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Abstract: S-hyoscyamine (S-hyo) is a toxic tropane alkaloid from plants of the solanaceae family, which is extracted for pharmaceutical purposes thereby undergoing racemization (atropine). Merely the S-hyo enantiomer acts as an antagonist of muscarinic receptors (MR). Nevertheless, racemic atropine is clinically administered in e.g. ophthalmology and for symptomatic therapy of acute poisoning with organophosphorus compounds (OPCs, e.g. pesticides, nerve agents). However, very limited data are available of comparative pharmacokinetics of S- and R-enantiomers in humans or other species. Therefore, we developed an enantioselective LC-ESI-MS/MS assay making use of rabbit serum containing atropinesterase (AtrE, EC 3.1.1.10) which is suitable for stereospecific hydrolysis of S-hyo into tropine and tropic acid while R-hyo is unaffected. For sample preparation plasma was incubated with human serum (not containing AtrE, procedure A) and with rabbit serum (procedure B). Afterwards, hyoscyamines were quantified by a validated previously published non-chiral LC-ESI-MS/MS method. Following procedure A the concentration of total hyo and following procedure B remaining R-hyo were determined. S-hyo was calculated by the difference between these concentrations. This assay
design allowed reproducible, precise (RSD 2-9%), accurate (93-101%) and selective determination of total and individual hyoscyamines. Potential therapeutics for OPC poisoning (carbamates, oximes) and thiono-pesticides did not interfere with the assay whereas some oxon-pesticides inhibited S-hyo hydrolysis. A control experiment was designed allowing to be aware of such interferences thus avoiding the use of false results. To validate this assay, results were compared to those from a novel isocratic chiral LC-ESI-MS/MS method. Separation of S-hyo (t(R) 31.1 ± 0.2 min) and R-hyo (t(R) 33.4 ± 0.2 min) was achieved on ?-glycoprotein (AGP) chiral stationary phase at 40°C (selectivity factor ? 1.07). Ammoniumformate (0.01 M, pH 8.0) with 3.75% (v/v) acetonitrile served as mobile phase (300 ?L min(-1)). Hyoscyamines were detected in the positive multiple reaction monitor mode. The enantioselective assay was applied to the analysis of atropine degradation in diluted rabbit serum in vitro as well as to human in vivo plasma samples from a pesticide-poisoned patient treated with atropine.

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