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Simultaneous Study of the Biodistribution of Radio-yttrium Complexed with EDTMP and Citrate Ligands in Tumour-bearing Rats

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The influence of the ligands ethylenediaminetetramethylene phosphonic acid (EDTMP) and citrate (CIT) on the biodistribution of radio-yttrium in rats bearing a DS-carcinosarcoma was compared. ^{88}Y-EDTMP and ^{87}Y-CIT were i.v. injected into the same animals. Faster blood clearance and higher renal excretion were observed for the EDTMP-ligand. Of high practical interest is the reduced liver uptake of radio-yttrium (by one order of magnitude) with the EDTMP complex. Since bone and tumour accumulation is only weakly influenced, high tumour-to-liver ratios (up to 14) were observed. We propose to use EDTMP or similar complex ligands for liver blocking when radionuclides like ^{90}Y, ^{169}Yb, ^{225}Ac or other group 3 elements are to be applied in endoradionuclide therapy technique.

Introduction

It has been reported (Goeckeler *et al.*, 1987; Singh *et al.*, 1989; Turner *et al.*, 1989) that ethylenediaminetetramethylene phosphonic acid (EDTMP) as complex ligand favours bone accumulation of ^{153}Sm. A palliative therapy of bone metastases is often performed with ^{90}Y administered as citrate (CIT). In order to study the influence of EDTMP on the yttrium biodistribution a direct comparison of the behaviour of EDTMP and CIT complexes in tumour-bearing rats was performed. In our present study ^{87}Y and ^{88}Y were chosen and injected as CIT and EDTMP complexes, respectively.

Experimental

Radionuclides

Carrier-free ^{87}Y was produced via the Rb (α, 2n) ^{87}Y reaction ($E_\alpha = 27$ MeV) by irradiation of natural RbCl at the Rossendorf U-120 cyclotron (Schomäcker *et al.*, 1987). Carrier-free ^{88}Y was produced via the proton-induced reaction ^{88}Sr (p, n) ^{88}Y by irradiation of natural $SrCl_2$ ($E_p = 13$ MeV). In both cases the irradiated chlorides were dissolved in 0.05 M HCl. 2 mg La^{3+} carrier were added, then a hydroxide precipitation was performed. The radio-yttrium was then separated by means of cation exchange chromatography via an Aminex A5 column using 0.1 M α-hydroxyisobutyric acid (pH = 5.0) as eluting agent which was then removed by evaporation. The residues were dissolved in 50 μL of 0.05 M HCl. The compositions of the injection solutions were:

for ^{88}Y-EDTMP: 5×10^{-3} M EDTMP, 8 mg/mL NaCl, pH 6.0,
for ^{87}Y-CIT: 3.3 mg/mL NaCIT, 4.5 mg/mL NaCl, pH 7.0.

EDTMP-ligand

The EDTMP-ligand was synthesized according to the method of Moedritzer and Irani (1966).

Animals

Male Wistar rats with an average weight of 200 g were used bearing a solid tumour implanted in the left thigh (DS-carcinosarcoma, 8 days post-implantation, dia ~2 cm).

Procedure

A solution of the corresponding ^{87}Y-CIT or ^{88}Y-EDTMP (0.5 mL) containing 0.55 MBq of ^{87}Y or 0.18 MBq of ^{88}Y was injected into a tail vein. Two series of experiments were carried out, each containing 3 animals: in one series ^{87}Y-CIT was injected first followed by ^{88}Y-EDTMP injection after 1, 2 or 4 h.

In the other series, the order of injection was reversed. Just before the second injection, a blood sample was taken for checking blood clearance from the first injected preparation. At 5 h after the second injection the animals were sacrificed and the organs were sampled.

The ^{87}Y and ^{88}Y contents of the collected urine and organ samples as well as of two ^{87}Y and ^{88}Y standard samples were determined by means of γ-spectroscopy 1 day after sampling (for achieving the radioactive decay equilibrium $^{87}Y/^{87m}Sr$). A high-purity Ge spectrometer was used for these measurements. Corrections were made for the radioactive decay and for the contamination of ^{88}Y in ^{87}Y due to the nuclear production reaction.

Results and Discussion

It is well known that the blood clearance for heavy radiolanthanides or yttrium injected as citrates proceeds fast (Beyer *et al.*, 1978, 1989, 1991; Schomäcker *et al.*, 1986), e.g. 1 h p.i. the blood level of radioactivity drops to a value below 0.5%/g when heavy rare earth citrates or Y-CIT were injected. 5 h p.i. the blood radioactivity is reduced by one more order of magnitude. Within the next few hours no significant changes in the biodistribution have been detected. Indeed, 1 h seemed to be sufficient for essentially completing the biodistribution of these complex compounds in rats. In order to be sure that ligand exchange reactions are negligible the two Y complexes were injected consecutively in the same animal, choosing variable time intervals between both injections (1, 2 and 4 h). The final biodistribution was then determined 5 h after the second injection. The experimental results are listed in Table 1.

Blood clearance

When Y-CIT was injected first, the radioactivity level in blood was $<0.5\%$/g at 1 h p.i., $<0.2\%$/g at 2 h p.i. and $<0.1\%$/g at 4 h p.i. When EDTMP was injected first, the radioactivity level was a factor of two smaller. At 5 h after the second injection, all radioactivity concentrations in blood were below the detection limit which was 0.05%/g.

