Prodrugs and active metabolites among antidepressive compounds

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Clinical effect of drugs is influenced by the composition of the pharmaceutical preparation but substantially by the fate of the drug in the body. Metabolism of the xenobiotic drug compounds may result in pharmacologically inactive metabolites, however, metabolites with higher pharmacological activity can also be produced. These active metabolites may have different pharmacokinetic properties than the parent drug. Co-existience of the parent drug and the active metabolite in the body may significantly modify the therapeutic effect. Knowledge-based system of pharmacokinetics and metabolism of the drugs has a high impact in understanding both the pharmacokinetic and the pharmacodynamic interactions. Cytochrome P450 isoenzymes taking part in the metabolic activity of the central nervous system is a developing area in metabolic studies. In the present study CYP isoenzymes with significant activity in the brain and the clinically important pharmacokinetic and metabolic data of antidepressive compounds are summarized.

Keywords: antidepressant, active metabolite, CYP isoenzymes in brain, pharmacokinetics, pharmacodynamic interaction

Over one hundred and fifty drugs on the market are known to have active metabolite(s) including several compounds used in antidepressive therapy. The overall progress of drug metabolism research resulted in the present regulations that no new compound can be registered without detailed information on its chemical metabolism, enzymatic, genetic and drug-drug as well as drug-food interactive aspects. As antidepressants are typically administered long-term, their drug-drug interaction profile as well as effect on the different cytochrome P450 isoenzymes (CYPs) also has great clinical importance.

Metabolic reactions are initially categorized as non-synthetic (phase I) and conjugation or synthetic (phase II) reactions. Phase I reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group. These metabolites can be inactive, although in some instances pharmacological activity is even enhanced. The vast majority of transformations are catalyzed by specific enzymes located in the endoplasmic reticulum, mitochondria, cytosol, lysosomes, or even the nuclear envelope or plasma membrane. In these oxidation-reduction processes, two microsomal enzymes play a key role, the hemoprotein cytochrome P450 (CYP) and the flavoprotein, NADPH-cytochrome P450 reductase. Several polymorphic variations in CYP enzymes, genetic variations in flavin monooxygenase (FMOs) (Koukouritaki et al., 2007) and dihydropyrimidine dehydrogenase (Harris et al., 1991) play an important role in individually altered drug response.

Phase II (synthetic) reactions involve conjugations with endogenous substrates (glucuronic acid, sulfuric acid, acetic acid, or amino acids) to form a highly polar conjugate that is readily excreted. Conjugate formation involves high-energy intermediates and specific transfer enzymes. Among conjugating enzymes thiopurine methyltransferase, N-acetyl transferase and glucuronyl transferase have been reported to show genetic variants (Gardiner et al., 2006).

It is well known that the principal organ for metabolic biotransformations is the liver, although every tissue has also some ability to metabolize drugs. Tissues beyond the liver with considerable metabolic activity

are the lung, gastrointestinal tract, kidney, while the metabolic activity of the brain is also noteworthy.

Metabolic pathways in the brain show some striking particularities mainly due to the blood-brain barrier (BBB) that blocks the free diffusion of polar solutes from the blood to the brain. The BBB is formed by endothelial cells with continuous tight junctions that exhibit very low pinocytotic activity and are surrounded by a basal membrane and extracellular matrix, pericytes and astrocyte foot processes. BBB is partially under the control of astroglia that can release chemical factors and signals that modulate the permeability of the main endothelium (Wolburg & Lippoldt, 2002; Abbott et al., 2006). However, it is striking how many drugs actually penetrate the BBB through an active transport mechanism for essential nutrients, precursors, and cofactors and exert important effects on brain functions (Alavijeh et al., 2005). The mutual function of the BBB and different factors (eg. inflammatory processes in the CNS, drugs) that may influence its effective functioning including its role in releasing drugs and their metabolites from the brain (brain-CSF barrier) is a developing field in neuropsychopharmacology (Spuch & Carro, 2011).

