Cardiac complications of antidepressants

Kardiologiczne powikłania leków przeciwdepresyjnych

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Praca finansowana z Zadania Badawczego Uniwersytetu Medycznego w Łodzi, Nr 502 -03/5 -062-02/502-54-062

Abstract

Depressive disorders are an independent risk factor for coronary heart disease. They are also a risk factor for death in patients suffering from ischemic heart disease. Modern antidepressants such as selective serotonin reuptake inhibitors (SSRI) and selective noradrenaline reuptake inhibitors (SNRI) increase the safety of therapy in patients with depressive disorders, mainly through their favorable profile of adverse effects. However, they are not free from faults, and some risk of cardiac side effects exists, as confirmed by scientific reports.

Keywords: SSRI, SNRI, heart arrhythmias, QTc interval

Streszczenie

Zaburzenia depresyjne są niezależnym czynnikiem ryzyka rozwoju choroby niedokrwiennej serca. Są również czynnikiem ryzyka zgonu u pacjentów chorujących na chorobę niedokrwienną serca. Nowoczesne leki przeciwdepresyjne takie jak selektywne inhibitory wychwytu zwrotnego serotoniny (SSRI) oraz selektywne inhibitory wychwytu zwrotnego noradrenaliny (SNRI) zwiększyły bezpieczeństwo terapii pacjentów z zaburzeniami depresyjnymi, głównie poprzez swój korzystniejszy profil działań niepożądanych. Mimo tego nie są wolne od wad i pewne ryzyko kardiologicznych działań niepożądanych istnieje, co potwierdzają doniesienia naukowe.

Słowa kluczowe: SSRI, SNRI, zaburzenia rytmu, odstęp QTc

Introduction

Depression is a frequent comorbid condition in cardiovascular patients. Depression coexistence in cardiovascular diseases seriously aggravates the course of the diseases, increases the risk of death for cardiovascular reasons and adversely affects therapeutic alliance [1,2]. The advent of new antidepressants has created better perspectives for depressive disorders treatment. Despite their numerous assets, first generation antidepressants produce some significant adverse effects, primarily in cardiovascular system. New generation drugs are similar in therapeutic effectiveness, however, meta-analyses suggest that escitalopram, sertraline, venlafaxine and mirtazapine have certain advantages over the others [3]. Drug selection is often determined by its mechanism of action or the incidence of adverse effects, especially when they affect the cardiovascular system. Consequently, the paper discusses the influence of selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) on cardiovascular system, more specifically on arrhythmia and conduction disturbances. SSRI and SNRI are among the most widely used antidepressants predominantly because of their favourable therapeutic profile, efficacy and little impact on cardiovascular system. In comparison with tricyclic antidepressants, they are less likely to cause cardiovascular side-effects and are safer in case of unintentional as well as intentional overdose. Significant and potentially risky adverse effects include among others: serotonin syndrome, epileptic seizure and cardiotoxicity [4]. The medications, which induce sudden cardiac death (SCD) or ventricular arrhythmia (VA) mainly by prolonging the QT interval are the problems that clinicians are faced with. The University of Arizona listed above 90 drugs which are known or suspected to prolong the QT interval [5]. The prevalence of long QT in psychiatric patients is estimated at 8% [6].

Potentially risky arrhythmia

Torsade de pointes (TdP) is a life-threatening polymorphic ventricular tachycardia which causes hemodynamic instability and which is associated with prolonged QT interval induced by premature ventricular contraction that appears after higher U wave amplitude following prolonged cardiac cycle. Prolonged episodes of tachycardia may transform themselves into ventricular fibrillation. Lengthened QT interval , cardiac cycle-dependent in-

crease of U wave amplitude, diversiform premature ventricular contractions or ventricular bigeminy often precede the occurrence of diverse pairs or series of 3 or more premature contractions [7]. The QT interval represents the electrical repolarization of the ventricles. Sudden QT lengthening can be observed in a number of clinical situations and it manifests itself by syncope or presyncope. It may also result in sudden death caused by polymorphic ventricular tachycardia (TdP). Risk factors of prolonged QT interval are described in Table 1 [8].

