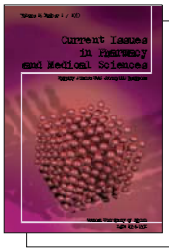

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Antidepressant drugs and cardio-vascular system

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ABSTRACT

Depression is becoming a more and more frequent problem in highly – developed countries. There exist many factors predisposing to the occurrence of the disease. To most commonly mentioned, are organic CNS damage, genetic factors, disorders in neurotransmitters, and hormone dysfunctions. The disease disturbs the functioning of many organs and systems, causing the increase in the risk of the progression of the coronary disease and venous thrombotic- embolic illness. Antidepressants constitute the heterogenic group in terms of their chemical structure and mechanisms of action. Today it is known that applying them indeed increases the risk of the development of disadvantageous changes in the cardio-vascular system. In this study, an attempt of synthetic analysis of the influence of medicines applied in the treatment of depression on cardiovascular diseases was undertaken.

Keywords: depression, antidepressant drugs, cardio-vascular system

INTRODUCTION

Depression is ranked among affective disorders. Lowering of the mood is a basic observed disturbance in depression, frequently accompanied by lowering of a drive, and appearance of damaging mechanisms of dreaming and complex biorhythms. Thinking is becoming monotonous and usually regards one's own frame of mind. Negative self-assessment and conviction about the incomplete value of own person prevent the patient from normal functioning in the society [1]. Apart from psychological manifestations, somatic manifestations like feeling of weakness or gastric problems are also frequent symptoms of depression.

The criterion of division of depressions bases on the number and intensification of manifestations. One distinguishes light, medium and severe type of depression [1]. Most dangerous depression syndromes are: depressions with high level of anxiety and motor excitement, depressive syndromes with drive inhibition, apathy, psychotic depressions (paranoid) and depressive stupefaction. The last of the mentioned types of the disorder is so deep that the patient is not able to maintain the contact with the surroundings. If worrying symptoms of affective disorders come up regularly at determined, permanent seasons, seasonal affective disorder (SAD) is being diagnosed.

Mechanisms responsible for coming into existence of depression are not exactly known. Customarily, it was thought that depression has been a result of failures in life, unfulfilled dreams or dramatic accidents. Today it is known that factors predisposing to the withdrawal of depression exist and they are: genetic disorders, neurotransmitter dysfunctions, hormonal disorders or CNS damage [1]. During depression, the levels of serotonine, noradrenaline and dopamine decrease. Antidepresive drugs can adverse this effect, but high level of the above neurotransmitters and simultaneous central and peripheral increasing of other neurotransmitters such as acetylocholine or histamine can increase side effects.

Depression episodes can be treated with psychotherapy, electric therapy, magnetic therapy, but most often antidepressive drug is the last choice. Antidepressants constitute the heterogenic group both in terms of the chemical structure and mechanisms of action. The main task of these drugs is an activation of noradrenergic and serotoninergic transmission. By accepting the kind of the mechanism of action resulting from administering the dose of the medicine as the criterion, it is possible to single out four groups of therapeutics. The biggest group is

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constituted by medicines with the predominating influence on the neuronal reuptake of monoamines. One can distinguish among them [2, 3]:

- nonselective monoamine reuptake inhibitors of numerous additional receptor action such as amitriptylin, imipramine, tricyclic antidepressants (TCAs),
- medicines selectively blocking the reuptake of the noradrenalin and serotonin (SNRI) – venlafaxine, milnacipran,
- selective noradrenalin inhibitors (NRI) – reboxetine, maprotyline,
- selective serotonin reuptake inhibitors (SSRI) – fluoxetine, fluvoxamine, sertraline, paroxetine,
- dopamine and serotonine reuptake inhibitors – bupropion,
- dopamine reuptake inhibitors – nomifensine, amineptine.

Monoamine oxidase inhibitors (MAOIs) constitute the second group of antidepressants. Their classification is based on the selectivity towards two main types of the monoamine oxidase. MAO-A in a preferential way oxidizes the serotonin, but also metabolizes the noradrenalin and the dopamine. MAO-B predominantly metabolizes dopamine. First-generation MAOIs applied in the treatment of depression are: phenelzine and tranylcypromine - irreversible MAO-A and MAO-B inhibitors. Moclobemide is a medicine of the second generation – a reversible MAO-A inhibitor. An example of the medicine of the third generation is selegiline which selectively inhibits MAO-B. Selegiline is applied in treatment of Parkinson's disease [4]. Nowadays only moclobemide is used. IMAO are rarely used due to their side effects and drug interactions.

The third group of medicines are the medicaments of prevailing blocking action of alpha 2 adrenergic receptor. The typical representatives of this group are mirtazapine and mianserin.

