

Cardiovascular side effects of newer antidepressants

Yeni antidepresanların kardiyovasküler yan etkileri

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ABSTRACT

We review the cardiovascular effects of newer antidepressants. Although further studies are warranted, the safety of the selective serotonin reuptake inhibitors and the serotonin norepinephrine reuptake inhibitors on patients with comorbid cardiac conditions is impressive. Newer antidepressants should be considered as first-line agents for the treatment of depression in patients with and without cardiovascular disease. (*Anadolu Kardiyol Derg 2007; 7: 305-9*)

Key words: Antidepressant drugs, atrial fibrillation, blood pressure, bradycardia, cardiac death, cardiovascular effects, electrocardiogram, hypertension, hypotension, QT interval, ventricular premature beats, tachycardia

ÖZET

Bu derlemede yeni antidepresanların kardiyovasküler yan etkilerini gözden geçirdik. İleride yeni çalışmaların yapılması gerekli olsa da, komorbid kardiyak problemleri olan hastalarda selektif serotonin geri alım inhibitörlerinin ve serotonin norepinefrin geri alım inhibitörlerinin güvenlik profilleri etkileyicidir. Yeni antidepresanlar, kardiyovasküler hastalıkları olan veya olmayan hastalarda depresyon tedavisinde birincil ajanlar olarak düşünülmelidirler. (*Anadolu Kardiyol Derg 2007; 7: 305-9*)

Anahtar kelimeler: Antidepresan ajanlar, atriyal fibrilasyon, kan basıncı, bradikardi, kardiyak ölüm, kardiyovasküler etkileri, elektrokardiogram, hipertansiyon, hipotansiyon, QT aralığı, ventriküler ektopik vurular, taşikardi

Introduction

Depression is frequently present in patients with coronary heart disease (CHD) and this cardiac illness may worsen depression (1). Depression may even contribute to cardiac deaths in patients with or without CHD (2-6). Treatment of depression may be associated with cardiovascular complications.

The therapeutic efficacy of antidepressant medications is similar. The choice of an antidepressant drug is often made based on its purported mechanism of action or its side effects (7), particularly as those side effects relate to the cardiovascular system.

An interesting clinical observation is that psychotropic agents, particularly antidepressant drugs, commonly affect the cardiovascular system and drugs used to treat heart disease commonly affect the central nervous system (CNS). Perhaps, the roles played by serotonin, norepinephrine, and dopamine in both depression and CHD account for this finding.

This article reviews the current literature on the cardiovascular effects of newer antidepressants. The benefits and risks of using newer antidepressants as first line agents for the treatment of depression in patients with and without cardiovascular disease are critically reviewed.

Serotonin syndrome

The serotonin syndrome (8) expresses itself clinically in three main areas. Cognitive effects include hypomania, hallucinations, agitation, confusion, and coma. That is, CNS hyperactivity is followed by CNS hypoactivity. Autonomic nervous system (ANS) effects include shivering, sweating, fever, hypertension, tachycardia, nausea, and diarrhea-that is, ANS hyperactivity. Somatic effects include myoclonus, hyperreflexia, and tremor. Additional features include insomnia, itching, and hives.

This syndrome is most often reported in patients taking two or more medications that increase CNS serotonin levels by different mechanisms. The most common drug combinations associated with serotonin syndrome involve the monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and the tricyclic antidepressants (TCAs) (9). Because of the dramatic rise in the use of SSRIs, it is predicted that emergency room physicians are going to encounter the serotonin syndrome more frequently than in the past (10).

When the clinician uses opioids to treat chest pain or other pain syndromes, certain combinations of drugs place the patient at increased risk for the serotonin syndrome and its cardiovascular complications. A recent review of the serotonin syndrome describes such combinations in detail (8). Antidepressant drugs

including SSRIs, trazodone, nefazodone, buspirone, clomipramine, venlafaxine, and duloxetine may be associated with the serotonin syndrome. Opioids associated with the serotonin syndrome include meperidine, fentanyl, tramadol, and pentazocine. When a patient taking an SSRI presents with chest pain, the clinician is advised to treat this pain with morphine rather than meperidine.

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Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors first appeared in the late 1980s (fluoxetine-Prozac, sertraline-Lustral, paroxetine-Paxil, fluvoxamine-Faverin, citalopram-Cipram, and escitalopram-Cipralext). This group of antidepressants has eclipsed all others because of their efficacy, ease of administration, and favorable side effect profile including favorable cardiac side effect profile (11). Compared with TCAs that block the reuptake of serotonin (5HT) and norepinephrine (NE), SSRIs are largely 5HT reuptake blockers and have little therapeutic effect on other neurotransmitters. Selective serotonin reuptake inhibitors are much less likely than TCAs to cause fatalities (particularly cardiac deaths) in overdoses (12). Also, TCAs may be associated with an increased risk of myocardial infarction compared with SSRIs (13).

