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Meeting abstract

A combined accelerator mass spectrometry/positron emission tomography microdose study to assess the plasma and brain tissue pharmacokinetics of ^{11}C- and ^{14}C-labelled verapamil in healthy volunteers

Claudia C Wagner[1], Marie Simpson[2], Graham Lappin[2], Rudolf Karch[3], Aiman Abrahim[1,4], Thomas Feurstein[1], Martin Bauer[1], Markus Zeitlinger[1], Kurt Kletter[5], Markus Müller[1] and Oliver Langer*[1,4]

Address: [1]Department of Clinical Pharmacology, Medical University of Vienna, 1090 Vienna, Austria, [2]Research and Development Unit, Xceleron Ltd, York, YO10 5NY, UK, [3]Department of Medical Computer Sciences, Medical University of Vienna, 1090 Vienna, Austria, [4]Department of Radiopharmaceuticals, Austrian Research Centers GmbH – ARC, 2444 Seibersdorf, Austria and [5]Department of Nuclear Medicine, Medical University of Vienna, 1090 Vienna, Austria

Email: Oliver Langer* - oliver.langer@meduniwien.ac.at

* Corresponding author

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Background

Microdose studies comprise the administration of a single subpharmacological dose of a carbon-14 (^{14}C)-labelled drug (<100 μg) to humans in order to describe the drug's pharmacokinetic (PK) profile in blood by means of accelerator mass spectrometry (AMS) analysis. As most drugs exert their pharmacological effect in tissue rather than in the central (blood) compartment, methodology is needed that allows for extending PK analysis from blood to different tissue compartments in microdose studies. In this pilot study we combined AMS analysis with the non-invasive nuclear imaging technique positron emission tomography (PET) in order to measure the PK profile of the model drug verapamil, at the same time in plasma and in brain tissue. Because dose linearity of PK parameters is a prerequisite for the prediction of therapeutic-dose from microdose PK data, we assessed the PK parameters of verapamil at two different doses.

Materials and methods

Six healthy volunteers received a microdose (0.05 mg) and a therapeutic dose (80 mg) of verapamil, labelled both with ^{14}C and the positron emitter carbon-11 (^{11}C), in a randomised cross-over fashion. The brain distribution of verapamil was measured by means of PET imaging whereas the drug's plasma PK was determined with AMS analysis. PET data were analysed by kinetic modelling in order to estimate the rate constants for the transfer of verapamil across the blood-brain barrier (BBB).

Results

We were able to simultaneously measure the plasma and brain tissue PK of verapamil by means of combined AMS and PET analysis. Both analytical approaches suggest that the PK of verapamil is linear over the employed dose range (0.05–80 mg). The rate constants for BBB transfer and the distribution volume (*DV*) of [^{11}C]verapamil were not statistically different ($p > 0.10$, paired *t*-test) for the microdose and the therapeutic dose (K_1 = 0.014 ± 0.002 ml · ml^{-1} · min^{-1}, k_2 = 0.036 ± 0.007 min^{-1} and *DV* = 0.41 ± 0.064 for the microdose and K_1 = 0.017 ± 0.0042 ml · ml^{-1} · min^{-1}, k_2 = 0.049 ± 0.008 min^{-1} and *DV* = 0.36 ± 0.066 for the therapeutic dose). Also, total ^{14}C concentration-time profiles (comprising both [^{14}C]verapamil and its

^{14}C-labelled metabolites) in plasma were nearly superimposable after administration of both doses.

Conclusion

Combining AMS and PET analysis is a powerful approach for gaining precise plasma and tissue PK data of drugs in humans. The proposed set-up might be useful in the early selection of drug candidates for further development.