ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LXV, N 1,4 SECTIO D 2010

[1]Chair and Department of Internal Medicine, Medical University of Lublin, Poland
[2]Chair and Department of Obstetrics and Perinatology, Medical University of Lublin, Poland

MARCIN TROJNAR[1], ŻANETA KIMBER-TROJNAR[2], JERZY MOSIEWICZ[1]

Calcium channel antagonists – their position in current general practice

Antagoniści kanału wapniowego – ich miejsce w obecnej praktyce lekarskiej

INTRODUCTION

Calcium channel antagonists (CCAs) represent a vast heterogeneous group of chemical compounds in terms of their structure and pharmacological profile. This is a relatively new class of drugs introduced to clinical practice barely half a century ago. From a molecular perspective all CCAs share a common property of blocking the L-type voltage- dependent calcium channels. Interestingly, data regarding inhibitory effects on other types of calcium channels (N, P/Q, R, T) are available for several CCAs [1]. On the basis of chemical structure 6 different classes of CCAs have been identified [2].

Although L-type calcium channels are distributed throughout various tissues, the effects of CCAs are expressed to the greatest degree within cardiovascular system [3]. For this reason they are widely used in cardiology. Cardiac pathology does not exhaust the list of clinical indications however. Other diseases calling for treatment with CCAs are quite diverse and go well beyond cardiovascular system dysfunction [4-7]. Major indications for CCAs are discussed below. The examples of commonly used CCAs and their therapeutic applications have been highlighted in Tab. 1.

Table 1. Examples of therapeutic applications of calcium channel antagonists

verapamil	coronary artery disease ventricle rate control supraventricular arrhythmia pulmonary arterial hypertension variant angina cluster headaches and mood disorders
amlodipine lacidipine nitrendipine	arterial hypertension variant angina
nifedipine	threatened preterm labor
nimodipine	subarachnoid hemorrhage
diltiazemu	coronary artery disease ventricle rate control supraventricular arrhythmia variant angina
flunarizine	epilepsy migraine
cinnarizine	brain ischaemia Meiniere's disease

ANTIHYPERTENSIVE TREATMENT

CCAs have been recognized as first-line therapy in arterial hypertension according to the guidelines approved by the European Society of Cardiology in 2003 [8]. In this respect CCAs are considered equal to other classes of antihypertensive drugs. Their hypotensive effect is most potent in case of class II CCAs. However, the potential to stimulate adrenergic nervous system in response to vasodilatation has limited the use of short acting agents i.e. nifedipine in clinical practice. In randomized trials this drug was proved to increase the incidence of unstable angina, myocardial infarction and the risk of death [9, 10]. Accordingly, long acting agents, e.g. amlodipine, lacidipine and felodipine are now favoured in antihypertensive treatment as they have no effect on noradrenaline serum concentrations and reactive tachycardia [11]. These drugs are especially useful in the elderly as no orthostatic hypotonia is observed. Moreover, they are considered optimal for treatment of isolated systolic arterial hypertension, often diagnosed in this patient population [12, 13].

Biological effects of CCAs include a considerable increase in coronary blood flow as well as a distinct decrease in overall heart muscle contractility resulting in improved left ventricle relaxation. These reactions are most pronounced for class I and class III CCAs, which may be generally considered an alternative to beta-blockers in case of contraindications for the latter, e.g. bronchial asthma [8, 14]. The well documented clinical trials APSIS and TIBET proved significant anti-

ischemic efficacy of CCAs. As far as management of stable angina is concerned the results obtained were comparable to those of beta-blockers [15, 16]. A further metaanalysis of 28 randomized trials involving approximately 19 thousand patients documented the positive therapeutic effect of theses drugs in patients with myocardial infarction in history [17]. CCAs are especially effective in Prinzmetal's or variant angina, which is associated with coronary artery spasm [14]. It is important to stress, however, that due to the aforementioned significant negative inotropic effect, CCAs should not be used in patients presenting heart failure symptoms. Otherwise further progression of the ventricle dysfunction may result. Verapamil is believed to be more affiliated to cardiomyocytes than diltiazem, which explains its stronger cardiodepresive effect [18].

