Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 62; Numer/Number 1/2011
ISSN 0423–104X

Bisphosphonates and the risk of atrial fibrillation

Bisfosfoniany a ryzyko migotania przedsionków

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Abstract

Osteoporosis is a growing problem in an ageing society. It affects women of post-menopausal age, as well as elderly subjects of both sexes, often with dysfunction of the cardiovascular system or with an increased risk of circulation disorders.

It has been found that the mortality rate of subjects with osteoporosis is comparable to that of patients suffering from such diseases as obturative pulmonary disease or myocardial ischaemia.

Bisphosphonates are the most thoroughly studied group of drugs prescribed for the treatment of osteoporosis. Their administration is, however, associated with a risk of adverse symptoms, which can occur as gastro-intestinal tract disturbances, muscular-osseous pains, mandible necrosis, atypical fractures and other symptoms. Recently, there has been discussion about an increased risk of atrial fibrillation in bisphosphonate-using female patients. This paper focuses on this particular problem, while summing up the actual status of knowledge regarding possible associations of bisphosphonates with cardiac rhythm disturbances. **(Pol J Endocrinol 2011; 62 (1): 93–96)**

Key words: *bisphosphonates, osteoporosis, atrial fibrillation*

Streszczenie

Osteoporoza jest narastającym problemem starzejącego się społeczeństwa. Dotyczy kobiet w wieku pomenopauzalnym i ludzi starszych obu płci, często z dysfunkcją układu sercowo-naczyniowego lub zwiększonym ryzykiem chorób układu krążenia. Stwierdzono, że śmiertelność osób chorujących na osteoporozę jest porównywalna z pacjentami chorującymi na takie choroby, jak obturacyjna choroba płuc, choroba niedokrwienna serca i inne.

Bisfosfoniany są najlepiej przebadaną grupą leków stosowanych w terapii osteoporozy. Z ich przyjmowaniem wiąże się ryzyko wystąpienia objawów niepożądanych, w tym zaburzeń ze strony przewodu pokarmowego, bólów mięśniowo-kostnych, martwicy żuchwy, atypowych złamań i innych. W ostatnim czasie pojawiły się informacje o wzroście ryzyka migotania przedsionków u pacjentek stosujących bisfosfoniany. Praca ma na celu zwrócenie uwagi na problem i podsumowanie aktualnego stanu wiedzy na temat powiązań bisfosfonianów z zaburzeniami rytmu serca. **(Endokrynol Pol 2011; 62 (1): 93–96)**

Słowa kluczowe: *bisfosfoniany, osteoporoza, migotanie przedsionków*

Introduction

Atrial fibrillation (AF) is the most frequent disturbance of cardiac rhythm observed in clinical practice, accounting for approximately one in three hospitalisations for abnormal cardiac rhythm, which, in turn, is associated with risks of increased morbidity and mortality rates with their related economic impacts [1]. During the last 20 years, the number of hospitalisations for atrial fibrillation has risen by 66%.

The number of atrial fibrillation incidents doubles with each life decade after the age of 55, attaining its peak between the 85th and the 94th years of life [2, 3]; after the 75th year of life, it affects more frequently women than men (60 vs. 40%) and grows twice as fast in Caucasians as opposed to the black population [4–6].

The initial information regarding AF episodes in the course of therapy with bisphosphonates appeared during the analysis of results of the HORIZON randomised, double-blind study (Pivotal Fracture Trial) [7] (Fig. 1). The patients who received zoledronate intravenously demonstrated more episodes of severe cardiac rhythm disturbances, such as atrial fibrillation, than did the placebo-receiving control group. The term 'severe incidents' refers to those cases which require hospitalisation, intensive treatment, lifestyle change and which are often terminated by the patient's death. In the reported study, the groups did not differ regarding the incidence of other cardiac rhythm disturbances.

