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Catabolism and excretion of the anti-pseudomonal antibiotic Murepavadin (POL7080) in humans

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Background: Murepavadin (POL7080) represents the first member of a novel class of outer membrane protein targeting antibiotics. Murepavidin is being developed by Polyphor for the treatment of serious infections by *Pseudomonas aeruginosa*. Degradation and route(s) of excretion of POL7080 were studied in healthy volunteers using plasma and urine samples collected from a clinical study.

Material/methods: An amount of 1.6 10-6 mol/kg POL7080 was administered to healthy volunteers by two hours intra-venous (i.v.) infusion every eight hours (q8h, seven infusions in total). Plasma and urine samples collected on day 3 during and after the last of the seven i.v. infusions were analyzed. Time-matched sample pools by either collection time point (plasma) or collection period (urine) were produced. The resulting pools were then analyzed by liquid chromatography coupled with high resolution mass spectrometry quantification (LC/HRMS). In a first phase, screening for POL7080-related material was performed. In a second step, those POL7080-related molecules generating the

highest mass area signals were quantified by one-point calibration using a specific analytical reference standard for each metabolite.

Results: In plasma intact POL7080 and five abundant POL7080-related molecules all with the same N-terminal sequence were detected. The exposure (AUC) of which was ranking in the order: POL7080>M3>M5>M7>M2>M4. On day 3 the kinetic of the system was at steady-state as indicated by (1) similar trough levels of POL7080–related molecules at the beginning and the end of the dosing interval and (2) the unchanged plasma concentration of a POL7080-related peptide (M7) over the entire dosing interval (48-56 h). M7 most likely was the terminal degradation fragment of the POL7080 degradation process. No POL7080 metabolites produced by phase I or II enzyme activity were found.

In urine only small quantities of intact POL7080 were detected. Indeed, excreted amounts of fragments M3, M5, and M7 were markedly higher, M2 and M4 similar to POL7080 quantities. The quantity ranking of fragments being the same as observed in plasma. Also in urine no POL7080 phase I or II metabolites were detectable. The total dose given to the study volunteers, based on their median body weight (81.5 kg) was equivalent to 1.3×10^{-4} mol. The total amount of POL7080-related material excreted into urine during the last eight hours dosing interval (48-56 h) was 1.4×10^{-4} mol.

Conclusions: POL7080 was degraded by proteolysis. Neither phase I nor phase II enzyme modified POL7080 metabolites were detectable in plasma or urine. The most abundant proteolytic fragments (M3, M5, M7, M2, M4) were found in both plasma and urine in the same quantity ranking. The total amount of POL7080-related material found in urine was equivalent to 108% of the administered dose and thus it is concluded that POL7080 material is entirely excreted into urine.