CALCIUM CURRENT BLOCKADE AND ARRHYTHMIA

Inhibition of calcium ion efflux into the pacemaker cells results in the marked shortening of the action potential duration, impairs impulse conductance in atrio-ventriular junction as well as prolongs the repolarization phase. Re-entry phenomenon is also known to be limited during treatment with CCAs. This profile of action justified the use of the discussed drugs as anti-arrhythmic agents, which are categorized as the fourth group according to Vaughan William's classification [19]. The anti-arrhythmic properties are associated with cardioselectivity, which refers especially to class I and class III CCAs [20]. Verapamil is widely used to target supraventricular tachycardia, although its effect in paroxysmal atrial fibrillation is limited. In chronic atrial fibrillation verapamil and diltiazem are safe and efficacious in control of ventricle response, however [14]. Some authors reported the important role of T-type calcium channel blockade in a more sustained effect to prevent atrial electrical remodelling [21]. Ventricle arrhythmia represents a contraindication for cardioselective CCAs unless it is of ischemic origin.

HEMODYNAMIC EFFECTS

In pulmonary arterial hypertension CCAs are known to be one of few groups of medications effective in control of this disease. To ensure optimal results the pulmonary vascular resistance test during cardiac catheterization is necessary prior to pharmacological treatment [4]. Diltiazem and nifedipine are used most often although dosage varies in individuals and usually exceeds considerably daily doses prescribed in angina.

CCAs are thought to prevent cardiac remodeling. This phenomenon is linked to the blockade of T-type calcium channels and does not appear equally clinically significant as with angiotensin converting enzyme (ACE) inhibition [22, 23].

CALCIUM CHANNEL ANTAGONISTS AND CIRCULATORY DYSFUNCTION

Another important clinical indication pointing to CCAs as the optimal treatment strategy includes circulatory dysfunction of central nervous system or peripheral vessels as seen in Raynaud's syndrome. Syst-Eur prospective randomized study targeting nitrendipine demonstrated a significant reduction in stroke in elderly patients with isolated systolic hypertension compared with placebo [24]. Nimodipine, which has a more marked effect on the cerebral circulation than on the peripheral circulation, is used in

the management of subarachnoid hemorrhage. Although the mechanism of action is not fully understood, current evidence suggests that it may result from an increase in collateral circulation due to dilation of the small cerebral resistance vessels and/or prevention of calcium overload in the neurons [7, 25].

ANTI-ATHEROMATIC PROPERTIES

There is an ample body of experimental data to suggest that CCAs can also play a significant role in inhibiting progression of atheromatic plaques [26]. In humans this effect was observed in carotid arteries. However, no evidence to back up this hypothesis with respect to coronary arteries has been produced. Results of several large clinical studies i.e. PREVENT, NICOLE, ELSA have led various authors to the conclusion that significant decrease in the incidence of coronary episodes can be associated with treatment based on amlodipine, nislopidine and lacidipine [27-29].

EFFECT ON SMOOTH MUSCLE TISSUE

Since CCAs present potent myorelaxing effect on smooth muscle tissue they have been used to manage reflux disease and threatened preterm labor [5, 30]. In obstetrics, nifedipine is considered a very effective agent limiting uterus contractions regardless of the aforementioned potential serious adverse effects identified for this drug. Considering young age of pregnant women and short-term administration of nifedipine, such an approach is believed to be safe and well tolerated [5].

NEUROLOGICAL CONDITIONS

Further clinical indications for use of CCAs involve treatment of chronic and neuropathic pain. The growing number of recently described agents that selectively target neuronal calcium channels appear promising for a variety of pain conditions [1, 31, 32]. Flunarizine and nicardipine can be effectively used in prophylaxis of migraine preventing reactive vasodilation by inhibiting the vasoconstriction during the prodromal phase [33]. Moreover, cluster headaches and mood disorders seem to be controlled to some extent with verapamil [34].

