Calcium-channel blockers and cardiac arrhythmias within the elderly population

**Sandra A Jones[†] &
Matthew K Lancaster**

[†]Author for correspondence
University of Hull,
Biomedical Sciences,
Hardy Building,
Kingston-upon-Hull,
HU6 7RX, UK
Tel.: +44 148 246 6463;
s.a.jones@hull.ac.uk

'Great care should be taken in prescribing the commonly-utilized CCBs to the elderly, as ... the risk of potentially precipitating SA node dysfunction is vastly increased.'

A recent study that examined the sinoatrial (SA) node, an area of tissue that acts as the normal cardiac pacemaker, demonstrated an increasing sensitivity to calcium-channel blockers (CCBs) with increasing age. CCBs, also known as calcium antagonists or calcium blockers, encompass the pharmaceutical drugs mibefradil, diltiazem, verapamil and nifedipine. These drugs are commonly prescribed in the treatment of hypertension owing to their actions of reducing the pumping strength of the heart and causing relaxation of blood vessels.

Pacemaker of the aging heart

The size of the elderly population is rapidly increasing. It has been predicted that by the year 2035, over a quarter of the Western population will be 65 years or older [1]. Abnormal rhythm disturbances, commonly referred to as arrhythmias, are highly prevalent in the elderly and affect more than 10% of the population who are less than 70 years of age [2]. Clinical studies performed on patients ranging from 14 to 84 years of age without a history of arrhythmias concluded that the elderly were at most risk of developing atrial arrhythmias [3]. Elderly patients demonstrate a slower conduction of the action potential compared with their young counterparts, a potential major contributing factor towards the initiation of conduction abnormalities and arrhythmias [4]. This also suggests that the mechanisms responsible for the induction of arrhythmias in the elderly could be different to those identified in the young [5].

Within the central area of the SA node, the L-type calcium current conducted by the Cav_{1.2} protein is responsible for the upstroke of the action potential; this is in contrast with atrial

and ventricular muscle where the voltage-gated sodium channel (Nav_{1.5}) is responsible [6]. With increasing age, there is an age-associated loss of Cav_{1.2} from the center of the SA node, and a loss of the gap-junction channel connexin 43, which is responsible for the intercellular propagation of the action potential across the heart [7,8]. The age-associated loss of these channels associates with significantly depressed conductivity and increases the potential for dysfunction of the SA node in the elderly population [4-8].

Calcium-channel blockers & the aging heart

Calcium channel blockers were developed in the 1970s, however, their use has become increasingly controversial owing to their association with the induction of bradycardia and the appearance of what can be described as an apparently failing SA node or sick-sinus syndrome [9]. It has been estimated that more cases of bradycardia requiring intervention, such as artificial pacemaker implantation, are caused by prescription drugs than by any natural degeneration of the pacemaker. In addition, the pacemaker of the aged individual frequently shows signs of being compromised and limited in response, making it evident that CCBs could be potentially problematic in the elderly.

'...mechanisms responsible for the induction of arrhythmias in the elderly could be different to those identified in the young.'

From a study of 2400 patients treated with the CCB mibefradil (Posicor®), 142 sudden deaths occurred and several pacemaker implants were required [10]. Further investigations demonstrated that mibefradil administration in the elderly was responsible for QT prolongation and increased the risk of life-threatening ventricular arrhythmias, which were alleviated following discontinuation [10]. As a result, mibefradil was withdrawn from the Western market owing to its association with the identified side effects, particularly bradycardia and appearance of the sick-sinus syndrome [10,11].