Excretion

When Y-CIT was injected first, about 15% of the injected dose is excreted (in urine). In the presence of EDTMP higher renal excretion rates were observed for both radionuclides (Table 1). The low renal excretion rate in one case (^{88}Y, $\Delta t = 4$ h) is possibly due to pathological reasons causing a high retention in the kidneys.

Liver

An accumulation of ^{87}Y of about 0.3%/g was measured when the Y-CIT complex is injected first. With ^{88}Y-EDTMP, however, extremely low liver accumulation (0.02–0.06%/g) is observed. When the

Table 1. Distribution of Y isotopes injected as CIT and EDTMP complexes in rats, related to injected dose and corresponding tumour-to-liver ratios of enrichment. Distribution at 5 h after second injection. Δt = time interval between first and second injection

Measured nuclide			^{87}Y					^{88}Y				Ratio tumour/liver	
First injected compound	Second injected compound	Δt (h)	Urine (%)	Kidney (%/g)	Liver (%/g)	Tumour (%/g)	Femur (%/g)	Urine (%)	Kidney (%/g)	Liver (%/g)	Tumour (%/g)	Femur (%/g)	^{87}Y	^{88}Y
^{87}Y-CIT	^{88}Y-EDTMP	1	15	2.7	0.36	0.45	3.00	35	0.3	0.02	0.29	2.35	1.25	14.5
		2	13	2.4	0.45	0.76	3.48	38	0.4	0.05	0.45	2.91	1.70	9.0
		4	10	2.9	0.58	0.61	4.74	7	12.2	0.06	0.56	5.08	1.05	9.3
^{88}Y-EDTMP	^{87}Y-CIT	1	28	0.4	0.03	0.37	2.53	24	0.3	0.03	0.39	2.24	12.3	13.0
		2	24	2.6	0.05	0.48	3.39	45	0.3	0.03	0.29	2.63	9.6	9.7
		4	27	2.1	0.54	0.44	3.92	45	0.4	0.03	0.34	3.64	0.8	11.3

EDTMP complex is injected first, a strong influence on the accumulation of ^{87}Y injected as CIT was measured even if the CIT complex was injected up to 2 h later: the ^{87}Y uptake in the liver is one order of magnitude smaller (Table 1). Obviously, already small amounts of EDTMP seem to be sufficient to prevent the normal uptake of yttrium by the liver. Using this technique, the liver can be excluded as a competing compartment. Although only shown for one animal, the "memory effect" is obviously gone after 4 h. The EDTMP seems to have no more influence on the distribution of the secondly injected ^{87}Y-CIT.

Tumour

The measured accumulation of ^{87}Y injected as CIT is in agreement with earlier experimental data (Beyer *et al.*, 1991). If EDTMP is used as the complexing ligand, the uptake of radio-yttrium is slightly lower, possibly caused by the higher renal excretion (Table 1). No influence of the order of administration of both complexes was seen.

Femur

The ^{87}Y-CIT shows the same uptake in bone of about 3–4%/g as reported earlier (Beyer *et al.*, 1978, 1989, 1991; Schomäcker *et al.*, 1986). When EDTMP is used as the complexing ligand, bone uptake is slightly smaller. No influence of the order of administration of both complexes is seen.

Ratios of enrichment

In order to characterize Y^{3+} complexes as compounds with tumouritropic and/or osteotropic potential, the ratios of radioactivity concentrations in tumour, in bone tissue and the various organs, respectively, are of special interest. Due to the fast clearance very high tumour-to-blood ratios are observed.

The tumour-to-liver ratio was described as being about 1 using the citrates of ^{167}Tm, ^{169}Yb and ^{87}Y (Beyer *et al.*, 1981, 1990, 1991a; Schomäcker *et al.*, 1986). This result is confirmed in the present paper when ^{87}Y-CIT is injected first. When EDTMP is used as the complexing ligand, significantly higher (by one order of magnitude) tumour-to-liver ratios are observed. Such high ratios are also seen with ^{87}Y injected as CIT, when the EDTMP complex has been injected 1 or 2 h before. When 4 h have elapsed since the first injection, the "normal" enrichment ratio of ^{87}Y injected as CIT is observed (Table 1). The much lower liver accumulation also leads to very high femur-to-liver ratios, if the EDTMP complex is injected first. Similar results have been reported by Schomäcker *et al.* (1991) using tumour-bearing mice. The effect of an enhancement of bone accumulation described by Goeckeler *et al.* (1987) and Singh *et al.* (1989) using ^{153}Sm and EDTMP as ligand, cannot be confirmed by our results using yttrium as the Me^{3+} ion. With the light rare earth elements like Sm, another behaviour may be possible.

The liver accumulation of radio-yttrium is clearly lower with EDTMP as ligand than with CIT as ligand, bone and tumour accumulation being comparable. The mechanism of liver-blocking has been unknown so far. The protection of the liver by EDTMP from Me^{3+} accumulation may be of practical importance to better diagnostic imaging and endoradionuclide therapy. The described observation will be followed up by further experiments.

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