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Chirality in Doping Analysis

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Many stimulants and narcotic analgesics are often abused in sports to enhance performance, therefore national and international sports federation forbid the use of these drugs. But some of these drugs are also detected in urine as metabolites after ingestion of other medicines. These drugs have also been of considerable interest in forensic science and toxicology.

An example is selegiline. Selegiline, the (R)-(-)-isomer of deprenyl, is less toxic and about a 500 times more potent inhibitor of MAO than its enantiomer, while (S)-(+)-deprenyl causes hyperthermia and excitation. The (S)-(+)-isomer is metabolized to (S)-(+)-methamphetamine and (S)-(+)-amphetamine the cause of undesired CNS stimulating action [1]. But the metabolic products of the (R)-(-)-isomer, (R)-(-)-methamphetamine and (R)-(-)-amphetamine are more potent inhibitors of MAO-A than their enantiomers [2] and their CNS stimulatory effect is weakly active (Table 1). On the basis of this property, the (R)-(-)-isomer of deprenyl only is used as an antidepressant and an anti-Parkinson drug.

As another example, dextromethorphan is the d-isomer of 3-methoxy-N-methylmorphinan. While the l-isomer (levomethorphan) is a potent narcotic analgesic, dextromethorphan is not a narcotic and is used only for its antitussive effects. Dextromethorphan is found in numerous cough syrups, tablets and capsules as the hydrobromide salts. It is converted to dextrophan and 3-hydroxymorphinan. The l-isomer of dextrophan is levorphanol, a synthetic compound having 4-5 times the analgesic potency of morphine [3] (Table 2) and the use of this drug was also forbidden by national and international sports federation.

In some cases the analytical results can be interpreted wrongly, because these enantiomers are not separated by conventional resolution methods. To avoid such false positives, the stereospecific separation method as a proof of identification of these drugs was studied. All enantiomers of amphetamine, methamphetamine and levorphanol were well separated through conversion to either the N-MTPA [α-methoxy-α-(trifluromethyl)-phenylacetyl] or O-MTPA derivatives. Also a thorough investigation of the metabolism of drugs that are metabilized to either banned drugs or their enantiomers may be essential for discrimination between the intake of banned drugs and medicines. It appeared from our metabolism study that parent compounds were excreted until 7 hours in human urine after administration of

selegiline and dextromethorphan. And desmethylselegiline was excreted until 2 days in urine after administration of selegiline. The sensitive detection of desmethylselegiline and parent drugs may also be useful tool for discrimination of selegilin users and dextromethorphan users.

(±)-deprenyl		
Enantiomer	(-)-deprenyl	(+)-deprenyl
MAO-inhibitor	strong	weak
Metabolite	(-)-amphetamine (-)-methamphetamine	(+)-amphetamine (+)-methamphetamine
CNS stimulating effect of metabolites	weak	strong

Table 1. The stereoselective action of the enantiomers of (±)-deprenyl and their metabolites

3-methoxy-N-methylmorphinan		
Enantiomer	dextromethorphan	levomethorphan
Narcotic analgesic	weak	strong
Antitussive effect	strong	weak
Metabolite	dextrophan	levorphanol
Narcotic analgesic of metabolite	weak	strong

Table 2. The stereoselective action of the enantiomers of 3-methoxy-N-methylmorphinan and their metabolite.

References

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