CALCIUM HOMEOSTASIS AND EPILEPSY

The fundamental role of calcium in both physiological and pathological activity of central nervous system explains promising results obtained in preclinical experiments focusing on CCAs in epilepsy. It is hoped that limiting entry of calcium ions into neurons will inhibit epileptic discharges in the brain [35]. Interference with neuronal calcium overload can also prevent the well known sequence of events including oxidative damage and cytoskeletal degeneration [36]. The resulting death of neurons is believed to be thus limited.

Available animal experiments indicated significant antiepileptic properties of flunarizine [6]. Other CCAs positively responding in electrical tests and chemically-induced convulsions included nitrendipine, nicardipine, nifedipine, niguldipine and nimodipine [37-39].

Impact of CCAs on epilepsy management is currently subject of debate since data obtained from numerous experiments are conflicting. Clinical trials have not provided consistent insight into this issue either. Overweg et al. reported a significant reduction in complex partial and tonic-clonic seizures,

which was documented in a placebo controlled clinical trial with flunarizine [40]. Another trial, by contrast, documented very low effectiveness of flunarizine in terms of antiepileptic effects [41].

The experimental evidence produced to date suggests that CCAs have unbalanced effects on antiseizure properties of antiepileptic drugs. It has been demonstrated that combining antiepileptic drugs with several CCAs displayed significant anticonvulsant effects in experimental models of epilepsy [37, 42-44]. Some authors, however, observed no such protective effect for other CCAs. Furthermore, Borowicz et al. pointed to a potent proconvulsive action for concomitant administration of niguldipine with carbamazepine or phenobarbital in amygdala-kindled rats [45].

The beneficial antiepileptic effects of add-on treatment are at present evaluated following initial promising reports of their anticonvulsant action in experimental animal models of epilepsy and pilot studies in human epilepsy. From a clinical perspective, however, results obtained in the preclinical phase seem to indicate that combining different antiepileptic agents is more beneficial than focusing on concomitant treatment involving antiepileptic drugs and CCAs.

EFFECT ON INFLAMMATORY REACTIONS

There has also been some concern with respect to anti-inflammatory properties of CCAs. These drugs are considered to play a certain role in the synthesis and release of chemical mediators of inflammation. The experimental studies in animal models have recently demonstrated the inhibitory effect of this group of medications on the overall inflammatory response [46, 47].

CONTRAINDICATIONS AND SIDE EFFECTS

CCAs are subject to certain limitations in clinical practice. The most important contraindications include heart failure, hypotonia, bradycardia, sick sinus syndrome, second- or third degree atrioventricular block, ventricular arrhythmia as well as atrial flutter/fibrillation coexisting with preexcitation syndrome, e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndrome [14]. The majority of available CCAs are contraindicated in pregnancy although nifedipine and verapamil are considered safe and can be used to control arterial hypertension in pregnant women, preferably in second and third trimester. CCAs are transferred to brest milk and therefore they should be discontinued during lactation. With respect to polytherapy and possible drug interactions it is important to point out the risk of concomitant treatment when combining beta-blockers and CCAs. Due to the cumulative cardio-depressive effect systolic ventricle dysfunction is likely to develop [12].

CCAs are considered safe and generally well tolerated if the contraindications mentioned above are observed. Depending on the class of the CCAs used, the most common adverse effects include ankle edema and flushing episodes (dihydropyridine derivatives), nausea and constipation (diltiazem, verapamil) as well as sporadic extrapyramidal symptoms (cinarizinne, flunarizine). Interestingly, pedal edema was reported in up to 30% of patients treated with amlodipine while remarkably lower percentage of patients was affected in lacidipine or lercanidipine groups [48, 49]. This symptom is associated with dilatation of arteries and increase in hydrostatic pressure leading to activation of rennin-angiotensin-aldosteron axis. Impairment of local autoregulation reflexes and excessive adrenergic nervous system activation were also thought to play a certain role [49]. Considering the outlined pathomechanism, combining CCAs with ACE inhibitors seems a reasonable therapeutic

approach, which is associated with a marked increase in tolerability. Less common side effects are allergic reactions, gingival hyperplasia and myopathy. Earlier data raised the possibility that CCAs might be associated with an increased risk of cancer [50]. According to more recent findings prior observations may have reflected the presence of other risk factors for cancer, such as increased cigarette smoking or alcohol use among people with cardiac disease treated with CCAs. Another trial demonstrated that the incidence of adverse effects such as cancer, gastrointestinal hemorrhage and dementia, which have been associated with the use of CCAs, did not differ between the control and active groups during the double-blind trial or during the extended follow-up period [24].