Biotransformation of drugs by brain tissue has been recently reviewed by Haining et al., 2007 and Dutheil et al., 2008. Levels of CYPs reported in the brain are low compared to the liver or intestine with the peculiarity that some of the CYP activity is found in the mitochondrial subcellular fraction (Dutheil et al., 2008). Major drug-metabolizing CYP families (CYP1, CYP2, CYP3 and CYP4), each having several isoforms were shown to play a role in metabolism in the brain tissue. CYP isoforms reported in the human brain and their contribution to the metabolism of antidepressants is summarized in Table 1.

CYP catalysed metabolic reactions in the brain can also be the target of interactions between endogenous substrates (neurotransmitters, neurosteroids, growth factors etc.) and drugs that penetrate the brain (DeVane et al., 2004; Nissbrandt et al., 2001).

Involvement of CYP isoenzymes in the metabolism of antidepressant drugs in the brain is summarized in Table 2.

Drug metabolism research has grown from the pioneering work of Friedrich Woehler in the early 19th century examining the potential chemical transformation of urea in the human body. Major drug-metabolizing reactions have been identified by the early part of the 20th century and the first summarizing work on metabolic reactions was published by R.T. Williams (Williams, 1959). Although Williams accepted the former view that all metabolic reactions are "detoxifications", even at that time there were examples known when a compound was actually made more active by metabolism (Prontosil, an azo dye with a very low antibacterial activity in vitro, but metabolized by azo reduction into the true antibacterial sulfonamide; the antihistamine terfenadine metabolized to its active metabolite fexofenadine, acetanilide metabolized to paracetamol). Phase II conjugations generally produce inactive metabolites, while the well-known exception is morphine-6-glucuronide.

Nowadays when research for factors determining individual drug response is in the focus of scientific interest it is worth to mention that individual genetic differences in drug metabolism may significantly modify drug response (Sárosi et al., 2008).

Active metabolite(s) of drugs may significantly modify clinical effect as these metabolites may have different pharmacokinetics than the parent compound. The most frequently found pharmacokinetic differences between the parent drug and the metabolite(s) are higher affinity of the metabolite(s) to plasma proteins and longer biological half life. It is worth to mention that not all active metabolites are clinically important. Only those ones can be considered clinically important that are produced in significant amount or are at least as active as the parent drug, or are produced in specific tissues, like the brain.

Pharmacokinetic properties and clinically important metabolites of antidepressants are summarized in Table 3, Table 4 and Table 5. In these tables only those drug-interactions were summarized that were qualified as "major", with significant clinical impact. In the practice it can often be seen that patients do not inform the medical staff about the use of OTC drugs, although administration of St John's Wort preparations, NSAID drugs, ginkgo preparations are well-known to interact with antidepressants. It is worth to mention that nefazodone is a strong CYP 3A4 inhibitor resulting in a series of clinically important interactions with CYP3A4 substrates.

To give a detailed review on all metabolic processes and drug interaction profile of antidepressants on the market is beyond the frame of the present publication. The use of comprehensive data-banks with reliable content and evidence-based drug information is inevitable and required in the practice.

Table 1 CYP isoforms present in the human brain and their role in the metabolism of psychoactive drugs

CYP isoform	Expression in brain region	Contribution to metabolism of the psychoactive compound
CYP1 family	cortex, cerebellum, basal ganglia, hippocampus, substantia nigra, pons, nuclei of a majority of astrocytes, neurons of cortex	
CYP1A1		polycylic aromatic hydrocarbons, carcinogens
CYP1A2		tryptophan, melatonin, caffeine
CYP1B1		estradiol
CYP2 family		
CYP2A6	no data on region-specificity	nicotine, serotonin, histamine, noradrenaline, dopamine, estrogen, androgen, corticosteroids (potential role of neurotransmitters in the regulation of drug metabolism in the brain)
CYP2A13	no data on region-specificity	to be determined
CYP2B1 CYP2B2	astrocytes of corpus callosum and olfactory bulb	to be determined
CYP2B6	both in neurons and astrocytes	nicotine, buproprion, l-deprenyl, cocain, carcinogens, phencyclidine, amphetamines
CYP2C CYP2C8	no data on region-specificity	arachidonic acid
CYP2D6	all regions with highest level in cerebellum	a large variety of psychoactive drugs (see Table 2 and for other details: http://www.drugbank.ca)
CYP2E	neurons of cerebral cortex, dentate gyrus, CA1, CA2, CA3 of hippocampus, Purkinje cells in the cerebellum	
CYP2E1		ethanol, dopamine
CYP2J2		arachidonic acid
CYP2U1	human brain- and thymus- specific isoform	arachidonic acid
CYP3 family	neurons of cerebellum, striatum, hippocampus, basal ganglia, frontal cortex	
CYP3A4		the most potent drug metabolizing isoform, a large variety of psychoactive drugs and neurosteroids: cortisol, testosterone, 17β-estradiol, progesterone
CYP3A5		function to be determined
CYP4 family	glial cells	
CYP4F11		arachidonic acid