Over the decade following SSRI introduction, there have been only two well documented cardiac deaths from overdose reported in the literature: one with fluoxetine (14), the other with citalopram (15). Although SSRIs are relatively free of major cardiovascular risks (16), they are not totally free of such effects, especially in patients with CHD (17).

The cardiovascular side effects of SSRIs include modest slowing of heart rate, minimal effect on either resting or postural blood pressure, and little influence on electrocardiographic PR interval, QRS duration, or QTc interval (18). However, there are cases of QTc interval prolongation, first-degree block, and orthostatic hypotension in SSRI-treated patients (17). Selective serotonin reuptake inhibitors may stimulate vasoconstriction with resultant myocardial ischemia (Prinzmetal's angina) in patients with and without CHD (19).

Fluoxetine

Besides 5HT reuptake inhibition, fluoxetine possesses some NE reuptake blockade and 5HT_{2c} agonist action (20). This drug may cause mild bradycardia (21, 22). In the largest series of overdoses cases, sinus tachycardia, ventricular trigeminy, and junctional rhythms occurred on doses as high as 1500 mg of fluoxetine alone (23, 24). Despite these case reports, fluoxetine cardiovascular toxicity is very rare. Out of about 15,000,000 treatment cases, there were only about 5000 reports (0.0003%) of possible cardiovascular side effects of any kind including electrocardiographic abnormalities and thrombophlebitis (25).

More recently, longer acting weekly fluoxetine (Prozac weekly) has been introduced. There is insufficient experience to determine if its cardiovascular profile differs from the older daily preparations of fluoxetine.

Citalopram

Citalopram was used for many years in Europe before FDA approval in 1998 in the United States for treatment of depression. It consists of an S and an R isomer. Except for the S isomer (escitalopram), citalopram is more selective for 5HT reuptake inhibition than other SSRIs (20).

Although citalopram does not cause significant QTc interval prolongation in humans, it does so in other animals, particularly beagle dogs (26). It can cause bradycardia (27). Tachycardia, orthostasis, and hypotension have been described in about 1% of cases. Rare cardiovascular side effects include hypertension, bradycardia, myocardial infarction, and stroke. Also, there have been rare cases of transient ischemic attacks, phlebitis, atrial fibrillation, cardiac arrest, and bundle branch block-the incidences of which are less than 1 in 1,000. There has been only one report of cardiac death following overdose on citalopram alone in Sweden (18). Five of the Swedish cases ingested over 1900 mg (almost 100 times the usual dose), and all of these patients had either electrocardiographic conduction delay or generalized seizures. Among the 18 patients, who ingested 600-1900 mge, six developed widened QRS complexes (18).

Escitalopram

Escitalopram (S-citalopram) is the therapeutically active isomer of citalopram (28). Approved by the FDA in 2002, it is a more selective SSRI than citalopram. The main advantage of escitalopram is the reduced antihistaminic activity and lack of the R isomer that may inhibit the metabolism of the S-isomer. In in-vitro studies, escitalopram has a lower pharmacokinetic drug-interaction profile than the parent compound point. These observations suggest that escitalopram has a more favorable cardiovascular safety profile than citalopram. At present, there is not enough experience with escitalopram to substantiate this claim.

Fluvoxamine

Fluvoxamine maleate belongs to a chemical series of aralkyl ketones-chemically unrelated to other SSRIs and with significant 5HT reuptake inhibitor activity. Fluvoxamine is not associated with significant electrocardiographic changes except for some ST segment changes (<1%) and atrioventricular and supraventricular blockade (<1 per 1000 cases) (29). Hypertension, hypotension, syncope, and tachycardia appear in about 1% of patients. There are rare reports of stroke, CHD, embolus, pericarditis, phlebitis, and pulmonary infarction (30). In a study of patients who had overdosed on fluvoxamine, only 15/310 developed sinus bradycardia (31). The drug has not been extensively studied for its cardiovascular effects in patients with cardiovascular disease.

Paroxetine

Besides its 5HT reuptake inhibition properties, paroxetine possesses muscarinic/cholinergic antagonist actions and some norepinephrine reuptake inhibition. In one clinical trial, 12% of patients receiving paroxetine experienced tachycardia (32). In other clinical trials, tachycardia, hypertension, and syncope are described in about 1% of the population. Infrequent side effects include bradycardia and hypotension. Thrombophlebitis and vascular headache are listed as rare side effects. Direct cardiac effects are rare and include congestive heart failure, myocardial infarction, and angina pectoris (33). Overall, paroxetine is considered to have a very favorable cardiovascular profile (33, 34).