The fourth group of medicines (atypical) is constituted by drugs of a diversified action e.g. tianeptine. Mechanism is neuronal reuptake of serotonin with antiserotonin effect [1,3]. Tianeptine is used mainly in treatment of slight mood disorders.

In treatment of unipolar and bipolar affective disorders, peculiarly in the preventive aspect lithium carbamazepine or valproic acid have also found their application.

AIM OF THE STUDY

The aim of the study was to assess concurrence of cardio–vascular disturbances and antidepressive treatment.

ANTIDEPRESSANTS AND VENOUS THROMBO – EMBOLIC DISEASE

Scientific material accessible to authors includes both demonstrative studies, descriptions of cases with the severe course of depression requiring hospital treatment, as well as cases of outpatients medical histories. One should pay attention to the fact that in the broader spectrum the threat of thrombotic-embolic illness observed at patients with different psychiatric problems, also with depression results in serious general state and the significant limitation of motor activity. Moreover, observation of adverse effects of psychoactive treatment of this group of patients suggests prothrombotic action of some antipsychotic medicines of 1st generation – e.g. of phenothiazines – and above all of 2nd generation – closapine and its derivatives. These are also applied in depression resistant to antidepressant medicines [1].

Findings of studies including application of appropriate antidepressants are diverging and point at the irrelevance with the incidence of venous thrombotic-embolic illness, or supporting venous thrombo-embolic disease being influenced by different antidepressants or only tricyclic antidepressants, i.e. amitryptyline [5]. Selective serotonin reuptake inhibitors (SSRIs), in relation to the beneficial profile of their influence for blood platelets, are willingly recommended for coexistence of depression and coronary disease. The majority of antidepressant drugs disturb the readiness of the blood platelets to aggregate [1]. Simultaneous applying of SSRIs and oral anticoagulants, i.e. warfarine, acenokumarol or acetylsalicylic acid can cause an increased risk of bleedings.

Venous thrombo–embolic disease cases during SSRI treatment with i.e. paroxetine, citalopram, escitalopram appear exquisitely rarely [1,6]. Available literature points only to single episodes of this type of a problem. It is probable, though, that as a result of blocking by the medicine the proteins transporting the serotonin there may come to an appreciable increase of its concentration in the vicinity of peculiar subtypes of cellular receptors. It is not possible to rule out similar mechanisms while taking other antidepressants such as serotonin and noradrenalin reuptake inhibitors (SNRIs), mainly wenlafaxine or NRI noradrenaline reuptake inhibitors (reboxetine) [7].

Moreover, some SSRIs such as paroxetine, belong to strong inhibitors of the P-450 cytochrome which participates in the metabolism of antipsychotic medicines. Course of complicated venous thrombo-embolic disease, mainly in the form of pulmonary embolic problem at persons with depression or, analysing the question more widely, at sick persons with psychiatric problems is often severe and burdened with great mortality [9]. It most often results from diagnostic problems, medical interview, subjective, object examination, from delayed recognizing of pulmonary embolism in this group of sick persons.

Mirtazapine, which belongs to alpha 2 adrenergic and serotonin receptors agonists is characterized by special ability for the activation of the TNF-á system. Isolated descriptions of venous thrombo-embolic disease associated

from mirtazapine is supplementing a lot of cases which are possible to be found in the description of adverse effects of medicines attached to every medicament container. Prothrombotic action of tricyclic antidepressants may result from structural resemblance to phenothiazines [7, 8].

Venous thrombotic-embolic complications of antipsychotic medicines especially of the 2nd generation medicines such as clozapine, olanzapine, quetiapine, risperidon appear more often than in case of antidepressants. Main recommendation for the use of antipsychotic medicines is schizophrenia and other psychoses, but these preparations are also applied in depression. According to some authors, the mechanism of prothrombotic action of clozapine can depend on the stimulation of producing antiphospho-lipid antibodies associated with the occurrence of the secondary antiphospho-lipid syndrome [9].

The increased venous thrombo-embolic disease risk is observed mainly in initial phases of the antidepressive treatment. Antipsychotic drugs are widely used in depression treatment. Indirect effect of antipsychotic medicines on the increase in the risk of falling ill with venous thrombo–embolic disease is expressed through the increase in the body weight and the increase in the concentration of homocysteine, leptine and prolactins. The raised level of these substances in the blood serum is a result of side effects of antipsychotic medicines. Evaluation of side effects of psychotropic drugs in the pathogenesis of the venous thrombo-embolic disease is hampered, on account of parallel or alternating application of different preparations. Polytherapy with both antidepressants and antipsychotic medicines supports summing up of different prothrombotic mechanisms and causes the elevation of a sedative effect [8, 10].