Table 1. Non-pharmacological risk factors of prolonged QT interval

Risk factors	Comments
Heart muscle damage	Myocardial infarction, heart failure, cardiomyopathy, myocarditis
Central Nervous System diseases	Intracerebral haematoma, CNS aneurysm, CNS carcinoma
Electrolyte imbalance	Hypokalemia, hypomagnesemia, hypocalcaemia
Hypothermia	PQ and QT intervals are prolonged and QRS complex is widened on the electrocardiogram. Heart rate slows down, premature systoles, ventricular and atrial fibrillation may occur.
Hepatic dysfunction	Impaired drug and hormone metabolism
Pheochromocytoma	
Female gender	Higher prevalence of tachycardia in females, 7 in 10 TdP patients are women

Principles of the QT interval measurement

The QT interval is measured from the beginning of QRS complex to the end of the T wave. In the analysis all the leads should be taken into account and the longest of all the measurements should be chosen to be compared with the reference values. The accuracy of the measurement is determined by the precise determination of the T wave end, which is a well-known problem in electrocardiography. In the standard 12-lead ECG, the lead providing the clearest recognition of the end of the T wave should be selected for the QT interval monitoring. The QT interval tends to be the longest in V_3 lead or V_4 lead, potentially because the leads are placed closest to the heart and therefore the T waves amplitude is high. Lead II is commonly used to measure the QT intervals and in patients with the normal T wave axis lead II provides a distinct positive T wave record. Moreover, if U waves are present, they are typically separated from T waves in Lead II, which makes the QT interval measurement more feasible than the QT_u. Regardless of the lead selection for heart rate monitoring, it is crucial to make the serious OT interval measurement invariably in the same lead. While monitoring patients in order to detect drug-associated QT interval prolongation, patients' QTc should be recorded in their history including their heart rate patterns measured prior to and at least 8h after drug administration. Additionally, QTc should be recorded and collected before and after drug dose increase.

Bazett's formula is the standard clinical correction calculating heart rate-corrected QT interval ($QTc = QT/(RR)^{1}/^{2}$). It should be remembered, however, that Bazett formula is applicable for the rate of 50-100/min as higher or lower rates result in overestimated or underestimated QTc respectively. Consequently, for the rates <50/min or >100/min Friderica's formula ($QTc = QT/(RR)^{1}/^{3}$| or Hodges formula (QTc = QT +1.75 x (heart rate – 60)) are used [9,10].

None of the formulas allows for individual differences and cases of extremely high or low HR values, which makes them less compelling in certain situations. They are also of limited utility in monitoring changes to the QT interval in drug-induced (including antidepressants) intoxication. In such cases, it is recommended to use nomograms designed by Foss et al. who suggested a graphic representation of the QT-RR relationship. Comparisons between Bazett's formula and the nomograms reveal considerable inconsistencies between the results obtained with both of the methods. Widely used Bazett's formula have yielded quite a large number of false positive results, which led to excessive cautiousness, unnecessarily long patients monitoring and prolonged hospitalisation as a result, as well as difficulty in identifying patients truly at risk of arrhythmia. The widest discrepancies were observed in the subjects with HR between 30 and 60 /min; in those cases monogram proved to be a considerably more sensitive method of risk evaluation [11].

It is estimated that <430ms is a normal value of QTc in males and <450ms in females. The intervals of >450ms in males and >470 in females are considered as prolonged. The QT interval lengthening above 500ms significantly increases the risk of serious arrhythmia, specifically TdP. However, TdP has most frequently been detected in subjects with QTc between 600 and 649ms.

Mechanism of TdP

Following catecholaminergic hypotheses, depression involves transmission deficits in three main neurotransmitter systems: serotoninergic, noradrenergic and dopaminergic. Slow decline in the neurotransmitters increases the stimulation of the sympathetic nervous system eventually resulting in its constant arousal, which does not leave other organs functioning unaffected [13].