Adapted from Wang et al., 2009

Table 2 Involvement of CYP isoenzymes in the metabolism of antidepressant drugs

Drug	Metabolic reaction	CYP 2D6	CYP 3A4	CYP2C9	CYP2C19
Amitriptyline	N-demethylation	+	+	+	+
Clomipramine	2-hydroxylation 8-hydroxylation N-demethylation	+ + -	- - +	- - -	- - +
Desipramine	Hydroxylation	+	-	-	-
Imipramine	2-hydroxylation N-demethylation	+	-	-	+
Mianserine	O-demethylation	+	-	-	-
Mirtazapine	N-demethylation 8-hydroxylation N-oxidation	- + +	+ - -	- - -	- - -
Nortriptyline	2-hydroxylation	+	-	-	-
Trimipramine	Demethylation 2-hydroxylation	+ -	- +	- -	+ -
Maprotiline	Demethylation N-oxidation	+ +	- -	- -	- -
Fluoxetine	N-demethylation	+	-	+	-
Fluvoxamine	Demethylation	+	-	-	-
Paroxetine	Demethylation	+	-	-	-
Citalopram	N-demethylation	-	+	-	+
Escitalopram	Demethylation Didesmethylation	+ +	+ -	- -	+ -
Atomoxetine	4-hydroxylation	+	-	-	-
Duloxetine	4-hydroxylation 5-hydroxylation	+ +	- -	- -	- -
Venlafaxine	O-demethylation N-demethylation	+ +	+ +	- -	- -
Reboxetine	O-dealkylation	-	+	-	-
Trazodone	Hydroxylation N-dealkylation	+ +	- -	- -	- -
Nefazodone	Hydroxylation	+	+	-	-
Agomelatine	Hydroxylation Demethylation	+ +	- -	+ +	+ +

Adapted from MICROMEDEX®, www.drugbank.ca, www.pharmindex.hu

Table 3 Clinically important pharmacokinetic data and active metabolites of tricyclic antidepressants and the tetracyclic mirtazapine

drug	elimination half life of the parent drug (h)	time of peak plasma concentration (h)	clinically important active metabolite	interacting drugs elevating plasma concentration of the TCA	interacting drugs lowering plasma concentration of the TCA
Amitriptyline	9-46	1-5	nortriptyline	cimetidine, SSRIs, haloperidol, phenothiazines, labetalol, diltiazem, quinidine, verapamil, propoxyphene, acute ethanol, oral contraceptives	barbiturates, carbamazepine, chronic alcohol, phenytoin
Nortriptyline	16-88	3-12	10-hydroxy-nortriptyline		
Imipramine	6-34	1.5-3	desipramine		
Desipramine	11-46	3-6	2-hydroxy-desipramine		
Trimipramine	23	2	desmethyl-trimipramine		
Clomipramine	20-24	2-6	desmethyl-clomipramine		
Doxepin	8-36	1-4	desmethyl-doxepine		
Mirtazapine	20-40 significantly longer in females	1.5-2	demethyl-mirtazapine		