Sertraline

Besides 5HT reuptake inhibition, sertraline has dopamine reuptake inhibitor action and sigma opioid receptor antagonistic activity. Sertraline does not have any significant electrocardiographic effects (35). Vascular effects of sertraline include infrequent hypertension, postural hypotension and, rarely, strokes.

Direct cardiac effects of sertraline include about a 1% occurrence of non-specific chest pain and palpitations, and rare occurrences of angina pectoris and myocardial infarction. Sertraline is effective in depressed patients with cardiovascular disease. Here, it has no significant effect on heart rate or supine or standing systolic or diastolic blood pressure (36).

Sertraline is the SSRI most systematically studied in depressed patients with CHD. The SADHART (Sertraline AntiDepressant Heart Attack Trial) study showed that sertraline is effective and safe in depressed patients with CHD but was underpowered to detect a mortality difference between sertraline and placebo (37). The ENRICH (ENhancing Recovery in Coronary Heart Disease) trial did not alter cardiovascular morbidity or mortality but showed that cognitive behavioral therapy is effective in depressed patients with CHD (38).

The antiplatelet action of sertraline is a double-edged sword (39). This drug may increase bleeding in patients with and without CHD. However, in patient with CHD receiving sertraline, this drug may further enhance the antiplatelet action of aspirin and clopidogrel and protect against progression of coronary atherosclerosis and its clinical consequences.

Combined serotonin and norepinephrine reuptake inhibitors (SNRIs)

Venlafaxine

Venlafaxine blocks the reuptake of 5HT and NE at sufficient doses in humans (40) and also is capable of weak DA reuptake at higher doses (41). At lower doses, the drug principally blocks 5HT reuptake and acts like an SSRI.

Arrhythmias, first-degree heart block, atrioventricular block, and bundle branch block are rare occurrences. Especially when given in higher doses, venlafaxine has a tendency to increase supine diastolic blood pressure (42). Mean increase in blood pressure was 7 mmHg after 6 weeks of treatment with doses above 300mg/day (43). When compared with placebo, venlafaxine increases heart rate by a mean of four beats/min relative to baseline. Rare drug-associated cardiovascular effects include hypotension, peripheral vascular disorder, and thrombophlebitis. Direct cardiac effects, such as angina pectoris, have been reported in <1% of the patients.

Duloxetine

Duloxetine, a relatively equipotent SNRI, is effective in the treatment of depression. It was not associated with clinically significant changes in standing blood pressure or heart rate. Blood pressure measurements in the supine position showed small increases in systolic and diastolic blood pressure and small decreases in heart rate (44). Abrupt discontinuation of duloxetine was associated with a small increase in heart rate and, in three subjects, transient sleep disturbance. No clinically important electrocardiographic changes have been found.

Selective norepinephrine reuptake inhibitors

Reboxetine

Reboxetine is a selective norepinephrine reuptake inhibitor used in the United Kingdom. It was never approved for treatment of depression in the United States because it was not superior to

placebo in clinical trials. Reboxetine when administered at approximately twice the recommended dose did not significantly affect the QTc interval but increased heart rate by about 11 beats per minute (45).

Atomoxetine

Atomoxetine is a highly selective norepinephrine reuptake inhibitor recently approved for the treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder (ADHD) (46, 47). Among adults, this drug was associated with a small but statistically significant increase in mean systolic blood pressure. Among children and adolescents, atomoxetine was associated with a small but statistically significant increase in mean diastolic blood pressure. The clinical relevance of these observations is uncertain. Compared with pretreatment measurements, heart rate tended to increase with atomoxetine treatment in all age groups. Blood pressure and heart rate increases usually occurred early in treatment, stabilized, and normalized when atomoxetine was stopped. This drug was not associated with QT interval prolongation. Palpitations occurred more frequently in adult patients taking atomoxetine compared with the placebo group. Cardiovascular-related events sufficient to lead to discontinuation were very uncommon in the adult group and absent in the children/adolescent group. Because this drug has just reached clinical practice, more definitive effects on the cardiovascular system await further elucidation.

Other antidepressants

Trazodone

Trazodone is a postsynaptic 5HT_{2A} antagonist and a 5HT reuptake inhibitor with antihistaminic properties. This drug lacks the quinidine-like properties of TCAs that lead to QTc interval prolongation. However, it can cause rare ventricular ectopy, including ventricular tachycardia (48). Postural hypotension with or without resultant syncope is its most well-known cardiovascular side effect. This side effect is much less likely to appear if the drug is taken with meals.