Our investigations into the dihydropyridine, nifedipine (Adalat®, Nifedical® and Procardia®), has continued to raise awareness of the potential hazards of CCB use in the elderly and the mechanisms behind this risk. We demonstrated that the sensitivity of the SA node to nifedipine increased with age, owing to a continued decline in the expression of Cav_{1.2} in the SA node and, thus, a reduction in the L-type calcium current [8]. Furthermore, data from epidemiology studies have confirmed an age-related risk of severe reactions exhibited by elderly patients administered nifedipine, even at low doses [12,13]. The current recommendation from the American Heart Association (AHA) to physicians is that “short-acting nifedipine should be used with great caution, especially at higher doses” and that “if patients are concerned about possible adverse effects of high doses of short-acting nifedipine, they should not stop taking their medication but consult their physician” [102]. Although there is no specific reference to the elderly, it is our opinion that physicians should consider the use of alternative treatments for elderly patients in respect of current findings and a full evaluation of each specific patient's condition.

‘...more cases of bradycardia requiring intervention, such as artificial pacemaker implantation, are caused by prescription drugs than by any natural degeneration of the pacemaker.’

Carosella *et al.* demonstrated that verapamil (Cordilox® and Securon®) was tolerated equally well by middle-aged and elderly patients with no apparent adverse reactions [12], however, a prolongation of the PR interval was detected in the elderly group. This conduction issue is perhaps to be expected if conduction of the action potential is compromised in the aged atria, which is also more sensitive to calcium-channel blockade [5,7,14]. Another issue is that verapamil elimination kinetics slow in the elderly and this leads to significantly greater SA node depression, in comparison with the actions of comparable verapamil doses in young individuals [15].

Recent reports favor the use of multitherapy when CCBs are deployed [16,17]. Elderly patients administered verapamil in conjunction with a β -blocker display significant improvement in exercise tolerance and an overall improvement in their quality of life [16]. This combination

therapy potentially permits a lower concentration of verapamil to be used, offering a greater degree of safety to the aged heart. Similarly, monotherapy of diltiazem (Tildiem®) has also proved successful in the elderly population [18], but the drug appears to have greater efficacy when used in combination with an angiotensin-converting enzyme inhibitor such as lisinopril [17,19]. This combination could also be exploited to improve the safety of use of such a CCB in the aged heart.

Conclusion

Great care should be taken in prescribing the commonly utilized CCBs to the elderly, as tolerance of the SA node to such interventions is reduced with age and the risk of potentially precipitating SA node dysfunction is vastly increased. Other considerations should also be undertaken, such as age-related changes in the clearance of the pharmacological drug from plasma, as this can yield an exaggerated dose in the elderly patient.