Autonomic nervous system centers are located in the encephalon and the spinal cord. The integration of its activities takes place in hypothalamus, limbic system and cerebral cortex and thus it is influenced by mental factors,

signals from afferent autonomic fibres and endocrine glands. Peripheral part of sympathetic nervous system is composed of preganglionic and postganglionic neurons. Preganglionic nerve cells come from the lateral horn of the spinal cord in Th1-Th5 regions and they form respectively superior, middle and inferior cervical cardiac nerves and thoracic cardiac nerves- from the thoracic sympathetic trunk (Th1-Th4). They converge in cervical ganglia and stellate ganglion to form the cardiac ganglion [14].

Between the surface of epicardial and endocardial layers of the cardiac muscle there are layers of transitional and M cells, which are capable of relatively disproportionate prolongation of their action potential by reducing slow delayed-rectifier potassium current (IKS), rapidly activating delayed-rectifier potassium current (IKR), inward rectifier potassium current (IKI), or as a result of intensified inward calcium current flow (ICA) or late sodium current (INA). Such disproportionate prolongation of action potential duration typically underlies the prolongation of the QT interval on the surface ECG, which represents the time interval between ventricular depolarization and repolarization. Clinical conditions, which cause a reduction in IKR or augmentation of late INA lead to preferential prolongation of the M cells action potential. The ensuing QT interval prolongation leads in turn to highly irregular prolongation of ventricular repolarization referred to as transmural dispersion of repolarization, which creates a vulnerable window for the development of reentry. The reduction in net repolarizing current accountable for repolarization time predisposes to the development of early afterdepolarization (EAD)-induced triggered activity in the M and Purkinje cells, which generates extrasystole that triggers TdP when it falls in the vulnerable period [15].

In the context of enhanced adrenergic system activity, dispersion of repolarization intensifies, which fosters cardiac arrhythmia [14].

Antidepressants in cardiac arrhythmia

Citalopram

Citalopram is the most widely used drug of the SSRI class registered to treat depression in above 30 million people in over 70 countries of the world [16]. In April 2011 US Food and Drug Administration (FDA) announced that there was a relationship between the drug dose and the long QT interval, and as a consequence dosing management was altered and reduced the maximum 24h dose to 40mg [17].

Almost a year later FDA restricted the maximum dose to 20 mg for subgroups of patients, including those older than 60 years and those taking an inhibitor of cytochrome P450 2 C19 [18]. Citalopram is lipophilic, it is easily absorbed in the digestive tract, its half-life is about 36 hours and maximum concentration is achieved only within 2 hours of the oral administration [19]. Citalopram is metabolized mostly by P-450 (CYP) and its hepatic isoenzymes CYP 3A4, CYP 2 C19, and to a lesser degree by CYP 2D6. Desmethylcitalopram (DCT) is the major metabolite which is further metabolized by CYP2D6 to a lesser metabolite, didesmethylcitalopram (DDCT). In humans unaltered form of citalopram is a dominating serum form; while being metabolized its metablolites constitute 1/2 and 1/10 of drug concentration respectively [20]. As a selective serotonin reuptake inhibitor, citalopram is a less efficacious norepinephrine and dopamine reuptake agent. Moreover, it binds with histamine receptors with affinities similar to clomipramine and this distinguishes citalopram from other SSRIs. Its lower affinity for muscarinic and adrenergic receptors may account for certain adverse effects such as constipation, orthostatic hypotension [21].

Citalopram overdose may result in long QT interval on electrogardiography. Moderately prolonged QT interval does not necessarily develop TdP ventricular arrhythmia, however, when it actually occurs, it encumbers high mortality. Although infrequent, citalopram-induced TdP has been well documented. Only 1 out of 13 individuals is thought to develop risky QT interval lengthening [22]. In order to assess the likelihood of the drug toxic influence it is essential to observe the patient and assess the relation between the dose applied, the drug concentration and the appearance of the first symptoms. When citalopram is overdosed, central nervous system is the first system at risk, followed by cardiac complications leading to proarrhythmic effect. The QT interval is one of the most important markers of ECG abnormalities. Prolonged QT interval increases the risk of TdP, which may be a direct cause of sudden cardiac death. Activated carbon in a single dose application i.e. 50g in solution produces clinical benefits in the shape of prolonged QT interval reduction, absorption fraction decline by 22% and clearance increased by 72%. Furthermore, drug concentration decline is more rapid than the ECG records suggest (ECG abnormalities are more durable). Additionally, activated carbon reduces the likelihood of abnormal QT-RR relation which in 60% of individuals is also associated with higher prevalence of TdP [22,23].