Adapted from MICROMEDEX®, www.drugbank.ca, www.pharmindex.hu

Table 4 Clinically important pharmacokinetic data, active metabolites and clinically important drug interactions of reuptake inhibitor antidepressants

drug	elimination half life (t½) of the parent drug (h)	time of peak plasma concentration (h)	active metabolite	interacting drugs
Citalopram	33-37	2-4	desmethylcitalopram didesmethyl-citalopram citalopam-N-oxid	***increased risk of bleeding:*** all NSAIDs, oral anticoagulants, antithrombotic agents ***risk of serotonin syndrome:*** all SSRIs, SNRIs, moclobemide, rasagiline, selegiline, St John's Wort, all antimigraine triptans, dextromethorphan, fluconazole, ginkgo biloba, Li ***cardiotoxicity*** (QT prolongation, torsades de pointes, cardiac arrest): droperidol ***neuroleptic malignant syndrome:*** metoclopramide
Escitalopram	22-32	3-6	desmethylcitalopram didesmethylcitalopram	see citalopram
Fluoxetine	1-3 days after acute administration; 4-6 days after chronic administration		norfluoxetine (elimination half life: 14-16 days !)	***increased risk of bleeding:*** all NSAIDs, oral anticoagulants, antithrombotic agents ***risk of serotonin syndrome:*** all TCAs, dextromethorphan, all antimigraine triptans, ginkgo, MAO-inhibitors, St John's Wort, tramadol ***cardiotoxicity*** (QT prolongation, torsades de pointes, cardiac arrest): all TCAs, all antiarrythmic agents, chloroquine, astemizole, droperidol, haloperidol, fluconazole, halothane, vasopressin, octreotide, spiramycin ***delirium and psychosis:*** clarithomycine, erythromycine ***hallucinations:*** zolpidem ***ergotism:*** all ergot-derivatives ***excessive hypoglycemia:*** glimepiride, glyburide, insulin ***neuroleptic malignant syndrome:*** metoclopramide

Fluvoxamine	15-16	3-8	fluvoxamine acid	see fluoxetine and ***increased central nervous system depression:*** melatonin ***bradycardia and hypotension:*** propranolol, ***toxic serum concentrations*** of theophylline
Paroxetine	15-22	3-5	none	***increased risk of bleeding:*** all NSAIDs, oral anticoagulants, antithrombotic agents ***risk of serotonin syndrome:*** all TCAs, dextromethorphan, all antimigraine triptans, ginkgo, MAO-inhibitors, St John's Wort, tramadol, fentanyl ***cardiotoxicity*** (QT prolongation, torsades de pointes, cardiac arrest): all TCAs, all antiarrythmic agents
Sertraline	32-36 19-22 (young males)	4-8	desmethylsertraline	see paroxetine and ***delirium and psychosis:*** chlarithomycine, erythromycine ***decreased plasma concentrations***: of the active metabolites of tamoxifen
Reboxetine	12-14	1.5 - 2	none	***elevated plasma concentration of reboxetine*** if combined with: ketoconazole, fluvoxamine, nefazodone, eryrthromycine ***no data on interaction*** with MAOIs, SSRIs, Li, loop diuretics
Venlafaxine	5	1-2	O-desmethyl-venlafaxine (elimination half life: 11 hours !) N-desmethyl-venlafaxine N,O-didesmethyl-venlafaxine	***increased risk of bleeding:*** all NSAIDs, oral anticoagulants, antithrombotic agents ***risk of serotonin syndrome:*** all TCAs, SSRIs, SNRIs, amoxicillin, dextromethorphan, all antimigraine triptans, ginkgo, MAO-inhibitors, St John's Wort, tramadol ***cardiotoxicity*** (QT prolongation, torsades de pointes, cardiac arrest): all TCAs, all antiarrythmic agents, fluoxetine, chloroquine, astemizole, droperidol, haloperidol, fluconazole, halothane, vasopressin octreotide, spiramycine ***neuroleptic malignant syndrome:*** metoclopramide ***increased risk of venlafaxine toxicity:*** cimetidine, clarithromycin, clozapine, itraconazole, ketoconazole, nefazodone, trazodone ***decreased metoprolol efficacy***
Duloxetine	8-17	6-10	none	***increased risk of bleeding:*** all NSAIDs, oral anticoagulants, antithrombotic agents ***risk of serotonin syndrome:*** all TCAs, SSRIs, SNRIs, amoxicillin, Li, dextromethorphan, all antimigraine triptans, ginkgo, MAO-inhibitors, St John's Wort, tramadol ***cardiotoxicity*** (QT prolongation, torsades de pointes, cardiac arrest): all TCAs, all antiarrythmic agents ***increase in serum concentration and toxicity:*** TCAs
Atomoxetine	4-5	1-2	4-hydroxyatomoxetine	***increase in heart rate and blood pressure:*** all β2-agonists ***increase in atomoxetine steady-state plasma concentrations:*** all TCAs, SSRIs, all antiarrythmic agents ***risk of serotonin syndrome:*** all TCAs, SSRIs, SNRIs, MAO-inhibitors