The appearance of that information prompted subsequent studies, including a retrospective analysis of the FIT study, in which alendronate, an oral form of bis-

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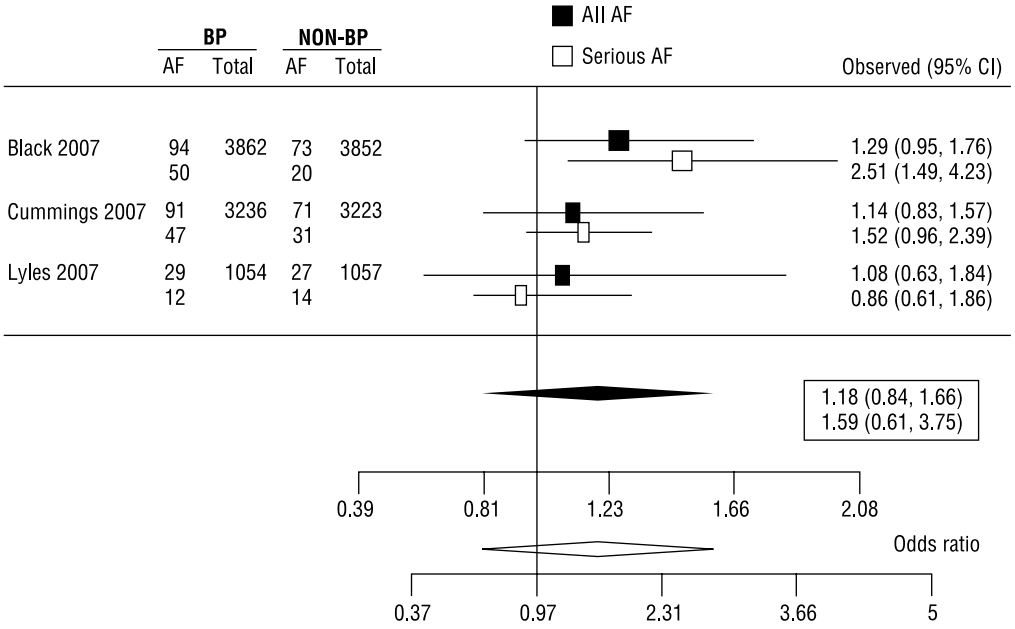


Figure 1. *The risk of atrial fibrillation (all cases, serious cases) following Mak et al. [18] in own modification. BP — bisphosphonates; AF — atrial fibrillation*

Rycina 1. *Ryzyko występowania migotania przedsionków (wszystkich przypadków, ciężkich przypadków) na podstawie Mak i wsp. [18] w modyfikacji własnej. BP — bisfosfoniany; AF — migotanie przedsionków*

phosphonate, was given at a dose of 10 mg daily to women with post-menopausal osteoporosis [8]. Despite the lack of statistically significant differences in bisphosphonate-administered patients, a tendency emerged towards a higher incidence of severe AF episodes vs. the placebo-receiving group (RR 1.51 with 95% CI, 0.97–2.40) [9]. The prevalence of all the AF incidents did not differ between the groups.

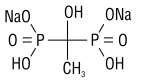
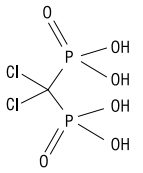
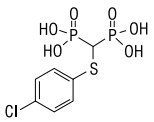
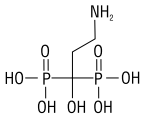
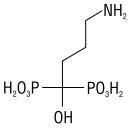
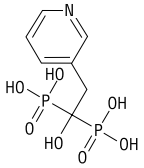
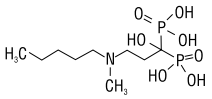
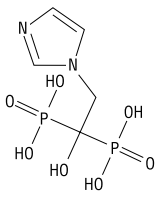
In another HORIZON study (Recurrent Fracture Trial) [10], no changes were demonstrated in the incidence of atrial fibrillation episodes, either severe or any other, between the group of zoledronate-using patients and the placebo group. Similarly, analysing the results from a randomised study with a control group of risedronate (another bisphosphonate) no differences were found between the active drug and the control [11].

In another study, a reverse situation was evaluated, i.e. the number of bisphosphonate-using subjects, both at the time of the study and at any other time, in a group of patients with AF episodes vs. a group of patients with no cardiac rhythm disturbances [12, 13]. In the first of those two studies, a group of 719 women with AF was compared to a group without cardiac rhythm disorders [12]. In the patients with AF, 6.55% of women had been treated with alendronate at any time, vs. 4.15% of women without AF ($p < 0.05$). It was concluded that the risk of AF was higher in the alendronate-using group vs. the alendronate-naïve group (RR 1.86, 95% CI, 1.09–3.15). Contrary to the findings in the American study group, the Danes did not find any increased risk of AF [13]. In a study group of 13,586 women with AF or flutter in their history, 3.2% had used bisphosphonates vs. the group of 68,054 healthy women, in whom bisphosphonates (etidronate or alendronate) had been used by 2.9% of the patients (RR 0.95, 95% CI, 0.84–1.07).

