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Mini Review

Hepatic First Pass Metabolism: The Implication on the Biological Activity of Atypical Antipsychotic Agents

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Abstract

Hepatic first pass metabolism is the metabolism of a drug in the liver received through the portal circulation prior to reaching systemic circulation. The liver is the principal organ of first pass metabolism in the body and has blood flow of about 20 - 25% of the total cardiac output. The objective of the study was to ascertain the effects of hepatic first pass metabolism on the biological activity of atypical antipsychotic agents. Scientific journals, official books and internet websites were the sources of the information. The results show amisulpride, aripiprazole, asenapine, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone to be the atypical antipsychotic agents. Some of them were found to undergo significant hepatic first pass metabolism. Poor bioavailability was observed with some of these atypical antipsychotics due to hepatic first pass metabolism. The therapeutic outcomes of orally administered atypical antipsychotic agents depict that there are relationships between threshold plasma drug levels and clinical responses. In summary, hepatic first pass metabolism has no drawbacks on the biological activity of clinically used atypical antipsychotic agents.

Keywords: *Hepatic First Pass Metabolism; Atypical Antipsychotics; Biological Activity*

Hepatic first pass metabolism is a biological process that allows a proportion of orally administered drug after being absorbed from the gastrointestinal tract (GIT) to be metabolized mostly by the liver before reaching the systemic circulation. The intestinal wall is also a common site of first pass metabolism. The degree of this pre-systemic metabolism by the liver is determined by the hepatic clearance or extraction for the drug [1]. Hepatic clearance is influenced by the extent of drug binding to blood proteins such as albumin as well as blood flow to active metabolic cells. A drug with high extraction ratio implies that its metabolism (elimination) is dependent on blood flow and hepatocyte function. Typical examples of drugs with high extraction ratio are antidepressants, calcium channel blockers chlorpromazine, glyceryl trinitrates, haloperidol, levodopa, morphine, propranolol etc. However, a drug that depends only on hepatocyte function for its metabolism is said to have low extraction ratio. Typical examples of such drugs are carbamazepine, diazepam, non-steroidal anti-inflammatory agents, phenytoin, warfarin etc.

As the principal organ of first pass metabolism in the body the liver has blood flow of about 20 - 25% of the total cardiac output of which about 20% of blood comes from the hepatic artery and the other 80% is from the portal circulation [2]. Many of the first pass metabolic enzymes in the liver include cytochromes P450, esterases, uridine diphosphate (UDP)-glucuronyltransferases and sulfotransferases [3].

Drugs such as midazolam and verapamil undergo intermediate first pass metabolism (35 - 36%) [4,5]; atorvastatin and tacrolimus high first pass metabolism (11 - 12%) [6]; ergotamine and lovastatin very high first pass metabolism (5% or less) [7,8].

The susceptibility of a drug to first pass metabolism by some of these enzymes has a very high influence on the oral bioavailability. The oral bioavailability has been observed to decrease as the level of first pass metabolism increases.

Bioavailability, describes the fraction of an administered drug dose that reaches the systemic circulation. It is the rate and extent at which the active drug is absorbed from the pharmaceutical dosage form and becomes available at the site of action for biological activity. This is achieved indirectly by measuring the amount of the drug in the plasma at periodic time intervals [9].

Atypical antipsychotic drugs are second-generation antipsychotic agents that are differentiated from conventional (typical or traditional) antipsychotics by their effectiveness (high biological activities), low or negligible levels of undesirable unwanted side effects [10]. Such undesirable unwanted side effects that are characteristics of typical antipsychotics are extrapyramidal symptoms (EPS), hyperprolactinaemia, tardive dyskinesia, neuroleptic malignant syndrome etc.

The advantages of atypical antipsychotic agents have over traditional antipsychotics might be because of their affinities for multiple receptors including dopamine D_2, 5-hydroxytryptamine (5-HT) 2A and 2C, histamine H_1, a-adrenergic and muscarinic receptors [11].

These atypical antipsychotics include amisulpride, aripiprazole, asenapine, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone.

