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Comparative Pharmacology of a Group of Polyoxometalates Possessing Broad-Spectrum Antiviral Activity

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The pharmacokinetics and anti-coagulant activity of a group of polyoxometalates possessing broad-spectrum antiviral activity (see abstract Yamamoto *et al.*) were compared. Compounds were administered i.v. to Wistar rats at 50 mg/kg. Serum, urine and tissues were collected for metal analysis by ICP-MS. The compounds showed initial rapid serum clearance (6 hr) followed by a long terminal elimination phase (168 hr), with $K_7H[Nb_6O_{19}].13H_2O$ (JM2768) being the most rapidly cleared. All compounds showed little or no urinary clearance over 48 hr (≤ 0.3-6.6%) with the exception of JM1596, $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}].20H_2O$ (≥ 50%). The compounds also had different tissue distribution and clearance properties. The partial thromboplastin time (PTT) was assayed *in vitro* as an indicator of the inhibition of the intrinsic coagulation system, a potential toxic effect. Inhibition of coagulation was only seen at concentrations several orders of magnitude higher than the effective *in vitro* viral inhibitory concentrations. The concentrations required to double PTT ranged from ≥ 50 μg/ml for $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}].20H_2O$ to 1000 μg/ml for $(Na/K)_6[Nb_4W_2O_{19}]$ (JM2800). These results indicate that the pharmacological properties of polyoxometalates are dependent upon chemical structure and could be controlled by chemical modification.

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A rapid, simple and sensitive HPLC-system for simultaneous analysis of AZT and its mono-, di- and triphosphate derivatives following cellular delivery with neoglycoproteins.

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To overcome toxicity problems and rapid metabolism and excretion of AZT in HIV-seropositive individuals, we investigated the options of selective delivery of AZT to those cell types infected with HIV-1. Based on the presence of sugar recognizing lectins in the cell membrane of various blood cell types, we designed so called neoglycoproteins (Human Serum Albumin chemically modified with various sugars). The monophosphate derivative of AZT (AZTMP) was coupled to the neoglycoproteins, differing in type and density of the sugar and net charge.

To study the kinetics of AZT and AZTMP in MT-4 cells, administered in a free form or coupled to the neoglycoproteins, we developed an HPLC-system, using a Novapak C18 column, isocratic elution and UV-detection. AZT, AZTMP, AZTDP and AZTTP were base-line separated within 10 min without interference of endogenous compounds after washing and lysing the cell pellets. Detectionlimits were about 10 ng. Extraction of AZT and its derivatives (from blood, urine and bile (rat/cat) and cells) was performed using SPE C18 disposable extraction columns.

Some of the neoglycoprotein-AZTMP conjugates were shown to be antivirally active against HIV-1 cytopathicity *in vitro* in MT-4 cells, being as potent as AZTMP itself. Only 15 to 20% of the drug was released in incubation medium through hydrolysis of the phosphoamide binding in the first 24 hrs, the time interval in which AZT exhibits its antiviral action. Cellular delivery experiments showed a completely altered, concentration dependent, delivery pattern of AZTMP when coupled to neoglycoproteins.