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Treatment of Depression in Patients on Anticoagulation Therapy: Antidepressant-Rivaroxaban Drug Interactions

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Abstract

The use of Oral Anticoagulants (OAC) is recommended for stroke prevention. Rivaroxaban is a new generation oral anticoagulant. Depression and anxiety are psychiatric disorders which frequently coexist with the Coronary Artery Disease (CAD) and other cardiovascular diseases. In the last decades, there has been an increase in the use of antidepressants. This literature review aims to provide a general view of pharmacokinetic knowledge of drug interactions between rivaroxaban and antidepressants. Since rivaroxaban is metabolized by CYP3A4, the use of antidepressants that are inhibitors of this isoenzyme, such as fluoxetine, sertraline, paroxetine and fluvoxamine must be avoided. Based on drug interactions in cytochrome p450, it has been concluded that the use of escitalopram, citalopram, venlafaxine, mirtazapine or milnacipran would be safer in these patients since these drugs have a minimum CYP 450 inhibition potential.

Keywords: Rivaroxaban; Depression; Metabolism; Anticoagulants; Antidepressants

Introduction

For many years, vitamin K antagonists were the only available oral anticoagulants for clinical use. Despite being effective, they presented problems such as slow onset of action, multiple interactions (food-drug and drug-drug), and an unpredictable pharmacodynamic answer, which demanded constant coagulation monitoring [1].

Nowadays, new anticoagulants are available in the market as an alternative to vitamin K antagonists. These substances have more predictable pharmacodynamics and pharmacokinetics, besides the fact that they lack the need for routine coagulation monitoring (INR: International normalized ratio) [2].

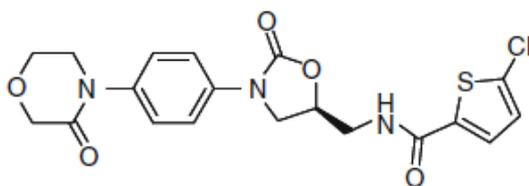Rivaroxaban is an example of the new oral anticoagulants (Figure 1) [3].

Figure 1: Chemical structure of rivaroxaban.

Rivaroxaban inhibits factor Xa in a concentration-dependent manner (inhibitory constant $[K_i]$, 0.4 nmol/L) and binds rapidly (kinetic association rate constant $[k_{on}]$, 1.7×10^7 mol/L^{-1}.s^{-1}) and reversibly (kinetic dissociation rate constant $[k_{off}]$, 5×10^{-3} s^{-1}) [4]. It is a selective inhibitor of factor Xa with oral bioavailability [5]. Factor Xa is essential for blood coagulation, being activated by both the intrinsic and extrinsic pathways of coagulation [1]. Factor Xa converts prothrombin into thrombin via the prothrombinase complex, causing the formation of fibrin clots and the activation of platelets by thrombin [6]. When compared to an adjusted dose of warfarin administered to patients with nonvalvular atrial fibrillation who were at moderate to high risk of stroke, rivaroxaban was not inferior to warfarin for the prevention of subsequent stroke or systemic embolism [7].

Rivaroxaban is rapidly absorbed and achieves maximum concentration (C_{max}) 2-4 h after tablet intake. Its oral absorption is close to 100% and its oral bioavailability is high (80-100%). Rivaroxaban's pharmacokinetics is close to linear, with high plasma protein binding (92-95%), serum albumin being its main binding component. Rivaroxaban is eliminated via two pathways. About 2/3 suffer metabolic degradation, half of which is excreted via the kidneys, while the other half is excreted in the feces. The remaining 1/3 of the administered dose is excreted directly via the kidneys as unchanged active substance in the urine, mainly via active renal secretion [1].

P-glycoprotein (P-gp) interferes with the intestinal absorption and renal excretion of rivaroxaban [8].

Rivaroxaban is metabolized by CYP3A4, CYP2J2 and by CYP independent mechanisms. CYP3A4 accounts for approximately 18% and CYP2J2 for approximately 14% of rivaroxaban total excretion. In addition to this oxidative biotransformation, non-CYP mediated amide hydrolysis accounts for 14% of rivaroxaban total excretion. The resulting metabolites are eliminated via renal and hepatobiliary routes [1]. Sick elderly presented higher plasma concentrations than younger patients, with 1.5 times higher levels, due mainly to a reduction (apparent) in the total and renal depuration rate [1].