Adapted from MICROMEDEX®, www.drugbank.ca, www.pharmindex.hu

Table 5 Clinically important pharmacokinetic data, active metabolites and major interacting drugs of phenylpiperazine antidepressants and agomelatine

drug	elimination half life (t½) of the parent drug (h)	time of peak plasma concentration (h)	active metabolite(s)	interacting drugs
Trazodone	7–8	1–2	m-chlorophenylpiperazine	***cardiotoxicity*** (QT interval prolongation and torsade de pointes): amiodaron, droperidol, saquinavir ***hypotension:*** phenothiazines ***increase in trazodone toxicity:*** all SSRIs, inidinavir ***sedation and potential coma:*** ginkgo ***serotonin syndrome:*** all MAO-inhibitor, St John's Wort, all SNRI ***tardive dyskinesia:*** metoclopramide
Nefazodone	1.9–5.3	1–2	m-chlorophenylpiperazine ($t_{1/2}$: 4- 9 h), hydroxy-nefazodone, desethyl hydroxy-nefazodone ($t_{1/2}$: 18- 33 h)	***increased risk of bleeding:*** all NSAIDs ***serotonin syndrome:*** all antimigraine triptans, allTCAs, SNRIs, MAO-inhibitors, St John's Wort ***cardiotoxicity*** (QT interval prolongation and torsade de pointes): astemizole, terfenadine, dronedarone, droperidol, pimozide ***rhabdomyolysis***: all statins ***toxic cabazitaxel plasma concentration, neuroleptic malignant syndrome:*** metoclopramide ***decreased nefazodone effect:*** carbamazepin ***fatal colchicine toxicity*** ***ergotism:*** ergot alkaloids ***increased risk of docetaxel toxicity, increased and prolonged opioid effects*** ***increased fluticasone plasma concentration and reduced plasma cortisol concentration***
Agomelatine	1–2	1–2	none	***extremely elevated agomelatine plasma level:*** fluvoxamine, ciprofloxacin, estrogens

Adapted from MICROMEDEX®, www.drugbank.ca, www.pharmindex.hu

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Antidepresszánsok és aktív metabolitjaik sorsa a szervezetben

A gyógyszerek klinikai hatása elsősorban a hatóanyag(ok) szervezetbeni sorsától függ, de a gyógyszerkészítmény egyéb összetevői is jelentősen befolyásolhatják. A hatóanyagok (döntően xenobiotikumok) a metabolizmus során általában inaktiválódnak, de gyakran képződnek farmakológiai hatásukat tekintve az eredeti hatóanyagnál aktívabb metabolitok. Ezek az aktív metabolitok az anyavegyülettől eltérő farmakokinetikai tulajdonsággal is rendelkezhetnek. Az anyavegyület és a metabolit(ok) együttes jelenléte a szervezetben jelentősen befolyásolhatja a gyógyszer klinikai hatását. Az anyavegyület és a metabolit(ok) farmakokinetikai és farmakodinámiás együtthatásai az egyéni gyógyszerválaszok megértésében nélkülözhetetlen tudásanyagot jelentenek. A központi idegrendszerben jelenlévő citokrómP450 izoenzimek, ezek szerepe a központi idegrendszeri metabolikus folyamatokban a metabolizmus-kutatásnak egy új, gyorsan fejlődő területe. Jelen közleményünkben a központi idegrendszerben szerepet játszó CYP izoenzimeket, a központi idegrendszer metabolikus folyamataiban betöltött szerepüket és az antidepresszánsok terápiás gyakorlatában fontos farmakokinetikai adatokat, valamint metabolikus folyamataikat foglaltuk össze.

Kulcsszavak: antidepresszáns, aktív metabolit, központi idegrendszeri CYP izoenzimek, farmakokinetikai és farmakodinámiás gyógyszer-együtthatások