METABOLIC PROFILE

Numerous studies have indicated that certain classes of antihypertensive medications present differential influence on carbohydrate and lipid metabolism in humans. CCAs are neutral in this respect. The use CCAs is not associated with the risk of new-onset diabetes, which has been proved for diuretics and beta-blockers [51]. Some reports suggest a beneficial effect of CCAs on lipid metabolism as well.

CONCLUDING REMARKS

In conclusion, it should be underlined that CCAs represent a versatile class of medications that are useful in the treatment of a broad spectrum of medical conditions. Thanks to sophisticated methods of synthesis these drugs have undoubtedly evolved in recent years but at the same time the older generations are still prescribed by physicians quite often. Considering the vital role of calcium ion in cell metabolism, further research will probably identify new indications for CCAs.

REFERENCES

1. Ebersberger A., Portz S., Meissner W., et al. Effects of N-, P/Q- and L-type calcium channel blockers on nociceptive neurones of the trigeminal nucleus with input from the dura. Cephalalgia 2004; 24: 250-261.
2. Kochegarov A.A. Pharmacological modulators of voltage-gated calcium channels and their therapeutical application. Cell Calcium 2003; 33: 145-162.
3. Romero M., Sanchez I., Pujol M.D. New advances in the field of calcium channel antagonists: cardiovascular effects and structure-activity relationships. Curr Med Chem Cardiovasc Hematol Agents 2003; 1: 113-141.
4. Archer S.L., Michelakis E.D. An evidence-based approach to the management of pulmonary arterial hypertension. Curr Opin Cardiol 2006; 21: 385-392.
5. Kimber-Trojnar Z., Leszczyńska-Gorzelak B., Marciniak B., et al. Tocolytic therapy in threatened preterm labor. [Article in Polish] Ginekol Pol 2010; 81: 120-124.
6. Binnie C.D. Flunarizine in epilepsy. Ann. of N. Y. Acad Sci 1988; 522: 710-711.
7. DiPalma J.R. Nimodipine in subarachnoid hemorrhage. Am Fam Physician 1989; 40: 143-145.

