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DERLEME / REVIEW

FARMAKOGENETİĞİN ANTİDEPRESANLARIN KLİNİK KULLANIMI ÜZERİNE ETKİSİ

THE INFLUENCE OF PHARMACOGENETICS IN THE CLINICAL USE OF ANTIDEPRESSANTS

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ÖZET

Kişiselleştirilmiş tıbba olan ilgi, farmakogenetik üzerine olan araştırmaları da teşvik etmektedir. İlaç geliştirmede yeni analitik metodların ortaya çıkması ve aynı zamanda insan genom teknolojisinde görülen olumlu gelişmeler araştırmacıların farmakogenetiğe olan ilgisini artırmıştır. Son yıllarda genetik biliminde olan bu tür gelişmeler farmakogenetik bilimine olumlu yönde katkı yapmıştır. Kişileştirilmiş tıp terimi aynı zamanda hedefe yönelik ilaç tedavisi ve kişinin genetiğine göre özel tedavi verme kavramlarını gündeme getirmiştir. İlaç tedavisinde görülen değişik yanıt oranları ve genetik farklılıkların ilaç tedavi başarı oranlarını etkilemesi farmakogenetik çalışmaları, psikofarmakoloji ve antidepresanlar üzerine odaklamıştır. Genetik faktörlerin antidepresan ilaç yanıtına yaklaşık %50 kadar katkısı olabileceği düşünülmektedir. Bunlara ek olarak kişinin genetik faktörleri, antidepresanların farmakokinetik ve farmakodinamik özelliklerini etkileyerek ilacın etki oranlarını değiştirebilir aynı zamanda ilacın kandaki konsantrasyon değişimine bağlı görülebilecek istenmeyen etki sıklığında artışa da sebep olabilmektedir. Serotonin taşıyıcılarını kodlayan genler olan, 5-HTTLPR ve SLC6A4 isimli genler yaygın olarak araştırılmakta ve antidepresan ilaç yanıtında temel farklılıkların bu genlerdeki değişimlerin olduğu sanılmaktadır. Ayrıca CYP 2D6 ve CYP 2C19'un aktivitelerindeki farklılıkların antidepresanların karaciğerdeki yıkım hızını, farmakokinetik özelliklerini etkileyebilmekte ve plazmadaki antidepresan kontsantrasyonlarını değiştirebilmektedir. Tüm bu faktörlerde olabilecek değişiklikler antidepresan tedavisine olan yanıtları değiştirebilmekte ve genetik farklılıklara bağlı doz ayarlaması yapılması gündeme gelmektedir. Bu derlemede, seçici serotonin geri alım inhibitörleri, serotonin-nöradrenalin geri alım inhibitörleri, trisiklik antidepresanlar ve mono-amin oksidaz inhibitörleri gibi farklı antidepresan gruplarının farmakogenetik özelliklerine odaklandık. Genetik varyasyonların, antidepresanların farmakokinetik ve farmakodinamik özellikleri üzerine olan etkilerini ve bu etkilerin antidepresanların kliniğine olan yansımalarını derledik.

ANAHTAR KELİMELER: Antidepresanlar, Farmakogenetik, Psikofarmakoloji

ABSTRACT

The interest on personalized medicine encourages researches on pharmacogenetics. The promotion of new analytical combinations in extensive drug development and also with the progression in the technologies for human gene cloning resulted in a great interest for pharmacogenetics. In last years the development on genetical sciences also influenced pharmacogenetics. Personalized medicine also includes areas such as stratified medicine and precision medicine and these terms are closely related with pharmacogenetics. Moderate response rates and the difference in drug effect on individuals focus pharmacogenetics on psychopharmacology area and antidepressants. It is considered that genetic factors may contribute %50 of antidepressant drug response. Additionally the genetical properties of the patient may effect the pharmacokinetics and pharmacodynamics of the antidepressants therefore the change in the effect and an increase in the side effects may be seen. The genes which codes serotonin transporter, 5-HTTLPR and SLC6A4 are commonly investigated and they are thought to be the main reasons of the difference in antidepressant drug responses. Also the difference in the activities of CYP 2D6 and CYP 2C19 may change the pharmacokinetics of the antidepressants and therefore the stable concentration of antidepressant leves in the plasma. These variations in the factors contributing to the drug levels may lead to a difference in the response rates of antidepressants. In this review, we focused on the pharmacogenetics of different classes of antidepressant drugs such as selective serotonine reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants and mono-amine oxidase inhibitors. We have compiled pharmacogenetic studies on antidepressants and effect of genetic variations on the drug responses.