The administration of a single dose of activated carbon should be confined to the situations when it is absolutely necessary as unjustified application diminishes the drug therapeutic activity [24]. The research conducted by Geoffrry on 62 patients revealed that activated carbon should be administered only when the citalopram dose reached or exceeded 600mg (≥600mg). Its application within 4 hours of the overdose produces the best effects.

Additional monitoring is recommended in patients who took ≥1000mg of citalopram. The study also demonstrated that monitoring can be discontinued if the patient's QT interval has remained normal for 13 hours after the overdose, as the risk of TdP after such period of time is < 1%. The authors of the study noted that after citalopram overdose maximum length of QT interval was achieved after 7.8 hours but the period was shortened and maximum QT interval was reduced after activated carbon application. Monitoring is also advisable when ≥600 mg of citalopram was taken and no activated carbon was administered within 4 hours of the overdose. It can also be considered in individual cases of people older than 41 years, with HR >95 bpm or when intoxication symptoms are present. However, Catalano et al. described a case of 21-year-old patient who demonstrated long QT interval symptoms for longer than 13 hours after 400mg of citalopram. The incident was explained by a negative influence of citalopram metabolite. Citalopram metabolite (DDCT) has cardiotoxic properties and it is responsible for QT interval prolongation. When DDCT concentration rises, QT interval lengthens. The highest DDCT concentration is detected between 6.6 and 7.3 hours after the drug intake, however, in some cases metabolism may slow down and maximum concentration is achieved after a longer period and thus the symptoms appear later than expected. In the above case, delayed metabolism might also have been caused by pharmacotherapy with aripiprazole and alcohol in blood at the moment of hospitalisation [26]. Tarabar et al. reported a similar case of a 36-year-old patient who took 3000mg of citalopram and displayed the above-mentioned ECG abnormalities only after 33 hours [27]. Longer QT intervals are not implausible in patients taking therapeutic doses of citalopram. Citalopram is metabolized among others by P450 2D6 which is affected by genetically-determined variability and in 2% of people it causes ultrafast metabolism of citalopram to its cardiotoxic metabolite DDCT increasing its serum concentration and generating overdose symptoms. The fact also explains why citalopram induces long QT interval more frequently than other SSRIs [28].

It should be emphasised that citalopram binds with potassium channels IKR encoded by hERG gene. As a result, potassium current flow from cardiomyocytes is inhibited, which results in longer repolarization [29,30].When applied in therapeutic doses, advantageous and safe citalopram profile can be ensured by simultaneous L-type calcium channels blocking which may be a preventive measure against TdP [27,31].

Escitalopram

Escitalopram is one of the new drugs of selective serotonin reuptake inhibitors class and the most selective one of the whole group. It is a widely prescribed antidepressive drug. The most common side effects are well tolerated, mild and transient, which is of importance in the therapy of depressive patients with suicidal attempts in history [32]. Bradycardia is one of the adverse effects of escitalopram and it is reported in approx. 11% of patients [33]. According to numerous reports, potential QT interval prolongation in ECG is the most serious adverse effect of escitalopram pharmacotherapy. This, in turn, may lead to the development of life-threatening TdP cardiac arrhythmia. Lack of possibility to determine a specific escitalopram dose the exceeding of which could cause arrhythmia is a serious problem. Gorp et al. included 78 patients after escitalopram overdose and in the course of the study they noticed that the risk of long QT interval on ECG was higher when the drug dose taken was >200mg. Administration of a single dose of activated carbon (SDAC) i.e. 50g is not recommended until >300mg of the drug is taken. When SDAC was not administered or it was administered but escitalopram dose taken was >400mg, the researchers additionally advise to monitor the patient for 12 hours or until the point of relationship QT interval and HR will be located below the cut-off line in the monogram [34].