Future perspective

Overall, it is difficult to conclusively state whether the susceptibility of the elderly patient to the toxicity of CCBs outweigh their merits, however, it does highlight the need to consider titrating drug doses relative to the patient's age or to use non-CCB alternatives. The majority of patients administered with CCBs by their physician are within the elderly classification, and their doses are usually titrated to exhibit a good control of blood pressure, whilst minimizing the chance of unwanted bradycardia. In the future, as the population becomes increasingly aged, awareness of these considerations needs to be maintained and increased so that when physicians are confronted by an elderly patient displaying cardiac rhythm disturbances, the first course of action is to consider changing their medication rather than to consider a cardiac pacemaker implant.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1. Lakatta E: Cardiovascular ageing in health sets the stage for cardiovascular disease. *Heart Lung Circ.* 11, 76–91 (2002).
2. Kannel WB, Abbott RD, Savage DD *et al.*: Coronary heart disease and atrial fibrillation: the Framingham study. *Am. Heart J.* 106, 389–396 (1983).
3. Sakabe K, Fukuda N, Nada T *et al.*: Age-related changes in the electrophysiologic properties of the atrium in patients with no history of atrial fibrillation. *Jpn. Heart J.* 44, 385–393 (2003).
4. Anyukhovsky EP, Sosunov EA, Chandra P *et al.*: Age-associated changes in electrophysiologic remodelling: a potential contributor to initiation of atrial fibrillation. *Cardiovasc. Res.* 66, 353–363 (2004).
5. Kostin S, Klein G, Szalay Z *et al.*: Structural correlate of atrial fibrillation in human patients. *Cardiovasc. Res.* 54, 361–379 (2002).
6. Boyett MR, Honjo H, Kodama I: The sinoatrial node, a heterogeneous pacemaker structure. *Cardiovas. Res.* 47, 658–687 (2000).
7. Jones SA, Lancaster MK, Boyett MR: Age-related changes of connexins and conduction within the sinoatrial node. *J. Physiol.* 560, 429–437 (2004).
8. Jones SA, Boyett MR, Lancaster MK: Declining into failure: the age-dependent loss of the L-type calcium channel within the sinoatrial node. *Circulation* 115, 1183–1190 (2007).
9. Van Wagoner DR, Pond AL, Lamorgese M *et al.*: Atrial L-type Ca^{2+} currents and human atrial fibrillation. *Circ. Res.* 85, 428–436 (1999).
10. Gläser S, Steinbach M, Opitz C *et al.*: Torsades de pointes caused by mibefradil. *Eur. J. Heart Fail.* 3, 627–630 (2001).
11. Mullins ME, Horowitz BZ, Linden DH *et al.*: Life-threatening interaction of mibefradil and β -blockers with dihydropyridine calcium channel blockers. *JAMA* 280, 157–158 (1998).
12. Pahor M, Manto A, Pedone C, Carosella L, Guralnik JM, Carbonin P: Age and severe adverse drug reactions caused by nifedipine and verapamil. *J. Clin. Epidemiol.* 49, 921–928 (1996).
13. Ishibashi Y, Shimada T, Yoshitomi H *et al.*: Sublingual nifedipine in elderly patients: even a low dose induces myocardial ischaemia. *Clin. Exp. Pharmacol. Physiol.* 26, 404–410 (1999).
14. Carosella L, Menichelli P, Alimenti M *et al.*: Verapamil disposition and cardiovascular effects in elderly patients after single intravenous and oral doses. *Cardiovasc. Drugs Ther.* 3, 417–425 (1989).
15. Schwartz JB: Aging alters verapamil elimination and dynamics: single dose and steady-state responses. *J. Pharmacol. Exp. Ther.* 255, 364–373 (1990).
16. Tsuneda T, Yamashita T, Fukunami M *et al.*: Rate control and quality of life in patients with permanent atrial fibrillation: the Quality of Life and Atrial Fibrillation (QOLAF) study. *Circ. J.* 70, 965–970 (2006).
17. Karotsis AK, Symeonidis A, Mastorantonakis SE *et al.*: Additional antihypertensive effect of drugs in hypertensive subjects uncontrolled on diltiazem monotherapy: a randomized controlled trial using office and home blood pressure monitoring. *Clin. Exp. Hypertens.* 28, 655–662 (2006).
18. Fogari R, Zoppi A, Mugellini A *et al.*: Effect of sustained-release diltiazem on ambulatory blood pressure and left ventricular mass in elderly patients with hypertension. *Curr. Ther. Res.* 59, 725–736 (1998).
19. Chan P, Lin CN, Tomlinson B *et al.*: Additive effects of diltiazem and lisinopril in the treatment of elderly patients with mild-to-moderate hypertension. *Am. J. Hypertens.* 10, 743–749. (1997).

Websites

101. Sasich LD, Wolfe SM: The withdrawal of the calcium-channel blocker mibefradil (Posicor®) from the market. HRG Publication 1441 (1998) www.citizen.org/publications/release.cfm?ID=6638
102. American Heart Association: information for patients, 2008 www.americanheart.org/presenter.jhtml?identifier=4460

Affiliations

- Sandra A Jones, PhD
University of Hull, Biomedical Sciences,
Hardy Building, Kingston-upon-Hull,
HU6 7RX, UK
Tél.: +44 148 246 6463;
s.a.jones@hull.ac.uk
- Matthew K Lancaster, PhD
University of Leeds, Institute of Membrane &
Systems Biology, Faculty of Biological Sciences,
Leeds, LS2 9JT, UK
Tél.: +44 113 343 4285;
m.k.lancaster@leeds.ac.uk