KEYWORDS: Antidepressant, Pharmacogenetics, Psychopharmacology

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INTRODUCTION

Depression is a psychological illness that may cause serious complications, may lead to insomnia, weight loss, and thoughts of death, as a result of emotional change in people. People feel unhappy and start to obsess over a certain period of time, the depression process may be a severe condition that needs to be treated. A person who is in the process of depression has to deal with many diseases because this mental illness may affect the whole body negatively.

Antidepressant drugs are used in the treatment of depression. Antidepressants are thought to show their activity by blocking the uptake of certain neurotransmitters and therefore increasing the amount of neurotransmitters in the synaptic cleft (1). Selective serotonin-reuptake inhibitors (SSRIs), Serotonin-norepinepinephrine reuptake inhibitor (SNRI), Monoamine oxidase inhibitors (MAOs), Tricyclic antidepressants (TCAs) are among the mostly prescriped antidepressants in the current practice. There are some important details that need to be considered in antidepressant drug selection. The effectiveness of the antidepressant, the possible side effects and whether the drug is safe are important for the treatment of the patient. In order to use a drug in the treatment of a patient, the absorption, distribution and elimination stages of the drug to be applied are important, and it is necessary to know the pharmacokinetics and pharmacodynamics of the drug as well (2). Also the genetical properties of the patient may effect the pharmacokinetics and pharmacodynamics of the antidepressants therefore the change in the effect and an increase in the side effects may be seen.

Pharmacogenomics is a science of genomics that investigates the effects of medication on the patients in different dimensions and the role of genetic variation, the mechanisms of drug effect on different individuals (3). P450, which is one of the cytochrome enzymes, is named as a group of isoenzymes that have the ability to carry oxygen and electrons to organic molecules, as well as to undergo oxidation and reduction. Cytochrome p450 carries oxygen to steroids, vitamins and fatty acids. Knowledge on p450 enzymes is an important factor for the interactions of drugs. Levels of p450 enzymes are different for each person. Among the p450 enzymes, those which may effect psychiatric drugs are; P450 2D6, 2C19, 1A2, 3A3, 3A4 and 2E1. Many drugs are metabolized by the P450 2D6. P450 2D6 is known as a useful marker in regulating dopaminergic activity as well as drug concentration (4).

In molecular level studies of pharmacogenetics, the cloning process based on P450 CYP2D6 has been started. Based on this results, it has gained a wide frame size with the identification of other human genes, including drug receptors and many drug transport systems, along with more than 20 drug metabolizing enzymes (5).

Single nucleotid polymorphism (SNP) is also considered as an important factor in the drug metabolism and differences in SNP may have influence on the drug effect. SNPs thought to have effects on the expression and antidepressant drug effect on the 5HT1A receptor which may particularly have impact on the effects of SSRI group antidepressants (6).

This review focuses on the influence of pharmacogenetics on the clinical use of the antidepressants and the effect of the genetic changes on the side effects and the treatment success of the antidepressants.

PHARMACOGENETICS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

SSRIs are the first-line treatment for major depressive and anxiety disorders. Sertraline, paroxetine, citalopram, escitalopram, fluoxetine and fluvoxamine are the commonly used SSRI class drugs. CYP2D6 and CYP2C19 gene polymorphisms are responsible for ensuring drug efficacy and protection as well as affecting the metabolism of SSRIs. Although pharmacokinetic data for drugs differ, in general all SSRIs reduce presynaptic serotonin reuptake and tend to selectively increase serotonergic activity (7).

The differences in the genes which encodes the serotonin transporter (SLC6A4) and the serotonin receptors ($5HT_{1A}$ and $5HT_{2A}$) may have effect on the clinical outcome of the patients which are prescribed SSRIs (8, 9). In a meta-analysis which analysed 33 studies it has been

stated that one of the studied variant of the SLC6A4 is the promoter region (5-HTTLPR) and the differences in 5-HTTLPR activity may effect the uptake of serotonin this is thought to have influence on the effects and side effects of the antidepressants especially SSRIs via effecting the pharmacokinetics of the drug (10). The biallelic short 'SS' and biallelic long 'LL' forms of the 5-HTTLPR genes are thought to effect the pharmacodynamics of antidepressants. In clinical studies it has been showed that 'LL' genotype had better response rate to SSRIs compared to the 'SS' genotype (11, 12). However in other clinical studies, no difference in the response rate between 'SS' and 'LL' genotype was seen (13, 14). These conflicting results showed that more clinical studies are needed on different 5-HTTLPR genotype in order to elucidate the effect of antidepressants on different 5-HTTLPR allel types.

