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Enantiomers: a new issue in pharmacotherapy of depression?

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Summary

Enantiomers as the drug forms being optically active have currently a considerable influence in most pharmacotherapy areas. They have aroused a large interest in the field of psychiatry and especially for treatment of depression. This is due to the fact that enantiomers (chiral forms) of many drugs may have different pharmacokinetic, pharmacological or pharmacogenetic profiles. Therefore, in many cases, the use of a single drug enantiomer might have had huge advantage over previously used forms and lead to strong improvement in current treatment. The stereoselective property of fluoxetine being such psychotropic drug is an example that belongs to the group of selective serotonin reuptake inhibitors (SSRIs).

Keywords: Fluoxetine, depression, psychiatry.

1. Introduction

Application of single enantiomers as medicinal agents gains increasingly growing importance in both the development and manufacturing of new antidepressant drugs and the in-depth understanding of differences between pharmacological mechanisms of medicinal preparations. New possibilities and opportunities arise in the field of chemical analysis distinguishing between individual enantiomer forms, the awareness is also growing with regard to differences between pharmaco-kinetic and pharmaco-dynamic parameters of these isomers that has to lead to regulation of the requirements on characterising the racemates of the drugs admissible to placing on the market in view of their enantiomeric composition. It seems that knowledge of concentrations of particular enantiomers of psychotropic drugs that show the difference in both their pharmaco-kinetic and pharmaco-dynamic properties is indispensable for assessment of their pharmacotherapeutic effectiveness. Moreover, the enantiomers may serve as the „pharmacological probes" useful for detailed familiarising with both the neuro-pharmacological mechanisms and the metabolic differences. Continuously increasing experimental and clinical data show that application of single enantiomers brings about considerably more benefits than application of racemic drug forms in treatment of psychical diseases, being depressions, in particular [1, 2]. Multiple psychotropic drugs are placed on the market in the form of racemate, i.e. a mix of enantiomers, thus

meaning these drugs show chiral feature, hence they occur in enantiomeric varieties. Fluoxetine, mianserine, mirtasepine, trimipramine and citalopram have to be mentioned within this group. Certain drugs which fall in this group are already manufactured in the form of single enantiomer forms, to only mention escitalopram, paroxetine or sertaline. Nevertheless, a lot of the current studies on depression and other diseases disregard the mostly important role of enantiomers in stereoselectiveness of metabolism, pharmacogenomics and in pharmacology and toxicology. Disregarding such important issue may lead to many inappropriate conclusions.

2. Enantiomers

The term chirality has to be first explained to understand precisely what the enantiomers exactly are. Chirality is defined as a geometric property of the rigid object structures of molecules, chemicals and drugs that reveal in the initial molecule and its mirror reflection image being not identical. This „not identical" feature consists of the lacking identity of a molecule's spatial structure against its mirror reflection image that results in the grounds of the total unavailability of the symmetry elements, or of the existence of a simple symmetry axis in the molecule itself. The molecule and its mirror reflection image are not identical and likewise all chiral objects also these cannot be superimposed by each other through spatial shifting and rotation. Relation between the molecule and its mirror reflection acts mutually likewise the right palm and the left one. The existence of asymmetric carbon atom in a given molecule, i.e. such one, of which 4 different atoms or atom groups are linked to, is a precondition of the chirality feature. Thus, the chirality is decisive for existence of enantiomers and it is the condition necessary for the occurrence of optical activity of the compound, i.e. the ability to rotation of the polarity of light. Two mirror reflections of the chiral molecules are defined as enantiomers. Likewise the palms mentioned above, the enantiomers occur in pairs. Both the pair forming enantiomer molecules have the same chemical composition and the bonds linking the atoms. They are featured by the same summary and the two-dimension molecular formula, but when in various chiral environments such as receptor and enzymatic systems they might present different properties. So, the enantiomers are featured by their identical stechiometric formulas, but they form many various, 3D spatial structures. Marking D from term dextro and L from term levo was applied to set out their absolute configuration and optical rotation. This type marking is currently applied to setting out the 3D spatial configuration of saccharides and amino acids.At present, , the R marking, after Latin sinister meaning „to the left" and the S after Latin rectus meaning „to the right", is applied to setting out the absolute 3D spatial configuration of the optical rotation of other compounds' chirality centres, while +/- marking applies to additional setting out the optical rotation. It has to be kept in mind that a chiral drug may contain more than one chirality centre, and where it is the case, the attribution of absolute configuration separate to each chirality centre is required. For a given pair of enantiomers, one of them may be market as (+) and the other one as (-), depending on direction of the rotary polarization of light. The (+) optical rotation is ascribed to determine dextrorotatory enantiomers, whereas the (-) to

the laevorotary ones. The racemic substances which consist of an enantiomer mix are marked as R, S or (±). As it was mentioned before, each target biological system for a given drug is chiral. The enzymatic and receptor systems, as well as many proteins, nucleinic acids and, polysaccharides, lipids and steroids may be the biological systems. Thus, most biological reactions in this type of systems run in a stereo-selective manner. Consequently, a drug in the form of racemic mix shows big differences in pharmacokinetics, therapeutic efficiency, toxicology and other biological properties.

