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A N A N T I C A L I N W I T H D RU G - B I N D I N G PROPERTIES: RESULTS OF A PILOT STUDY TO REVERSE DIGOXIN-TOXICITY IN RATS

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Objectives: Anticalins may be promising candidates for antidotes; however, no animal study has investigated both pharmacokinetic and clinical effects of an engineered lipocalin tailored with high affinity for digoxin.

Methods: Intravenous digoxin (2.5-50 ∝ g/kg/min) was administered continuously to anesthetized and artificially ventilated rats until first changes in the ECG occurred (dose finding study) or a priori for 30 minutes (kinetic study). Anticalin DigA16(H86N) (DigiCal), was administered intravenously at absolute doses of 1, 5, 10 and 20 mg, respectively, the control group received isotonic saline instead. Haemodynamic changes, several ECG-parameters as well as digoxin concentrations in plasma were monitored continuously until death or when the animals were euthanized.

Results: Free digoxin in plasma ultrafiltrate declined dramatically after DigiCal administration within one minute and maintained in the presumably non-toxic range for a longer period of time. There was also a significant trend to longer survival, less ECG- alterations and arrhythmia, and improved haemodynamics of animals receiving higher doses of DigiCal compared to the low-dose DigiCal or placebo group. Infusion of a lower digoxin dose (2.5 ∝g/kg/min) resulted in a more sustained reduction of free digoxin in plasma after DigiCal administration compared to a higher digoxin dose (25 ∝ g/kg/min), whereas ECG and haemodynamic parameters did not relevantly differ, reflecting the known relative insensitivity of rats towards digoxin toxicity. Notably, we observed a re- increase of free digoxin in plasma some time after bolus administration of the DigiCal, which was presumably due to its fast renal clearance. ***Conclusion:*** Anticalins with appropriately engineered drug-binding activities and, possibly, prolonged plasma half-life may offer prospects for next-generation antidotal therapy.