The mechanism of action for atypical antipsychotics indicates that the dopamine pathway is still considered the primary common target just like traditional antipsychotics, Out of 5 types of dopamine receptors in human beings (namely 1, 2, 3, 4, 5 receptors): types 1 and 5 are called "D_1like" class of receptors because of their similarity in structure and drug sensitivity, while dopamine receptor types 2, 3, and 4 that have significantly different sensitivities to antipsychotic agents are grouped as the "D_2like" class of receptors. Of the three "D_2like" receptors, only the D_2 receptors in the brain are blocked (60 - 80%) by antipsychotic drugs (typical and atypical respectively) and for typical antipsychotics this blockade is in direct relation to their clinical antipsychotic potencies [12]. However, with atypical antipsychotics the level of D_2 receptor blockade in relation to their antipsychotic effects is more complicated [13] and has been explained by three theories namely (a) the "fast-off-D_2" theory [14,15], (b) the dopamine-serotonin antagonism theory [15] and (c) inverse agonism theory [12].

Clinically, atypical antipsychotic agents are highly effective in the treatment of schizophrenia and bipolar disorders.

The objective of the present study was to evaluate the influence of hepatic first pass metabolism on the biological activity of atypical antipsychotic agents.

Literature search has revealed that a number of atypical antipsychotics are significantly affected by hepatic first pass metabolism.

They include:

(i) Amisulpride: The drug is a substituted benzamide derivative. Undergoes significant hepatic first metabolism after oral administration and has an absolute bioavailability of 50% [16].

(ii) Aripiprazole: It could be a "third-generation" antipsychotic agent. The drug has oral bioavailability of 87% after oral administration, hence its hepatic first metabolism is very limited [17,18].

(iii) Asenapine: The drug has absolute bioavailability of 35% therefore indicating extensive hepatic first metabolism after oral administration. The hepatic metabolism is by UGT1A4 (direct glucuronidation) and by CYP-450 isoenzymes (oxidative metabolism) [19].

(iv) Clozapine: The drug is a benzodiazepine derivative. After oral administration, only about 27 - 50% of the dose is bioavailable due to extensive first-pass metabolism [20].

(v) Iloperidone: The drug is devoid of hepatic first pass metabolism since it is almost completely absorbed following oral administration with bioavailability of about 96% [21].

(vi) Olanzapine: It is a thienobenzodiazepine derivative. Out of 85% of an oral drug dose that is absorbed by gastrointestinal tract following oral administration only about 60% is bioavailable as a result of inactivation by first-pass hepatic metabolism. The drug inactivation by hepatic first pass metabolism leads to the N-glucuronide, N-desmethylolanzapine and olanzapine-N-oxide via uridine diphosphate glucuronyltransferase (UDPGT), cytochrome P450 (CYP) 1A2 and flavin monoxygenase (FMO), respectively [22].

(vii) Paliperidone (Hydroxy risperidone): It is a benzisoxazole derivative and a major active metabolite of risperidone. Its hepatic first pass metabolism is very significantly brought to a minimum due to its formulation into paliperidone extended-release product [23].

(viii) Quetiapine: The drug has limited hepatic first pass metabolism because it has fairly good oral bioavailability of about 70% [20]. Two of the metabolites namely 7-hydroxy-quetiapine and 7-hydroxy-N-desalkyl-quetiapine are pharmacologically active [24].

(ix) Risperidone: It is a benzimidazole derivative. The drug has good oral bioavailability (about 70 - 85%) after oral administration and therefore limited hepatic first pass metabolism.

The inactivation of the drug is by CYP2D6 and, to a lesser extent, CYP3A4. However, alicyclic dehydroxylation and oxidative N-dealkylation are other minor metabolic pathways [25].

(x) Ziprasidone: It is a benzothiazolylpiperazine derivative. Following oral administration, the absolute bioavailability is 60% indicating substantial hepatic first pass metabolism [26].

Despite the significant effects of hepatic first pass metabolism on some of these atypical antipsychotics, they all provide the required clinical responses (biological activities) because they seem to possess threshold plasma levels. Several reports have assessed the relationship between threshold plasma drug levels and clinical responses [27,28].

For example, a threshold plasma level of 350 - 420 ng/ml of clozapine is linked with an increased probability of a good clinical response to the therapeutic agent [29,30].

Conclusion

The liver receives blood flow of about 20 - 25% of the total cardiac output and it is the principal organ of metabolism in the body. The hepatic clearance or extraction for a drug determines its hepatic first pass metabolism. Hepatic first pass metabolism of atypical antipsychotics leads to poor bioavailability because they tend to be metabolized before adequate plasma concentrations are reached. The clinical efficacy of orally administered atypical antipsychotic agents, provide evidence that there exists a relationship between threshold plasma

drug levels and clinical responses. Finally, the study has shown that hepatic first pass metabolism has no drawbacks on the biological activity of atypical antipsychotic agents.

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