ANTIDEPRESSANTS AND THE HEART RHYTHM DISTURBANCE

Out of all groups of medicines applied in the pharmacotherapy of depression, the ones demonstrating the highest level of toxicity are tricyclic antidepressants (TCAs). They constitute the most frequent cause of poisonings and are a reason of the hospitalization at wards of toxicology. They are responsible for 91% of cases of overdosing and cause the 84% of the total number of deaths caused by antidepressive drugs. Simultaneously they are most frequent antidepressants prescribed in Poland. The strongest toxic action of this group of medicines is connected with the influence on the nervous system and the cardiovascular system. In poisoning with smaller doses, side effects appear such as anti-cholinergic syndrome i.e. enlargement of pupils, blunt vision, dryness of mucous membranes, worsening the peristalsis of intestines, miction stopping, tangling. There sometimes comes to the depression of the respiratory system [9, 10].

In poisonings with large doses, tachycardia is observed, supraventricular and ventricular cardiac arrhythmia, including the ventricular *torsade de pointes* tachycardia and atrial fibrillation [11]. In the ECG record, one may observe wider QRS records and extending the QT interval. First symptoms of poisoning appear already after 1 hour since the time of taking the medicine, whereas full clinical picture, particularly of cardiotoxicity develops within 6 first hours. One should emphasize it that tricyclic antidepressive drugs, as well as other antidepressants can cause the considerable inhibition of the peristalsis of intestines which results in increased absorbing of active substances and the escalation of cardiotoxicity of medicines from this group.

Based on literature data, it is known that amitriptyline and its other derivatives are the most frequent medicines causing the acquired long QT syndrome (acquired long QT syndrome, acLQTS). Excessively long QT space can lead to life threat, which is visible as ventricular arrhythmia in the form of the multiform ventricular *torsade de pointes* (TdP) tachycardia or atrial fibrillation [12]. The cardiac arrhythmia of this type often causes the loss of consciousness or the sudden cardiac arrest, causing the sudden cardiac death. A blockade of potassium channels is causing the syndrome of acquired long QT in myocytes of the ventricle of the hearts which play the crucial role in the final phase of the repolarization.

At patients accepting derivatives of amitriptyline, symptoms of serious poisoning manifest themselves as antycholinergic syndrome, with neurological disorders, and at overdosing – with depression of the respiratory system, with the long QT syndrome with the ventricular tachycardia, the hypotonia and convulsive attacks [13]. One should emphasize that the majority of these manifestations are caused by large doses of the taken medicines. In cases of the acute poisoning immediate hospitalization is needed.

The core base of action of selective serotonin reuptake inhibitors (SSRIs) is an increase in the concentration of the serotonin in the synaptic space [14,15]. Nevertheless, the majority of adverse effects rises as a result of interaction of this group of medicines (fluoxetine, paroxetine) with preparations modulating P-450 cytochrome. SSRIs access into interactions with main anti-arrhythmic medicines i.e. β-blockers, the antihistamine and calcium-channel blockers (CCBs). SSRIs can cause heart rhythm disturbances, although bradycardia or tachycardia are common clinical manifestations of drug interaction. A blockade of this atrioventricular bundle, or direct damaging of the cardiac muscle are the mechanisms responsible for the dysrhythmia [15].

Nevertheless, SSRIs are safe and side effects are a rare occurrence, especially cardiotoxic manifestations. Treat-

ment with fluoxetine is safe at cardiological patients, but on account of the increased risk of bleedings resulting from the digestive tract from applying derivatives of the salicylic acid, this treatment must be contraindicated. SSRIs can increase adverse effect of medicines as anti-aggregation of platelets due to derivatives of the acetylsalicylic acid.

Newer drugs such as wenlafexine, duloxetine, bupropion, mirtazapine, trazodon, monoamine oxidase inhibitors, extremely rarely trigger the adverse effects concerning cardiovascular system. Only in the case of wenlafexine, episodes of this type are more often observed. As a result of interaction with other medicines this medicament can cause rises and drops of the blood pressure and the bradycardia [16]. However, a direct influence on the heart was not proven as for mirtazapine. In case of this medicine, exaggerated increase in the body weight and appearing of manifestations of the metabolic syndrome are observed [17]. There is a lack of information if duloxetine exerts the detrimental effect on the cardiac muscle. In randomized clinical research based on not very big material it was demonstrated that only bupropion can affect the growth of the systolic pressure [15].

CONCLUSIONS

Due to the indisputable influence of the majority of antidepressants on the cardiovascular system and demonstrated interactions with pharmacological therapeutics universally used in therapy of heart diseases, extraordinary caution is recommended at the classification of patients with depression to the determined type to the pharmacotherapy.

Based on the cited above literature, it is known that medicines mainly from the group of tricyclic antidepressants demonstrate direct adverse effect to the cardiac muscle and blood vessels. Overdosing of this group of pharmacological therapeutics is possible and it involves serious complications.

On account of the behavioural disorder appearing at depression, the illness by itself often makes the effective cardiological treatment impossible causing the increase in the risk of cardiovascular episodes.

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