Oxidation of Antipsychotics

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Contributor: Aiperi Khasanova , Natalia Shnayder , Regina Nasyrova

Antipsychotics (APs) are psychotropic drugs that generally have a psycholeptic effect, capable of reducing psychotic symptoms and psychomotor agitation. This class of drugs is widely used in psychiatric practice, especially for the treatment of psychosis in schizophrenia and other psychotic disorders. Most APs pass through a biotransformation process, or metabolism, after they enter the body before being eliminated. There are three phases of AP metabolism. Cytochrome P450 (CYP) monooxygenase (mixed-function oxidase) plays a central role in most AP biotransformation. CYP's functional activity depends on gene–drug and drug–drug interaction and influences on the occurrence of adverse drug reactions (ADRs). So, it is extremely important for a practicing psychiatrist to know the oxidation pathway of APs, since most of them are metabolized in the liver. This is important both to prevent ADRs and to avoid unwanted drug–drug interactions, which will undoubtedly increase the effectiveness and safety of AP therapy.

oxidation antipsychotics cytochrome P450 enzymes

Antipsychotics (APs) are a class of psychotrophic medication primarily used to manage psychosis (including delusions, hallucinations, paranoia, or disordered thought), especially for the treatment of psychosis in schizophrenia and other psychotic disorders [1][2]. They, along with mood stabilizers, are also the first line of treatment for bipolar affective disorder [3]. First-generation APs (FGAs), conventional or typical antipsychotics, have significant potential to cause extrapyramidal syndrome (akathisia, acute distonic reactions, tardive dyskinesia, pseudoparkinsonism, and others) [4]. The main difference between FGAs and second generation APs (SGAs) is the predisposition to cause these type of adverse drug reactions (ADRs) [5]. In other respects, such as other ADRs and their mechanism of action, the two classes have substantial overlap and comparable efficacy [6].

Most APs pass through a biotransformation process, or metabolism, after they enter the body before being eliminated [7]. In the course of biotransformation, APs are converted into more water-soluble suspensions, and, therefore, are subsequently more easily excreted from the body.

In the process of AP metabolism, most initial APs lose their pharmacological action and are removed from the body through excretion. During biotransformation, produced metabolites usually are more polar or charged than the parent APs, which increases the rate of clearance; this modification can also decrease reabsorption in the tubules [8].

In the process of biotransformation, APs usually become less pharmacologically active or completely inactive compounds, but also newly formed metabolites can be equally pharmacologically active and even more pharmacologically active compounds if the original APs was a prodrug. As a result of AP biotransformation new

metabolites are formed: With changed and new pharmacological actions, these new metabolites may have both lower and higher potencies in comparison with initial APs; new metabolites may also have a toxic effect, or new metabolites may be active, if the parent APs were prodrugs [9].

Biotransformation reactions of drugs and endogenous substances often develop over sequential stages, such reactions occur with the participation of enzymes and enzyme systems. Most APs undergo biotransformation in the liver, also some APs are metabolized in other organs and tissues [10].

Biotransformation reactions occur with the participation of specific enzymes or enzyme systems. These enzymes can catalyze both xenobiotic metabolism, in this case APs, and substances with endogenic origin, such as hormones. Most often, AP biotransformation reactions occur in the liver; however, individual APs undergo these reactions to a greater or lesser extent in other organs and tissues of the human body.

The process of APs biotransformation is quite changeable, and this variability depends on many factors, for example:

- Nutritional status;
- Hormonal status;
- Genetic factors;
- Previous therapy with APs or other classes of drugs;
- Comorbid somatic, neurological, or mental disorders;
- Age (for example, very old patients or children often have a greater sensitivity to APs, due in part to the involutional or immature state of the enzyme systems by which APs are metabolized);
- Functional state of the liver [11].