In many cases, one enantiomer of the racemic mix exhibits advantageous therapeutic action, while another one could contribute to showing the opposite effects, or complicate the assessment of absorption, distribution, metabolism and excretion [3].

3. The importance of enantiomers in psychiatric and biological systems

Enantiomers of the chiral drug forms show their similar physical and chemical properties, but only when they are in achiral environment. Their behaviour is quite different when in chiral environments in which one enantiomer shows different chemical and pharmacological properties than another one occurring in the same racemic mix. Since vital biological systems are chiral, then each of individual enantiomers of a given drug can behave quite differently under ***in vivo*** conditions. In other words, for prevailing majority of cases, the R enantiomer of a drug shows different behaviour in relation to the S enantiomer of the same drug ingested by patient. For a chiral drug, one has to take into account the occurrence of this substance in the form of two enantiomers, and should consider these enantiomers as the two separate drugs featured by different properties. Through application of a single enantiomer in therapy one could avoid the very essential, from a clinical point of view, undesirable side effects. For example, in clinical doses, the desirable anaesthetization effects with application of ketamine relate rather to the (+) enantiomer, while its undesirable psychoactive effects relate rather to the (-) enantiomer [4]. The difference between the two enantiomers of a given drug and their interaction with hypothetical biological system is shown in Fig 1.

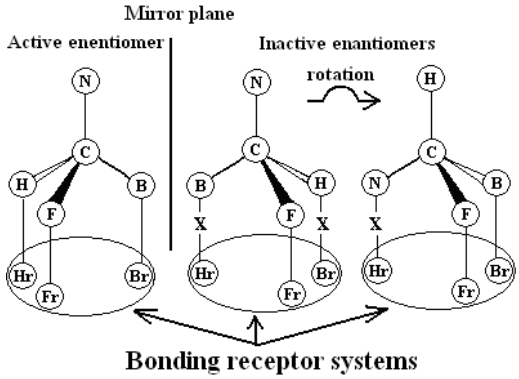

Figure 1. **Hypothetical interaction between the two enantiomers of a chiral drug and the biological bonding spots**

In this case, only one of the enantiomers shows biological action, while the another one does not. The functional groups of the drug are marked as the H, F and B. These groups interact with their corresponding regions bonding the Hr, Fr and Br in an active spot of the biological system, while triggering desirable therapeutic effect. Active enantiomer form has created the 3D spatial structure is such way that the H functional group interacts with its complementary Hr group in an active spot, the F functional group interacts with its complementary Fr group, and the B group of the enantiomer molecule interacts with its corresponding Br group. Inactive enantiomer forms are not in position to bond in such similar way with given active spots, since their functional group creates no complementary bonds with the active spots in biological systems.

There are several reasons for which application of single enantiomer drugs instead of their racemates is justified in general therapy, and particularly in psychiatric treatment. Firstly, the application of a drug in the form of single enantiomer allows for reduction of the drug total dose administered to a patient, while the same treatment parameters and results are retained. For many cases, that is reflected by the fact that application of a single enantiomer results in considerably higher therapeutic effectiveness than a racemic drug administered. Antidepressant drugs are very good application example of such type treatment method. Secondly, the assessment of the dose-response type parameters becomes more simple and precise than in the case of applying a racemate. Thirdly, application of one enantiomer might reduce the clinically essential pharmacokinetic and pharmacodynamic differences between patients. Considerable reduction in toxicity of a given drug that results from elimination of inactively therapeutic another enantiomer occurring in the racemic mix is a very essential strength of application of a single enantiomer [5]. The evidences presented above show new opportunities to usage and application of the respective drug form, particularly the psychotropic drugs applicable to psychiatry.