The studies on the genotypes of $5HT_{1A}$ and $5HT_{2A}$ receptors have shown different results on antidepressant effects. In a study conducted with 65 patients, the results showed that the G allel carriers of $5HT_{1A}$ receptors might be more resistant to antidepressant treatment (15). In a study on 19 geriatric patients using citalopram, remission rates were found different in diverse $5HT_{1A}$ genotypes (16). On the other hand in other clinical studies, no relationship was found with SSRI treatment success and $5HT_{1A}$ receptor polymorphism (17, 18). The trials on the $5HT_{2A}$ receptor polymorphism have shown contradictory results in the antidepressant response. It was shown that genetic variations which effected the $5HT_{2A}$ receptor activity could influence pharmacodynamics of the drug and this may change the response of the citalopram treatment (19).

However other clinical studies failed to replicate this result and the changes in the genotype of $5HT_{2A}$ receptor did not show any influence on the antidepressant activity (20, 21). There is need for more clinical studies on the different genotypes of $5HT_{1A}$ and $5HT_{2A}$ receptors in order the show their influence on the treatment with SSRIs and the other group of antidepressants.

PHARMACOGENETICS OF SEROTONIN NORADRENALIN REUPTAKE INHIBITORS (SNRI)

SNRIs are considered as a class of antidepressants that include duloxetine, venlafaxine and desvenlafaxine. These antidepressants are used for the treatment of general anxiety disorders in many countries. Apart from these, they are also used in the treatment of diabetic neuropathy and major depressive disorder. In the first stage of depression in the psychiatric disease class, it is now treated with SNRIs and SSRIs instead of the old antidepressants (22). SNRIs also have effects on reducing pain transmission (23).

Venlafaxine is mainly metabolised by CYP 2D6 enzyme (24). There are different phenotypes of CYP 2D6 enzyme and activity of this enzyme may differ with each phenotype. Ultra-rapid metaboliser (UM), intermediate metaboliser (IM) and poor metaboliser (PM) phenotypes of CYP 2D6 had been identified (24). Royal Dutch Pharmacist Association (KNMP) recommends that patient which have CYP 2D6 PM and IM phenotype to avoid the use of venlafaxine and UM phenotype patients the standart dose of venlafaxine should be increased to %150 of the standart dose for therapeutic effect (25). On the other hand in diverse clinical studies no difference in therapeutic effect and side effect were seen with varied types of CYP 2D6 phenotypes (26, 27). It is also thought that the polymorphism on the genes which regulates norepinephrine transporter (NET) on neurons may influence the effects of SNRIs. In a clinical study conducted on nearly 1000 patients on the effect of NET polymorphism showed no correlance between NET polymorphism and Venlafaxine response (28).

Duloxetine is metabolised by CYP 2D6 and CYP 1A2 enzymes (29). In the caucasian population approximately %5-10 is estimated to lack the sufficient CYP 2D6 metabolism and therefore they are accepted as poor metabolizers (29). The effects of CYP 2D6 enzyme on duloxetine was examined between poor metabolizer and normal metabolizer patients and the pharmacological parameters were found similar, it was stated that other than CYP 2D6 enzyme, CYP 1A2 enzyme or other parameters may influence duloxetine's effect (30). In a different study con-

ducted on major depressive patients receiving duloxetin treatment, it was shown that CYP 2D6 genetic polymorphism affects the safety and efficacy of duloxetine (31). These differences in the genetics of CYP enzymes may alter the pharmacokinetics of SNRIs and therefore effect the clinical outcome of the patients.

PHARMACOGENETICS OF TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants (TCAs) are used for 70 years since their development as antidepressants. And 30 years later, without the SSRIs being discovered, it came to the fore as the basis of psychopharmacotherapy. Tricyclic antidepressants are divided into 2 groups as tertiary amines and secondary amines. A potent inhibitor of 5-HT reuptake is tertiary amines. Secondary amines, on the other hand, have a great effect on the norepinephrine carrier. Similar to SSRIs, tricyclic antidepressants also establish a strong bond with proteins, but are metabolized with CYP enzymes. TCAs may cause serious side effects in overdose (32).