Escitalopram, whose half time is 27-32h, is s-enantiomer of citalopram and it is twice as strong as citalopram in corresponding doses. Escitalopram is decomposed by CYP3A4 to the main metabolite s-DCT, which is then metabolized to s-DDCY by CYP2C19. The dominating form of escitalopram in blood serum is its unchanged form, with s-DCT constituting approx. ⅓; s-DDCT is immeasurable in humans [36]. By contrast, citalopram is a racemic mixture of s- and r-enantiomer and its curative effect results exclusively from the presence of the s form, which is probably limited by allosteric impact of r-enantiomer on serotonin transporter [37]. The general pharmacological, pharmacokinetic and toxicological profile of escitalppram is similar to the one of citalopram, therefore the symptoms of both drugs overdose may be alike [38]. A study of 795 subjects from a toxicological center showed that escitalopram appears to be much less toxic than citalopram even in the cases of a considerable overdose [39]. Nevertheless, there have been reports of the long QT interval occurring after a moderately overdosed escitalopram or even when it was applied in therapeutic doses [41]. One explanation of such phenomena is that there is a potential overlap of several risk factors of long QT interval [29]. Genetic variability in CYP2D6 which results in ultrarapid drug metabolism to its smaller, cardiotoxic metabolite s-DDCT [36] or the fact that s-DDCT might have a greater cardiotoxic potential than racemic DDCT in a corresponding dose might also account for the phenomena [40].

On balance, escitalopram-induced risk of longer QT interval is similar to the risk after citalopram intake,

however, escitalopram has developed serious health consequences far less frequently [33,39]. Such situations are considered to be more likely with extremely supratherapeutic doses [42].

Sertraline

Sertraline is regarded as the safest and the best-analyzed antidepressant for people at cardiovascular risk. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) proved its safety and significance for post-myocardial infarction patients who demonstrated fewer cardiovascular events and reduced mortality rate. Furthermore, sertraline applied in non-depressive patients after myocardial infarction prevented life-threatening events [43,44]. Sertraline is also recommended for stable patients with ischemic heart disease without clinical symptoms of depression who are being prepared for implantable cardioverter-defibrillator (ICD) implantation. Such practice reduces the frequency of extrasystoles, favourably affects certain left ventricle parameters, and above all, improves life quality [45].

Most likely, sertraline plays a protective role in heart failure pathophysiology and in arrhythmogenesis by coupling with G protein receptors, participating in mitochondrial activity, sympathetic nervous system stimulation as well as intracellular calcium oscillation [45]. Sertraline is considered not to have any adverse influence on ECG; typical therapy- associated cardiological symptoms concern <1% of patients and include non-specific chest pain, angina pectoris, palpitations, minor hypertension, orthostatic hypotension. However, sertraline is commonly considered as a drug with no significant impact on RR and HR values both in vertical and horizontal positions [46].

One case of sertraline overdosing in suicidal attempt has been reported. The taken drug dose of 2250 mg resulted in longer QT intervals. The parameter returned to normal values when the drug application was discontinued. After a couple of days, sertraline was again introduced into treatment and no further long QT interval incidence was detected [47].

Sertraline has been shown to be an antiplatelet agent so in some cases it may cause bleeding. When co-administered with aspirin and/or clopidogrel, sertraline can potentiate their effect, which in some cases may be a desired therapeutic effect [48]. Sertraline can be applied to patients with previous incidences of antidepressant-induced long QT interval or to individuals at risk of ventricular arrhythmia [49].

Paroxetine

Except for being a selective serotonin reuptake inhibitor, paroxetine is also somewhat a muscarinic and cholinergic receptor antagonist. It re-uptakes norepinephrine to some degree. This may explain why it can cause tachycardia in up to 12% of patients [50]. In another study, bradycardia was detected as an adverse effect [51].

Despite single reports of QT interval-prolonging potential [29,54], paroxetine is generally regarded as a safe drug of favourable cardiological profile, which is sustained even in high-dose therapy or in overdose incidences [52,53]. There have been reports of congenital defects in cardiovascular system in children whose mothers were administered paroxetine during pregnancy [55,56].

Fluoxetine and fluvoxamine

No harmful and unfavourable impact of fluoxetine on the cardiac muscle and cardiovascular system has been reported. Only several cases of long QT interval have been recorded [57,58] including cases of combination therapy [59] or even an infant born by a mother taking fluoxamine [60]. Bradycaria is the most common complication [61], whereas in overdosing incidents, i.e. intake > 1500mg, sinus tachycardia, ventricular trigeminy and junctional rhythm have been found [62,63].