Summing up those two clinical studies, a higher incidence of severe episodes of AF was found. This may suggest that in patients predisposed to cardiac rhythm disturbances for any reason, an administration of bisphosphonates may initiate cardiac rhythm disorders. Until more data is collected on the relationship between bisphosphonates and atrial fibrillation, the therapy should be implemented with great care regarding all patients with cardiovascular diseases, giving priority to the therapeutic advantages over the possible danger of complications. On the other hand, the lack of data from prospective studies should not limit the possibility of bisphosphonate applications, nor be the reason for therapy withdrawal [14].

Analysing various parameters emphasised the role of gender (more often men), ageing, the quantity of used drugs, and the use of hypertensives, as risk factors for AF [15]. Moreover, it has been observed that, in the course of alendronate therapy of patients with diabetes mellitus, the risk of atrial fibrillation was higher than in subjects without metabolic disorders [12]. The prevalence of atrial fibrillation and flutter was also compared, as well as the cases of acute coronary incidents in

Table I. *Biochemical structure and division of bisphospho-nates according to antiresorptive potential*
Tabela I. *Struktura biochemiczna i podział bisfosfonianów według potencjału antyresorpcyjnego*

Generation	Chemical structure — lateral chain	Biochemical structure	Drug	Antiresorptive potential
I	Alkyl		Etidronate	1
	Halide		Clodronate	10
II	Cyclic		Tiludronate	10
	Cyclic		Pamidronate	100
	Amine		Alendronate	100–1000
III	Pyridinyl Cyclic		Risedronate	1000–10 000
	Cyclic		Ibandronate	1000–10 000
	Cyclic		Zoledronate	↑ 10 000

27 out of 257 patients treated for osteoporosis with alendronate at a daily dose of 10 mg, a weekly dose of 70 mg, and with raloxifene [16].

Compared to raloxifene, alendronate did not increase the risk of AF or acute coronary syndromes. However, analysing a group of patients with cardiological problems in their history and who had received drugs for circulation diseases for at least one year, a statistically significant increase in the number of acute coronary syndromes was found vs. the medical agents of the SERM group. In turn, alendronate, when received less frequently, exerted a smaller risk vs. its form ad-

ministered once daily. The authors drew the conclusion that chronic administration of alendronate should not be suggested to women with cardiological problems in their history.

Cardiac complications appeared more frequently after strong bisphosphonates (Table I), i.e. zoledronate and alendronate [17, 18]. The mechanism by which bisphosphonates induce AF has yet to be entirely understood. Perhaps, the drugs enhance the susceptibility towards cardiac rhythm disorders, decreasing the concentrations of calcium and phosphates [19, 21], similarly as in hypocalcaemia in the course of secondary hyperparathyroidism in dialysed subjects [22]. The atrium demonstrates high sensitivity to calcium concentration reductions [23]. It seems, however, that in the case of bisphosphonates, there is too little data to back up such a thesis [17]. This is confirmed by the observations of Black et al. [7] who found no differences after zoledronate in calcium or phosphate concentrations in patients with or without AF.

The arrhythmogenic activity of proinflammatory cytokines, secreted during parenteral administration of bisphosphonates, may be regarded as another explanation of the issue [24, 25]. However, analysing the time of the complication's appearance in various studies, it was found that atrial fibrillation could not be regarded as an acute complication of the applied therapy [7, 9]. Most often, the incident occurred after at least one year of therapy, enhancing after four years of zoledronate administration and after a period longer than 30 days from infusion (47–50 days). Another aspect should also be taken into consideration. Certain adverse effects, e.g. influenza-like symptoms, occur after nitrogen containing bisphosphonates, including alendronate and zoledronate [26]. There have been few studies concerning AF in the course of aminobisphosphonates, and their results are unclear [17, 18]. Even if no greater number of incidents were observed after alendronate as opposed to etidronate [13], the difference against alendronate was distinct in a group of patients with increased morbidity and using multiple drugs [15].

Summing up, doctors and patients should pay attention to the advantages and risks associated with the use of drugs. In women at high risk of AF and small risk of fractures, a particularly close consideration of the issue would be advisable. But for most patients at high risk of fractures, the advantages of bisphosphonate therapy may be more important for their general health status than the risks of atrial fibrillation [7, 9, 10].

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