TCAs initially aid their therapeutic effects by inhibiting the reuptake of serotonin and norepinephrine on neurons. Since tricyclic antidepressants also inhibit different receptors (H1 histamine, alpha 1 α1-adrenergic and muscarinic receptors), side effects are quite common. Tricyclic antidepressants are continued to be used in certain types of depression. Considering amitriptyline, it is mainly metabolized through the CYP2C19 and CYP2D6 pathways. Nortriptyline, a tricyclic antidepressant, also broken down in active metabolites in the metabolism process with CYP2C19 (33). It is considered that patients carrying two allels of poor metaboliser CYP2C19 gene may have a risk of diminished theraupetic effect (34). On the other hand ultra-rapid and rapid metaboliser CYP2C19 gene carrying patients may have a risk of serious side effects due to the change in the pharmacokinetics of the drug. Like CYP2C19 gene, CYP2D6 ultra-rapid and rapid metabolisers may experience less theraupetic effect whereas in CYP2D6 poor metaboliser patients side effect may be seen more commonly (35). It is considered that in patients which experience serious side effect with normal doses of TCAs and patients who does not respond the TCA therapy, a pharmacogenetic test should be considered and dose adjustments should be made according to the genotype of the patient (36).

PHARMACOGENETICS OF MAO INHIBITORS

MAOI are known as the first antidepressants. MAO, one of those responsible for catalyzing serotonin, also mediated the emergence of tricyclic antidepressants. MAO catalyzes oxidative deamination of monoamines. There are 2 types, MAO-A and MAO-B. Serotonin, melatonin, noradrenaline primarily metabolised by MAO-A whereas phenetylamine and benzylamine are metabolised by MAO-B. Both forms catalyzes dopamine, tyramine and trypthamine equally (37).

Isocarboxazide, moclobemide, rasagiline, selegiline and tranylcypromine are among the widely used MAOI. Moclobemide is a major substrate of CYP2D6 and CYP2C19 (38). Therefore ultra-rapid and rapid metabolisers of CYP2D6 and CYP2C19 may have a diminished theraupeutic effect on the other hand in poor metabolisers of CYP2D6 and CYP2C19, pharmacokinetics of the drugs may change and sufficient clinical effect with moclobemide may not be seen. Tranylcypromine is transported by SLC6A4 (39). In clinical studies conducted on 300 patients, it was shown that SSRIs effect may change due to genetic variations in SLC6A4 gene (40, 41). It is thought that genetic variations on SLC6A4 may change the pharmacodynamics and therefore clinical effect of tranylcypromine, clinical studies should be made on this topic in order the elucidate the influence of SLC6A4 gene variations on tranylcypromine effect.

Drug response rates may be diverse in different individuals . Every person has a different genetic code and therefore the effect and duration of drugs likely to vary in different people. Antidepressant response is highly effected by differences in CYP2D6 and CYP 2C19 activity and these differences effect the pharmacokinetic properties of antidepressants. Inadequate antidepressant response rates may be seen in patients taking antidepressants, especially those degraded by CYP2D6 and CYP 2C19. In

some patients however the side effects of these antidepressants are more common. In these patients genetic tests should be carried out in order to elucidate CYP 2D6 and CYP 2C19 polymorphism. For patients with CYP2D6 / CYP2C19 genetic variants that have an impact on the activation and safety of the drug, it is believed that modification to pharmacotherapy could potentially improve clinical outcomes and thus reduce the initial treatment failure rate.

It is considered that the variations in genes which codes serotonin reseptors $5HT_{1A}$ and $5HT_{2A}$ may effect the antidepressant response especially SSRIs. The genetical differences on 5-HTTLPR gene which effects serotonin receptors could change the pharmacodynamics of SSRIs and may have influence on the SSRI response. However there are conflicting results on clinical trials, more data on the genetic variants of serotonin receptors are needed.

Pharmacogenetics is developing with the progress in the genetical sciences. This development in pharmacogenetics will provide personalised and precise medicine for each individial. We hope that this will maintain better treatment outcomes and less side effects for the patients.

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