Poster

[P25-11] P25-11: Clinical toxicology (1)

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[P25-11-1] In vitro monoamine oxidase inhibition potential of new psychoactive substances of the alpha-methyltryptamine type

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Background

Alpha-methylated tryptamines are new psychoactive substances (NPS). In contrast to authorized medicines, NPS are marketed without preclinical (safety) studies. As alpha-methyltryptamine (AMT) was identified to be a monoamine oxidase (MAO) inhibitor this effect should be tested also for other alpha-methylated tryptamines. This is important for assessing possible pharmacological (serotonergic/adrenergic) effects and risks for drug-drug interactions in case of co-administration with medicines or other NPS, which are often combined in NPS products. Therefore, the MAO inhibition potential of 13 AMT derivatives was investigated.

Methods

A procedure was developed based on the incubation of the recombinant human MAO isoforms A and B or human hepatic S9 fraction followed by hydrophilic interaction liquid chromatography-high resolution-tandem mass spectrometry analysis and was validated in accordance to international guidelines. Kynuramine was used as non-selective MAO substrate and IC_{50} values of compounds, showing statistically significant inhibition in the prescreening procedure, were determined by plotting the relative metabolite concentration formed over the logarithm of the inhibitor concentration. For comparison, the known MAO inhibitors 5-IT, harmine, harmaline, yohimbine, and selegiline were incubated, too. To identify the mode of inhibition, K_i values of inhibitors were calculated but also experimentally determined. Incubation of the human S9 fraction was used to simulate MAO inhibition in human liver containing both isoforms in different abundances.

Results

AMT and all tested derivatives showed MAO A inhibition properties with IC_{50} values between 0.049 and 166 M, while four derivatives inhibited also MAO B with IC_{50} values between 82 and 376 M. 7-Me-AMT provided the lowest IC_{50} value against MAO A activity, which was in the range of harmine and harmaline. It was identified as competitive MAO A inhibitor. AMT, 7-Me-AMT, and 9 further derivatives were able to inhibit MAO activity significantly in the S9 fraction.

Conclusions

Considering expected plasma concentrations of tested compounds, clinically relevant MAO inhibition might be observed after intake of AMT-related NPS. Thus, serotonergic and noradrenergic effects are likely as well as severe interactions with drugs (of abuse) particularly acting as monoamine reuptake inhibitors. However, as in vitro assays have only limited conclusiveness, clinical studies are needed for a final assessment.