Administration of rivaroxaban with CYP3A4 and P-gp inhibitors, such as ketoconazole or ritonavir, caused an increase in its serum levels, maximizing significantly the pharmacodynamic effects, with an increased risk of bleeding [9]. However, due to the multiple pathways

for elimination of rivaroxaban, the drugs that inhibit only one of these pathways (CYP3A4 or P-gp), and those that moderately inhibit both pathways have no relevant clinical effect. Care should be taken with the concomitant administration of moderate inhibitors to patients with chronic renal disease [9].

Concomitant use with CYP3A4 inducers (e.g. rifampicin) has the potential to decrease plasma rivaroxaban concentration and reduce therapeutic efficacy.

Depression and anxiety are psychiatric disorders that frequently coexist with Coronary Artery Disease (CAD) and other cardiovascular diseases [10]. The use of antidepressants has increased in the last decades [11].

The main classes of antidepressants are the Tricyclic Antidepressants (TCAs), the Monoamine Oxidase Inhibitors (MAOIs) and the selective serotonin reuptake inhibitors. The tricyclic antidepressants are not normally recommended for patients with cardiovascular diseases because of their side effects, such as orthostatic hypotension, sinus tachycardia and arrhythmias [12]. The Monoamine Inhibitors (MAOIs), on the other hand, can increase blood pressure and cause hypertensive crises, the most serious toxic effect of this class, which usually happens when MAOIs are combined with foods containing tyramine (e.g. red wine, aged cheese) or sympathomimetic amines [12].

The Selective Serotonin Reuptake Inhibitors (SSRIs) are the most prescribed antidepressants. The SSRIs may cause an increase in the risk of bleeding through various different mechanisms, such as the platelet aggregation dysfunction, depletion of platelet serotonin levels, and low platelet count [13].

The increased risk of bleeding associated with rivaroxaban and certain antidepressants may result in an additive effect when these therapies are used together.

Rivaroxaban administered to patients under therapy with antidepressants may also result in drug interaction via pharmacodynamic and pharmacokinetic mechanisms. Among the antidepressants, the fluoxetine slightly inhibits CYP3A4. Its metabolite norfluoxetine is a more potent CYP3A4 inhibitor than fluoxetine [14]. Fluoxetine is also an inhibitor of P-glycoproteins. Fluvoxamine is a moderate inhibitor of CYP3A4. It is the most potent CYP3A4 inhibitor among the serotonin reuptake inhibitors. Among the other second-generation antidepressants, nefazodone is a strong inhibitor of the CYP3A4 isoenzyme, while paroxetine and sertraline are weak CYP3A4 [15] inhibitors. Escitalopram, citalopram, venlafaxine, mirtazapine and milnacipran are not inhibitors of CYP3A4 [15].

Among the MAOIs, tranylcypromine is a CYP2A6 inhibitor, a CYP450 isoenzyme of secondary importance. It apparently does not inhibit other CYP450 enzymes, having, therefore, low potential for pharmacokinetic interactions [16].

The safe and effective use of a treatment is a constant challenge for public health professionals and organizations all over the world [17]. About 6.7% of hospitalized patients have serious adverse drug reactions [18]. The use of cytochrome P450 (CYP) pharmacogenetics in depressed patients being administered rivaroxaban may be an alternative to help identify the best antidepressant-rivaroxaban association. However, the drugs currently available for the treatment of depression have some kind of metabolism related to cytochrome p450, making the choice of drug difficult [19]. This should motivate research

for the development of substances with a lower potential for drug interaction.

Therefore, since rivaroxaban is metabolized by CYP3A4, antidepressants that are inhibitors of this isoenzyme, such as fluoxetine, sertraline, paroxetine and fluvoxamine must be avoided. Based on drug interactions in cytochrome p450, the use of escitalopram, citalopram, venlafaxine, mirtazapine or milnacipran would be safer in such patients since these drugs have a minimum CYP 450 inhibition potential.

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