Basically, there are three phases of APs biotransformation: phase I (modification), phase II (conjugation), phase III (excretion) (**Figure 1**). It is noticeable that biotransformation phases I and II can be sequential, or can take place in reverse order or simultaneously, as a single reaction [12].

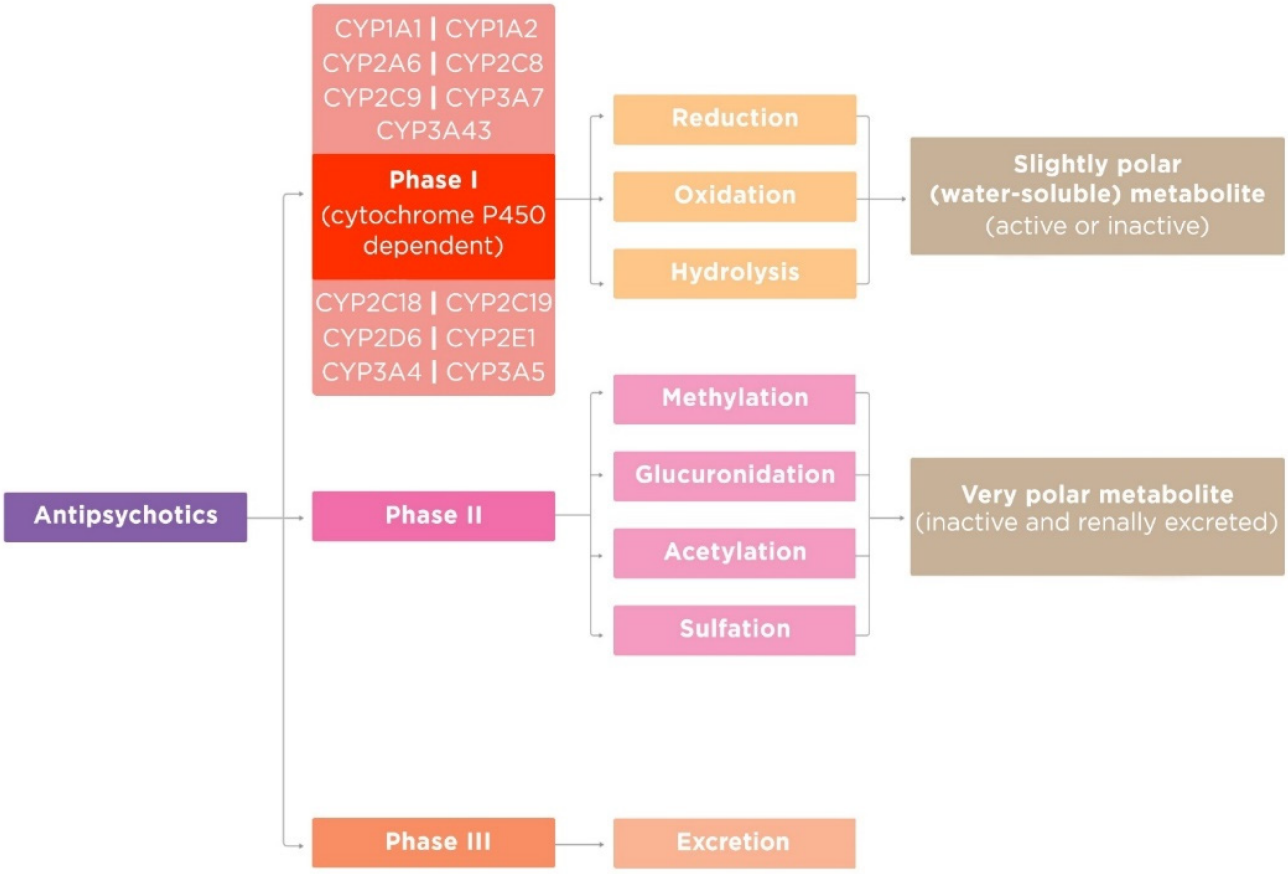

Figure 1. Antipsychotic metabolism phases.

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