4. Fluoxetine as an example of enantiomeric drug applicable to treatment of depression

Fluoxetine is the drug which proves that stereospecific antidepressant drugs could have very high therapeutic and commercial potential. It is the drug belonging to the third generation of antidepressant agents. It is currently applied for health care purposes only in serious cases of drug-resistant depression. The mechanism of pharmacological action of fluoxetine consists in halting the serotonine back-capture and to a minor degree – of catecholic amines. Fluoxetine is metabolised in liver to several metabolites, including principally to norfluoxetine - active metabolite. Action of this drug occurs after at least 2–4 weeks of treatment and it retains up to 5 weeks. Application of the high doses for a longer time prolongs the drug activity period. As results from certain studies, fluoxetine is also an antagonist of the 5-HT_{2C} receptor that makes fluoxetine an atypical selective inhibitor of the serotonine back-capture [6]. Beyond treatment of depression, it applies to treatment of obsessions. Likewise every drug, also the fluoxetine causes many side effects, including: the feeling of tiredness, sleep disorder, nervousness, fear, weakness of muscular strength, headaches and suffering from verti-

go, stomach and intestinal disturbances (reduced feeling hungry, more seldom nausea, vomiting, diarrhoea, dyspepsia). Also allergic reactions may appear, throat dryness, fever, elapsing balding, excessive perspiration, bad mood, aches muscles and joints, bleeding, disturbances of liver functions, reduced libido, and disturbed urination.

Fluoxetine, (*N*-methyl-3-phenyl-3-[4-(trifluormethyl)phenoxy]propane-1-amine) is a compound having molar weight 309.3 g/mol. Similarly to all drugs from the SSRI group, the fluoxetine has chiral structure (Fig. 2) and occurs in the form of racemic mix [7, 8]. The S-fluoxetine enantiomer is metabolised principally to the S-norfluoxetine, whereas the R-fluoxetine is metabolised respectively to the R-norfluoxetine. The S-enantiomers show stronger action when compared against the R-enantiomer forms: about 1.5 times higher for the fluoxetine forms, and 20 times as much for norfluoxetine [9, 10].

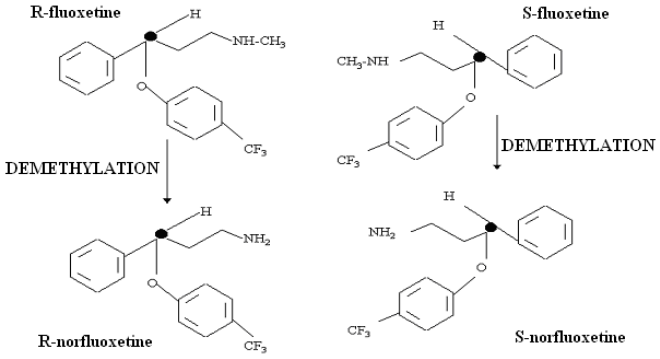

Figure 2. **Origination of norfluoxetine enantiomers in N-demethylation) process of the fluoxetine enantiomers. The „●" symbol stands for a chiral carbon atom**

It was found on the basis of the test results that after 23 days of treatment with fluoxetine, the concentration of the S-fluoxetine enantiomer was higher than that of the S-norfluoxetine with prompt-metabolising patients. For slow-metabolising patients, the results were quite different. The in vitro tests have shown that the stereoselective metabolism of fluoxetine to norfluoxetine depends on the CYP2D6 and CYP2C9 cytochromes, and to a lesser degree from the CYP2C19 that are involved in N-demethylation process of fluoxetine towards formation of the R-norfluoxetine [11]. However, on the other hand, the CYP2D6 shows the higher activity in relation to the S-fluoxetine, than the R-fluoxetine does. It is also noteworthy that the S-fluoxetine and the S-norfluoxetine are the stronger inhibitors of the CYP2D6 cytochrome than their corresponding R-enantiomers [12, 13, 14].

5. Summary.

Both the S- and the R-fluoxetine, as well as the S-norfluoxetine have to be considered the separate drugs falling in the group of selective inhibitors of the serotonine back-capture featuring by potential clinical importance, due to the fact that these

enantiomers and the R-norfluoxetine are strong inhibitors of the CYP2D6 cytochrome. Psychotropic chiral drugs provide very useful tool to examine many neuropharmacological mechanisms, as well as to functioning enzymatic systems which participate to metabolism [1, 2].

The influence of chiral drugs on pharmacogenomical parameters has to be always taken into account when making assessments of any studies.

The growing availability of drugs in the form of single enantiomer forms provides new opportunities to physicians while giving them the more effective, safe and better tolerated treatment of patients. It should be also kept in mind that each enantiomer of given chiral drug may distinguish by its own, concrete pharmacological profile, and each constituent enantiomer of a racemic drug may have the properties other than a racemic drug of general use.

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