1.1. Bupropion and cardiac ischaemia

introduction

Bupropion (Zyban®, Wellbutrin®, Quomen®, Elontril®, Zyntabac®) is a selective norepinephrine and dopamine reuptake inhibitor which has been registered in the Netherlands since 1999. Its use is indicated for treatment of depression (Wellbutrin® and Elontril®) and as aid for smoking cessation (Zyban®, Quomen® and Zyntabac®). No exact data on use of bupropion in the Dutch population are accessible. Given the fact that bupropion as an aid in smoking cessation is not reimbursed by health care insurances, the data from the Drug Information System of the Dutch Health Care Insurance Board (n=1,402 in 2007) are probably an underestimation of the number of patients who use this drug. Headache, nausea, vomiting, sleeplessness are among the most common adverse reactions of bupropion. Tachycardia and palpitations are described as potential cardiac side-effects. Non-specified chest pain has been the subject of Lareb attention [1] and is mentioned under the System Organ Class (SOC) general disorders and administration site conditions without referring to ischaemia [2].
It is advised to use bupropion with caution in patients with cardiovascular disorder however it is stated in the SmPC that bupropion is in general well tolerated in patients with ischaemic cardiovascular conditions.
Bupropion is metabolised by CYP2D6 and, to a lesser extend by other systems as CYP3A4 [2]

Reports

On November 18th 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of myocardial infarction associated to the use of bupropion, one report of an acute coronary syndrome in association to this drug and another three reports of angina pectoris. Data are shown in table 1. In all reports bupropion was used for smoking cessation. Co-medication was not reported in these seven cases. Latencies ranged from 90 minutes to six weeks.

Table 1: Reports of cardiac ischaemia associated to bupropion.

Patient, Number, Sex, Age	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A, 28417 F, 59	bupropion tablet 150mg tobacco use disorder, unspecified use	not reported	myocardial infarction	5 days discontinued not reported
B, 31087 M, 54	bupropion tablet 150mg tobacco use disorder, unspecified use	not reported	myocardial infarction	6 weeks unknown unknown
C, 31482 F, 50	bupropion tablet 150mg	not reported	myocardial infarction	6 days discontinued not recovered
D, 59899 M, 51	bupropion tablet 150mg heavy smoker	not reported	acute coronary syndrome	90 minutes discontinued recovered with sequels
E, 30765 F, 35	bupropion tablet 150mg	not reported	angina pectoris, dizziness, mouth dry, nausea, tachycardia	not reported discontinued recovered
F, 51917 M, 55	bupropion tablet 150mg drug dependence	not reported	angina pectoris, electrocardiogram abnormal non-	“few” weeks unknown unknown

G, 29089 M, 33	bupropion tablet 150mg tobacco use disorder, unspecified use	not reported	specific anginal pain	5 hours discontinued not reported

All three cases of myocardial infarctions were confirmed by electrocardiography or laboratory testing. In patient A it concerned an inferior infarction (Ck max 3610). In patient C, an inferolateral infarction presented itself as collapse due to an unspecified cardiac arrhythmia necessitating out of hospital cardiac resuscitation. in the remaining case no information on location was provided by the reporter. All three cases required PTCA treatment.
In the patient in whom an acute coronary syndrome was reported, ischaemia was objectified by a clearly raised troponin (10.9).
Three cases of angina pectoris were reported. Patient E was admitted to hospital admission for typical anginal symptoms, chest pain radiating to shoulder and left arm; troponin remained negative, exercise testing after onset of medicinal therapy did not lead to symptoms, however ECG testing showed increased depression of II, III, AVF leads (inferior wall leads). Patient F reported typical symptoms for cardiac ischaemia sternal pain radiating to jaws combined with ECG-abnormalities which led to admission to a cardiology department. It was not specified whether symptoms were part of a myocardial infarction or anginal pain. In one case (patient G) the information provided by the reporting general practitioner was not sufficient to distinguish whether the reported symptoms were part of an ischaemic event or that the complaints concerned unspecific chest pain.

Other sources

Literature

Myocardial ischaemia in relation to use of bupropion is the subject of three case reports. The first case-report concerns a 21 year old male with beside his smoking habits no risk factors for cardiovascular disease. He underwent an inferolateral myocardial infarction shortly after starting bupropion and pseudoephrine, the latter drug for intercurrent flu [3]. Secondly Patterson and Herity presented in a letter an inferoposterolateral myocardial infarction two weeks after start of bupropion therapy in a 43-year-old male, with a smoking history of 26 pack years but also without other relevant medical history [4].
Finally George, Kunwar and Awasti presented a case of myocardial infarction in a male using methylphenidate, bupropion and erythromycin. It was suggested that an interaction with erythromycin led to increased bupropion levels which in its turn were believed to be causative for the myocardial infarction [5].

Furthermore in two publications with other subjects, occurrence of myocardial infarction shortly after onset of bupropion therapy was mentioned. In the first case bupropion was started three weeks before the myocardial infarction. In the second case no latency was specified [6,7].

Databases

The number of reports for ischaemic cardiovascular events does not result in disproportionality in the Lareb database.
In the WHO database on November 24 myocardial was reported 165 times in bupropion users. Angina pectoris was reported 71 times, unstable angina pectoris five times, coronary arteriospasm in six cases and ten cases of unspecified cardiac ischaemia. This number of cases however does not result in a positive disproportionality for occurrence of myocardial ischemic disease compared to incidence of these conditions in users of other drugs.
On December 8 2008 the Eudravigilance database contained 141 reports of ischaemic coronary events, all rated serious. Age ranged from 15 to 83 years old, patients were in 99 reports of male sex and in 33 cases female. Myocardial infarction was reported explicitly in 103 reports. In 40 reports myocardial ischaemia led to decease, in eight reports to disability. Twenty-two reports concerned patients of young age (less than 35 years of age).

Other SmPCs

The FDA mentions myocardial infarctions in its SmPC for bupropion [8].

Mechanism

In the case report by Pederson Kurtz and Garbe, coronary angiogram showed normal arteries, leading to postulation of vasospasm of the coronary artery by both bupropion and pseudoephrine as underlying mechanism. Furthermore due to its noradrenergic action, use of bupropion may lead to an increase in cardiac frequency or blood pressure [3], which can induce earlier manifestation of coronary stenosis.

Discussion

The six relevant cases of myocardial infarction, acute coronary syndrome and angina pectoris are supported by case reports in literature. All ischaemic events occurred in persons with few indications for other risk factors for cardiovascular events then the smoking habit. The possible link between use of bupropion and these events is further supported by the short time frame in which the events occurred. In all cases, events were related to use of bupropion for smoking cessation which implies a maximum duration of use of two months. However this indication also implies a huge potential for confounding or under-attributing of the ischemic cardiovascular events to bupropion. Since all cases were related to smoking cessation it cannot be excluded that the condition of the cessation itself or other measures taken to achieve this goal like application of oral or transdermal nicotin could be involved in the reported coronary events. Given the potential for confounding and given the published data on use of bupropion in a population which started using bupropion after myocardial infarction [9], this report does not claim to be conclusive on this subject. However given the aspects supporting the possible relationship between use of bupropion and the occurring of the cardiovascular event this subject merits further attention.

References

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This signal has been raised on February 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).