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Short communication

Psychopharmaca: from pharmacokinetics to clinical outcomes

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Introduction

Clinical outcomes of active substances depend on their pharmacokinetics and pharmacodynamics. Pharmacokinetics illustrates the passage of active substances through the body in spatial and temporal terms and is defined by the processes of release from dosage forms, absorption form the site of administration to the central circulation, distribution throughout the body, metabolism and elimination from the body. Basic mechanisms of these processes are convection and diffusion with the exception of metabolism, where chemical transformation occurs. Pharmacokinetics thus ensures regardless of the mode of application the transfer of the active substance from the site of administration to the site of action, i.e. to the biophase where the targets are located. On the other hand, pharmacodynamics studies the processes that begin to take place between the active substance and the target when the active substance reaches the target. Targets are either receptors or enzymes, they may be carriers or ion channels. The result of the interaction between the active substance and the target is a measurable clinical effect such as drop in blood pressure, drop in cholesterol levels, drop in body temperature, relief of pain, recovery from infection, reduction of symptoms and signs of depression or psychosis and more (Derendorf and Schmidt, 2020).

Pharmacokinetics and pharmacodynamics are very often influenced by polymorphisms of genes encoding enzymes, carriers, receptors and ion channels which pharmacogenetics deals with.

Selected examples of psychopharmaca in the light of the influence of pharmacokinetics and pharmacogenetics on clinical outcomes will be presented below.

Pharmacokinetic and pharmacodynamic parameters

Basic pharmacokinetic information represents the relationship between concentration and time in the form of an appropriate curve showing plasma levels of active substance. From this curve one can calculate the primary and secondary parameters. Primary parameters are k_a (absorption rate constant), F (extent of absorption), Cl_p (total clearance) and V_d (volume of distribution). Secondary parameters are k_e (elimination rate constant), $t_{1/2}$ (biological half-life) and AUC (area under the curve).

Basic pharmacodynamic information is presented by E_{max} plot that shows relationship between effect and concentration of active substance. Two parameters can be identified from this plot, E_{max} (the maximal effect that an active substance can elicit, indicates efficacy) and EC_{50} (the concentration of an active substance required to produce 50% of maximum effect, indicates potency). Moreover, from E_{max} plot we can obtain therapeutic range which tells us in which range of plasma concentrations we can expect desired effect.

By merging the two curves we obtain the time course of the dependence of the effect on time, which allows us to predict the time of onset of the effect, the strength of the effect and the duration of the effect (Derendorf and Schmidt, 2020).

Examples of psychopharmaca

Midazolam is a benzodiazepine-type active substance used for anesthesia, procedural sedation, trouble sleeping and severe agitation. Its EC_{50} amounts to 0,1 mg/L and is lower than in the case of oxazepam and clobazam which are used in a similar indication. This means that midazolam shows greater potency than the

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other two benzodiazepines. Consequently, the largest dose of midazolam is 15 mg to reach therapeutic range 0,08 – 0,12 mg/L and is smaller than in the case of oxazepam and clobazam, both with maximal dose of 30 mg. Midazolam elimination half-life of 1.5–2.5 h allows duration of action up to 6 h in the case of instant release oral formulation.

Fluphenazine is a phenothiazine-type of a high-potency classical antipsychotic used for treating acute and chronic psychotic conditions, including schizophrenia and manic and hypomanic disorder. Its potency is 50 times higher than in the case of chlorpromazine, which means that a 50-fold lower daily dose of up to 10 mg in the case of peroral administration is required for approximately the same effect. Therapeutic range is 1 - 4 µg/L and can be achieved either orally in a 1-, 2- or 5-mg film coated immediate release tablet or by deep intramuscular injection into the gluteal muscle in a dose of 25 mg in the form of decanoate. As $t_{1/2}$ of elimination amounts up to 17 h oral daily dose is usually divided into two doses to maintain plasma concentrations within therapeutic range for a long period assuming absorption from the gastrointestinal tract is very rapid ($k_a > k_e$). In the case of intramuscular injection, the situation is reversed. As the rate-limiting step is hydrolysis of ester in gluteal muscle, which takes place very slowly, the absorption is significantly prolonged ($t_{1/2}$ of absorption is 231 h, $k_a < k_e$) thus allowing dosing every three weeks. Even in this case, plasma concentrations are maintained within the therapeutic range whereby concordance is ensured. In both cases, the dosage regimen should be adjusted so that plasma concentrations do not significantly exceed 2.7 µg/L due to the increased likelihood of adverse reactions.

Paliperidone (9-hydroxyrisperidone) is an atypical antipsychotic that is used in the treatment of schizophrenia and schizoaffective disorder. It is available as prolonged release tablets and intramuscular injections in the form of palmitate. The mechanism of the latter mode of application and consequent pharmacokinetics and clinical efficacy are comparable to those in the case of fluphenazine, i.e. long term hydrolysis of ester in deltoid or gluteal muscle which provides a biological half-life of tens of days, even up to 130, thus allowing application once a month or even once every three or six months with very small peak-to-trough ratio of paliperidone at steady state ranging from 1.56 to 1.70. However, paliperidone alone has a biological half-life of 23 h, which allows once a day oral application in the form of prolonged release tablets to reduce fluctuations in plasma concentrations, similar as in the case of intramuscular injections, in order to optimize clinical efficacy.

Risperidone is an atypical antipsychotic used to treat schizophrenia and bipolar disorder. Extrapyramidal disorders (parkinsonism, dystonia, tardive dyskinesia, restlessness) are the main side effects of risperidone therapy, occurring more frequently at doses higher than 4 mg daily. Moreover, the elimination rate of risperidone is highly variable, biological half-life ranges from 3 to 24 h, indicating an important role of CYP2D6 genotype in conversion of risperidone to 9-hydroxyrisperidone which is the major (90%) metabolic pathway.

A prospective study was conducted at the University Medical Centre Maribor and at the Faculty of Pharmacy Ljubljana to characterize the metabolism of risperidone to (+)- and (-)-9-hydroxyrisperidone in vivo and to evaluate the influence of CYP2D6 genotype. A population pharmacokinetic modeling approach was used to estimate the interindividual variability of the pharmacokinetic parameters in 50 hospitalized patients with acute episode of schizophrenia. CYP2D6 genotype remarkably influenced the formation clearances of the risperidone metabolites, while creatinine clearance was related to the plasma clearance of 9-hydroxyrisperidone. CYP2D6 genotype was also associated with the average plasma concentration of risperidone active moiety (a sum of all three active compounds). In comparison to the patients with CYP2D6*1/*1 genotype, average steady-state plasma concentration of risperidone active moiety was 3.3- and 1.6-fold higher in poor metabolizers (both alleles nonfunctional; CYP2D6*3 or *4) and intermediate metabolizers (one nonfunctional allele and one allele for diminished enzyme activity; CYP2D6*10 or *41), respectively. Additionally, average plasma concentration of risperidone active moiety was higher in the patients with dystonia ($p=0.0066$) and parkinsonism ($p=0.046$). The results of this study imply the potential role of CYP2D6 genotyping in personalizing risperidone therapy in patients with schizophrenia to reduce the incidence of adverse extrapyramidal disorders (Locatelli et al., 2010)

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