8. European Society of Hypertension-European Society of Cardiology Guidelines for the Management of Arterial Hypertension. J Hypertens 2003; 221: 1011-1053.
9. Beevers D.G., Sleight P. Czy stosowanie antagonistów wapnia z grupy pochodnych dwuhydropirydyny o krótkim czasie działania w leczeniu nadciśnienia tętniczego może być ryzykowne dla chorych. BMJ (wyd. polskie) 1996; 312: 1143.
10. Grossman E., Messerrli F.H., Grodzicki T., et al. Should a moratorium be placed on sublingual nifedypine capsules given for hypertesive emergencies and pseudoemergencies? JAMA 1996; 276: 1328-1331.
11. Binggeli C., Corti R., Sudano I., et al. Effects of chronic calcium channel blockade on sympathetic nerve activity in hypertension. Hypertension 2002; 39: 892-896.
12. Sica D.A. Pharmacotherapy review: calcium channel blockers. J Clin Hypertens (Greenwich) 2006; 8: 53-56.
13. Pannarale G., Licitra R., Leonetti S., et al. Evaluation of systolic blood pressure control in elderly patients with isolated systolic hypertension. Eur Rev Med Pharmacol Sci 2006; 10: 111-114.
14. Opie L.H. Calcium antagonists. Mechanisms, therapeutic indications and reservations: a Review. *QJM* 1984; 53: 1-16.
15. Fox K.M., Mulcahy D., Findlay I., et al. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedypine SR and their combination on exercise test and total ischaemic burden in 608 patients with stable angina. Eur Heart J 1996; 17: 96-103.
16. Rehnqvist N., Hjemdahl P., Billing E., et al. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). Eur Heart J 1996; 17: 76-81.
17. Held P.H., Yusuf S., Furberg C.D. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. BMJ 1989, 299: 1187-1192.
18. Striessnig J., Grabner M., Mitterdorfer J., et al. Structural basis of drug binding to L Ca2+ channels. Trends Pharmacol Sci 1998; 19: 108-115.
19. Roden D.M. Antiarrhythmic drugs: from mechanisms to clinical practice. Heart 2000; 84: 339-346.
20. Godfraind T. Calcium-channel modulators for cardiovascular disease. Expert Opin Emerg Drugs 2006; 11: 49-73.
21. Ohashi N., Mitamura H., Tanimoto K., et al. Comparison between calcium channel blocking drugs with different potencies for T- and L-type channels in preventing atrial electrical remodeling. J Cardiovasc Pharmacol 2004; 44: 386-392.
22. Jugdutt B.I., Menon V., Kumar D., et al. Vascular remodeling during healing after myocardial infarction in the dog model: effects of reperfusion, amlodipine and enalapril. J Am Coll Cardiol 2002; 39: 1538-1545.
23. Nuss H.B., Houser S.R. T-type Ca2+ current is expressed in hypertrophied adult feline left ventricular myocytes. Circ Res 1993; 73: 777-782.
24. Staessen J.A., Thijs L., Birkenhäger W.H., et al. Update on the systolic hypertension in Europe (Syst-Eur) trial. The Syst-Eur Investigators. Hypertension 1999; 33: 1476-1477.
25. Young W.L., Josovitz K., Morales O., et al. The effect of nimodipine on post-ischemic cerebral glucose utilization and blood flow in the rat. Anesthesiology 1987; 67: 54-59.
26. Garcia-Perez B., Ayala I., Castells M.T., et al. Effects of nifedipine, verapamil and diltiazem on serum

biochemical parameters and aortic composition of atherosclerotic chickens. Biomed Pharmacother 2005; 59: 1-7.

27. Dens J.A., Desmet W.J., Coussement P., et al. Long-term effects of nisoldypine on the progression of coronary atherosclerosis and the occurrence of clinical events: the NICOLE study. Heart 2003; 89: 887-892.
28. Pitt B., Byington R.P., Furberg C.D., et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. Circulation 2000; 102: 1503-1510.
29. Zanchetti A., Bond M.G., Hennig M., et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation 2002; 106: 2422-2427.
30. Storr M., Allescher H.D., Classen M. Current concepts on pathophysiology, diagnosis and treatment of diffuse oesophageal spasm. Drugs 2001; 61: 579-591.
31. Anand P. Neurotrophic factors and their receptors in human sensory neuropathies. Prog Brain Res 2004; 146: 477-492.
32. Yaksh T.L. Calcium channels as therapeutic targets in neuropathic pain. J Pain 2006; 7: 13-30.
33. Gobel H., Heinze A., Heinze-Kuhn K. Prophylactic measures and acute treatment of migraine. [Article in German] Schmerz. 2006; 20: 541-554.
34. Leone M., D'Amico D., Frediani F., et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. Neurology 2000; 54: 1382-1385.
35. Uematsu D., Araki N., Greenberg J.H., et al. Alterations in cytosolic free calcium in the cat cortex during bicuculline-induced epilepsy. Brain Res Bull 1990; 24: 285-288.
36. Kristian T., Siesjo B.K. Calcium in ischemic cell death. Stroke 1998; 29: 705-718.
37. Czuczwar S.J., Gąsior M., Janusz W., et al. Influence of flunarizine, nicardipine and nimodipine on the anticonvulsant activity of different antiepileptic drugs in mice. Neuropharmacol 1992; 31: 1179-1183.
38. De Sarro G.B., Meldrum B.S., Nistico G. Anticonvulsant effects of some calcium entry blockers in DBA/2 mice. Br J Pharmacol 1988; 93: 247-256.
39. O'Neill S.K., Bolger G.T. The effects of dihydropyridine calcium channel modulators on pentylenetetrazole convulsions. Brain Res Bull 1990; 25: 211-214.
40. Overweg J., Binnie C.D., Meijer J.W., et al. Double-blind placebo-controlled trial of flunarizine as add-on therapy in epilepsy. Epilepsia 1984; 25: 217-222.
41. Nakane Y., Seino M., Yaqi K., et al. Effects of flunarizine on intractable epilepsy. Arzneimittelforschung 1989; 39: 793-798.
42. Borowicz K.K., Gąsior M., Kleinrok Z., et al. Influence of isradipine, niguldipine and dantrolene on the anticonvulsive action of conventional antiepileptics in mice. Eur J Pharmacol 1997; 323: 45-51.
43. Czuczwar S.J., Chodkowska A., Kleinrok Z., et al. Effects of calcium channel inhibitors upon the efficacy of common antiepileptic drugs. Eur J Pharmacol 1990; 176: 75-83.
44. Kamiński R., Jasiński M., Jagiełło-Wójtowicz E., et al. Effect of amlodipine upon the protective activity of antiepileptic drugs against maximal electroshock-induced seizures in mice. Pharmacol Res 1999; 40: 319-325.

