.

PHARMACOKINETIC PROPERTIES

Bohlooli et al. [13] developed an HPLC method to study the pharmacokinetics of these drugs in rabbits. They showed that following IV administration of 500 μg/kg of mebudipine to rabbits, it was rapidly distributed in animal body with a V_{ss} value of 5.34 l/Kg and $t_{1/2}$ value of 2.07 min. Similarly, the study of the pharmacokinetics of dibudipine in rats showed [14] that dibudipine declined in a bi-exponential fashion after IV injection in rats with a $t_{1/2}$ beta of 2.5 hours. Oral bioavailability was found to be very low similar to other DHPs. However, its distribution was found to be fast in various tissues such as liver, heart, brain, and kidney. In all examined tissues, with the exception of the brain, the concentrations of dibudipine were higher than the plasma levels. Similar results were found for mebudipine in rats [15]. A low oral bioavailability and a two compartmental kinetics model with a C_{max} value of 25.9 ng/ml after an oral dose of 10 mg/kg were observed [15]. The metabolism of these calcium-channel blockers mebudipine and dibudipine by isolated rat hepatocytes were studied by Bohlooli under in-vitro condition [16]. It was shown that these compounds were metabolized extensively through oxidative pathways and by O-glucuronidation. In contrast to nifedipine, these compounds did not show evidence of lactone formation which is produced by hydroxylation followed by internal esterification. In a previous study, mebudipine and dibudipine were demonstrated to have identical pharmacological effects as the prototype 1,4-DHP nifedipine [8]. In this study, it was demonstrated that the substitution of the methyl-ester moiety with t-butyl esters as in mebudipine and dibudipine lead to a reduction in the conversion of the parent 1,4 DHP to the inactive metabolites (Fig 2 and Fig 3).

CONCLUSION

These newer 1,4-DHPs address the problem of the short half-life of nifedipine, and are metabolically stable, possess comparable pharmacological activity to nifedipine and are therefore suitable for further development as potential therapeutic alternatives to the existing 1,4-DHP calcium-channel blockers [16].

REFERENCES

1. Fleckenstein A. Specific Pharmacology of calcium in myocardium, cardiac pacemakers and vascular smooth muscle. *Annu Rev Pharmacol Toxicol* 1977;**17:**149-166

2. Weiner DA. Calcium-channel blockers. *Med Clin North Am* 1988;**72:**83-115.
3. Epstein M. The calcium antagonist controversy: The emerging importance of drug formulation as a determinant of risk. *Am J Cardiol* 1997;**79(10A):**9-19.
4. Aouam K, Berdeaux A. Dihydropyridines from the first to the fourth generation: better effects and safety. *Therapie* 2003;**58(4):**333-339.
5. Mahmoudian M, Richards WG. QSAR of binding of dihydropyridine-type calcium antagonists to their receptor on ileal smooth muscle preparations. *J Pharm Pharmacol* 1985;**38:**272-276.
6. Rodenkirchen R, Bayer R, Steiner R, Boggert F, Meyer H, Moller E. Structure-activity studies on nifedipine in isolated cardiac muscle. *Naunyn Schmiedebergs Arch Pharmacol* 1979;**310:**69-78.
7. Mahmoudian M, Richards WG. A Quantum chemical study of structure-activity relationships of dihydropyridine calcium antagonists. *J Sci I R Iran* 1990;**1(4):**261-265.
8. Mahmoudian M, Mirkhani H, Nehardani Z, Ghiaaee S. Synthesis and Biological activity of two new calcium-cchannel blockers, mebudipine and dibudipine. *J Pharm Pharmacol* 1997;**49:**1229-1233.
9. Mirkhani H, Omrani GR, Ghiaee S, Mahmoudian M. Effect of Mebudipine and dibudipine, two new calcium-channel blockers, on rat left atrium, rat blood pressure and human internternal mammary artery. *J Pharm Pharmacol* 1999;**51:**617-622.
10. Mirkhani H, Dirin M, Youssed-Zayeh I. Mechanism of vasoselective action of mebudipine, a new calcium-channel blocker. *Pharmacology* 2003 (accepted for publication).
11. Faizi M, Janahmadi H, Mahmoudian, M. The effect of mebudipine and dibudipine, two new Ca channel blockers, in comparison with nifedipine on Ca spikes of F1 neuronal doma membrane in Helix aspersa. *Acta Physiol Hun* 2003;**90(3):**243-254.
12. Bai R, Janahmadi M, Green GGR, Sanders DJ. Effect of calcium-channel blockers on transient outward currents F76 and D1 neuronal soma membrane of the subesophageal ganglion of Helix aspersa. *J Membr Biol* 2000;**175:**179-185.
13. Bohlooli S, Keyhanfar F, Mahmoudian M. High performance liquid chromatography of mebudipine: application to pharmacokinetic study. *J Pharm Pharm Sci* 2001;**4(3):**244-247.
14. Bohlooli S, Keyhanfar F, Ghiaee S, Mahmoudian M. Application of a new high performance liquid chromatography method to the pharmacokinetics of dibudipine in rats. J Pharm Pharm Sci; 2003;**6(3):**346-351.
15. Bohlooli S, Keyhanfar F, Mahmoudian M. Pharmacokinetics of mebudipine, a new calcium antagonist, after single intravenous dose and oral administration in Rats. *Biopharm Drug Dispos* 2004;**25:** In press.
16. Bohlooli S. The study of the pharmacokinetics properties of Mebudipine and dibudipine, two new calcium-channel blockers. [Ph.D. dissertation], Tehran: Iran University of Medical Sciences; 2003.

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