Nefazodone

Nefazodone is structurally related to trazodone. It is less antihistaminic and has a longer half-life than trazodone. Nefazodone has more alpha-1 adrenoceptor antagonistic activity that is thought to be relevant in vivo in humans. It acts by blocking 5HT_{2A} receptors. Nefazodone has a lower frequency of orthostatic hypotension and priapism than trazodone (49). The reported frequency of orthostatic hypotension is 2.8% and bradycardia is 1.5% (50). Ventricular systoles are infrequent with this drug and atrioventricular blockade occurs in less than one per 10,000 cases of drug administration. Hypertension and syncope occur infrequently with nefazodone. Angina pectoris and congestive heart failure are rarely due to nefazodone treatment. Because of its cytochrome P450 3A4 blocking action, nefazodone can interfere with the metabolism of terfenadine, an antihistamine associated with cardiotoxicity. This combination should be avoided. Co-administration of cisapride, astemizole, and pimozone are also contraindicated because of the risk of QTc prolongation due to 3A4 blocking action. Digoxin levels should also be monitored if nefazodone is taken concurrently, because both drugs are protein-bound. Nefazodone does not significantly alter warfarin levels (51).

Mirtazapine

Mirtazapine has a tetracyclic chemical structure unrelated to SSRIs, TCAs, or MAOIs. It is an antagonist at central presynaptic alpha-adrenergic inhibitory autoreceptors and heteroreceptors, which increases the central noradrenergic and serotonergic activity and 5HT_{2A} receptor blockade that may enhance cortical dopamine neurotransmission (52). The drug is not associated with clinically significant electrocardiographic abnormalities. Infrequent cardiovascular side effects of mirtazapine include ventricular extrasystoles and bradycardia. Rare drug-associated cardiac effects include atrial fibrillation, myocardial infarction, angina pectoris, and left heart failure. It has a moderate peripheral alpha-blocker activity, which can result in a 7% incidence of orthostatic hypotension. Therefore, mirtazapine should be used with caution in patients who have cardiac illness, which can be aggravated by hypotension. Mirtazapine does not cause any significant increase in blood pressure, but can increase the heart rate, which can be explained by its mild anticholinergic activity. It is a relatively new antidepressant and has not been studied in patients with concomitant cardiac disease.

The Myocardial Infarction and Depression-Intervention Trial (MIND-IT), currently underway in the Netherlands, examines mirtazapine, citalopram, and placebo in depressed post-myocardial infarction patients (53). This study may contribute to our knowledge in this area.

Bupropion

Bupropion is chemically unrelated to other antidepressants, but is structurally related to amphetamines. Its antidepressant effects appear related to noradrenergic and dopamine reuptake inhibition. Bupropion is also an effective agent for facilitating smoking cessation; an area of increased concern in cardiac patients (54).

Compared with TCAs, bupropion has a superior cardiovascular side effect profile. Bupropion causes no problems with cardiac conduction, contractility, or orthostatic hypotension in patients with preexisting cardiac disease. Palpitations were reported in 2% of the cases. Postural hypotension, stroke, tachycardia and phlebitis are infrequently described, and syncope is rare. Bupropion can elevate blood pressure in certain patients but does alter heart rate (55).

When bupropion is used as either an antidepressant or anti-smoking agent and combined with a nicotine transdermal system, the incidence of hypertension reaches as high as 6.1%. Therefore, blood pressure should be monitored carefully if both bupropion and nicotine replacement strategies are used simultaneously. Bupropion's favorable cardiac safety profile and its effectiveness as both an antidepressant and anti-smoking agent make this medication unique among the antidepressants.

Drug combinations

Commonly, clinicians use various combinations of antidepressant drugs when treating depressed patients. For example, bupropion with its adrenergic effects may be combined with an SSRI to gain dual neurotransmitter action and reduce the sexual side effects of SSRIs. When patients also suffer from CHD, the clinicians must be particularly sensitive to various drug interactions that may adversely affect the cardiovascular system and/or drugs used to treat the cardiac manifestations of CHD.

A comprehensive review of drug combinations either in the form of several antidepressant drugs or antidepressant drugs combined with other psychotropic agents is beyond the scope of this paper. However, at a bare minimum, clinicians should be familiar with the effects that antidepressant drugs have on the metabolic pathways of co-prescribed psychotropic and non-psychotropic agents and the metabolic pathways by which antidepressant drugs are metabolized.

Conclusion

The wide clinical experience with and good cardiovascular profile of SSRIs compared with TCAs leave them the antidepressant drugs of choice in depressed patients with CHD. Nevertheless, clinicians using SSRIs must keep in mind that these drugs may be associated with the serotonin syndrome, tachycardia, arrhythmias, and other cardiovascular findings reviewed in this paper.

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