45. Borowicz K.K., Kleinrok Z., Czuczwar S.J. Niguldipine impairs the protective activity of carbamazepine and phenobarbital in amygdala-kindled seizures in rats. Eur Neuropsychopharmacol 2002; 12: 225-233.
46. Abdollahi M., Nikfar S., Abdoli N. Potentiation by nitric oxide synthase inhibitor and calcium channel blocker of aspartame-induced antinociception in the mouse formalin test. Fundam Clin Pharmacol 2001; 15: 117–123.
47. Suleyman H., Halici Z., Hacimuftuoglu A., et al. Role of adrenal gland hormones in antiinflammatory effect of calcium channel blockers. Pharmacol Rep. 2006; 58: 692-699.
48. Andresdottir M.B., van Hamersvelt H.W., van Helden M.J., et al. Ankle edema formation during treatment with the calcium channel blockers lacidipine and amlodipine: a single-centre study. J Cardiovasc Pharmacol 2000; 35: 25-30.
49. Weir M.R. Incidence of pedal edema formation with dihydropyridine calcium channel blockers: issues and practical significance. J Clin Hypertens 2003; 5: 330-335.
50. Braun S., Boyko V., Behar S., et al. Calcium channel blocking agents and risk of cancer in patients with coronary heart disease. J Am Coll Cardiol 1998; 31: 804-808.
51. Sarafidis P.A., Bakris G.L. Antihypertensive therapy and the risk of new-onset diabetes. Diabetes Care 2006; 29: 1167-1169.

ABSTRACT

Calcium channel antagonists (CCAs) represent a versatile class of medications that are commonly used to manage a relatively broad spectrum of clinical conditions. The initial reports regarding their significant role in clinical practice date back only a few decades. The aim of this review was to collect current literature data on indications for the use of CCAs. Results obtained from randomized trials are referred to in this paper. The impact of CCAs on cardiovascular system is discussed thoroughly, less common medical situations justifying the use of CCAs including peripheral circulation dysfunction and epilepsy are reported as well.

STRESZCZENIE

Antagoniści kanału wapniowego (AKW) stanowią heterogenną grupę leków, które są powszechnie stosowane w różnych stanach klinicznych zaledwie od kilku dekad. Celem niniejszej pracy było zebranie aktualnych danych literaturowych dotyczących wskazań do stosowania AKW. W artykule przytoczono obiektywne wyniki uzyskane w dobrze udokumentowanych randomizowanych badaniach klinicznych. Dodatkowo autorzy w szczegółowy sposób omówili wpływ AKW na czynność układu sercowo-naczyniowego, a także odnieśli się do rzadszych wskazań uzasadniających zastosowanie AKW, takich jak zaburzenia krążenia obwodowego czy padaczka.

Key words: Calcium channels, coronary artery disease, hypertension, epilepsy