Similarly, fluvoxoamine is considered to have an advantageous influence on cardiovascular system [64]. Furthermore, it might favourably affect the system via sigma-1 receptor [65]. Fluvoxamine pharmacotherapy is not linked to any recorded ECG abnormalities, 5% of patients may report bradycardia, and 1% may report tachycardia as a complication. Moreover, arterial hypertension or hypotension, syncope, and, extremely rarely, stroke may occur. One case of post- fluvoxamine therapy Brugada syndrome has been recorded, however, it has not been decided whether the drug was the cause or only the trigger of the complication [66].

Venlafaxine and duloxetine

Selective noradrenaline reuptake inhibitors (SNRI) may adversely affect the cardiac failure in previously stable patients. It is probably associated with increased norepinephrine concentration in the circulatory system and peripheral tissues as a result of the reuptake, which can have a negative influence on the sympathetic nervous system via β-adrenergic receptors. This can result in increased blood pressure and heart rate which, in turn, may lead to myocardial ischemia, stable angina pectoris or heart failure deterioration. >300 mg of venlafaxine and >60 mg of duloxetine are sufficient for noradrenaline reuptake activity to be observed [67].

Venlafaxine and duolexine have a greater potential than SSRI. Both of them are capable of considerable dopaminergic, cholinergic, adrenergic, histaminergic, glutaminergic and opioid activity and both inhibit monoamine oxidase [67].

Venlafaxine may cause the QT interval to lengthen but so far no incidence of arrhythmia as a consequence of long QT interval has been reported [68,69,70]. Other ECG irregularities which may be generated by SNRI include: right bundle branch block (RBBB), left anterior hemiblock (LAH), simultaneous LAH+LBBB, first-degree atrioventricular block (AV 1), broadening of the QRS complex QRS> 120ms. Such events are dose-dependent and can occur at the dose >5g [71]. Fangio et al. described a case of severe cardiac failure as a complication accompanying venlafaxine supplementation dose >5,5 g [72], whereas the application of the dose > 8g was reported to be associated with convulsions and serotoninergic syndrome [73,74]. Additionally, venlafaxine may increase defibrilation threshold in patients with implantable cardioverter-defibrilator (ICD) [75]. Therefore, in venlafaxine therapy the patients' blood pressure, heart rate and ECG should be monitored [76].

It appears that venlafaxine should not be administered in patients with established cardiac organic impairment or clinically pronounced arrhythmias and in patients with unstable arterial blood pressure.

Duloxetine has not been reported to be linked to the events of long QT interval or arrhythmia. In rare cases, duloxetine applied in doses up to 4000mg/d may be connected with insignificant arterial blood pressure and heart rate increase [77]. Abrupt discontinuation of duloxetine is associated with mild heart rate increase and transient sleeping disorders [46]. Analysis of suprathe-rapeutic duloxetine dosing demonstrated that it was linked exclusively with arterial blood pressure and heart rate increase which return to baseline values within 2 days of the drug discontinuation [78].

Summary

New generation antidepressants such as SSRI and SNRI are a well-discussed and well-documented therapeutic option for patients with depressive disorders. It should be highlighted that depression is an independent risk factor of ischemic heart disease. Coexisting depression is also a risk factor of death in ischemic heart disease patients [79].

Despite their safe receptor profile, and thereby a relatively safe adverse effects profile, it should be noted that the drug class is not deprived of the risk of cardiac complications. It is advisable that patients with positive cardiovascular history, specifically with arrhythmia, unstable coronary heart disease, and uncontrollable hypertension should have their ECG monitored. Potentially proarrhythmic drug introduction or dose increase in therapies should be accompanied by the QT interval observation. Once a longer QT interval > 0,5s has been detected, the long QT-inducing drug application should be interrupted and ECG monitoring should be continued until the drug has been removed from organism and QT interval shortening has been identified. When such drug application is regarded as necessary in patients with long QT interval history, heart rate monitoring in hospital may be recommended [7].

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