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Radioprotection of the Kidney with Degradable Microspheres

A pilot study in the dog with repeated irradiation

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ABSTRACT

The left kidney of 9 dogs was irradiated daily for three days with 300 kVp X-rays. Radioprotection was attempted in 5 of the kidneys by administration of degradable microspheres in the renal artery, immediately before irradiation. Protected kidneys received 3 x 8 or 3 x 12 Gy in midplane dose, unprotected kidneys 3 x 5.2 or 3 x 8 Gy. A protective effect due to induced hypoxia could be demonstrated in creatinine clearance, which was significantly higher in protected than in unprotected kidneys at 7 - 13 weeks after irradiation.

INTRODUCTION

Doses above 23 Gy are associated with a considerable risk of renal failure when given with conventional fractionation to the whole of both kidneys (8,9). The low tolerance of kidneys to radiation often excludes irradiation with doses high enough for eradication of near-by tumours.

In order to be able to increase the total dose to tumours in the vicinity of the kidneys a selective renal radioprotection is needed. Since the kidney has most often one dominant arterial supply, and this is suitable for catheterization, the anatomical possibilities for selective administration of agents modifying radiation effects are at hand.

Molecular oxygen is the single most efficient factor for modifying the radiosensitivity of all biologial systems (2,7). This fact was exploited by Steckel et al (11), who induced hypoxic protection of the kidneys of dogs by selective infusion of epinephrine into the renal artery.

An alternative way to induce a protective local hypoxia is intraarterial injection of starch microspheres, degradable by endogenous amylase (1). In experiments with single doses of X-rays to skin and gut of the rat, a protection amounting to a dose modification factor (DMF) of 0.50 - 0.44 (OER 2.0-2.3 /Oxygen Enhancement Ratio/) was found (4,5). In experiments with single doses of X-rays to rat kidneys a protective effect was found also in terms of survival and preserved kidney function (3).

Single arterial injections of degradable microspheres into the dog kidney have shown that a circulation blockage can be induced, lasting long enough to permit irradiation under deep hypoxia and without impairment of kidney function (12).

Radiotherapy by single doses is usually not an effective means for good therapeutic results and the treatment is conventionally administered in several fractions. One of the primary aims of the present study was to test whether it is possible to achieve a selective kidney protection by degradable microspheres also in a fractionated irradiation regime.

MATERIAL AND METHODS

Nine mongrel dogs were used. They had free access to food and water and had an average weight of 25 kg. They were given 3000 IU Combiotic^{R} i.m. as infection prophylaxis on catheterisation days.

The nine left kidneys were irradiated once daily for three consecutive days, five after intraarterial injection of starch microspheres and four without (Table).

The degradable microspheres consisted of cross-linked starch molecules (Pharmacia, Sweden, batch 658,588). The microspheres had a diameter of 14 - 58 μm and were suspended in saline (60 mg/ml = 1,600,000 spheres/ml). In terms of microsphere mass the degrading half-times in 20 ml buffered saline with 240 and 1500 IU standard amylase were 41 and 20 min, respectively.

The dogs were anaestethetized with Nembutal^{R} (40 mg/kg) i.m. and intubated. Supplementary anaestesia was given with Pentothal^{R} when called for.

In the protected group an incision was made in the left groin and a catheter (Radicath abdominal child catheter, 1.6 mm o.d., Radiplast^{R}, Uppsala, Sweden) introduced in the femoral artery. The tip of the catheter was advanced into the aorta and introduced into the left renal artery under fluoroscopic control. The same femoral artery was used at all three instances when possible. The final position of the catheter was verified by injection of a small amount of contrast medium (Renografin 60^{R}) into the renal artery. The projections of the kidney outline in three directions were indicated on the skin by ink and by lead beads.

The anaestetized dog was gently placed in the irradiation position on its right side. The irradiation field was centered over the left kidney with its central axis pointing 35° below the horizontal plane. In order to avoid excessive skin damage an oval entrance field was shaped by a 3 mm lead shild. The renal circulation was then blocked with two injections of 1 ml microsphere solution through the catheter; the injections were spaced 2 min in time. Irradiation was started 4 min after the first injection.

Irradiation was performed with 300 kVp X-rays (GE Maxtron 300, 20 mA, added filter 0.26 mm Cu + 1,04 mm Al, HVT 1.10 mm Cu. SSD 25 cm).

Split renal function tests were performed 46 to 90 days after the last irradiation. In the dog glomerular filtration rate (GFR) is equivalent to the renal plasma clearance of exogeneous creatinine (10), which was determined according to the procedure given by Frazier (6). This involves a 20 min clearance period 45 min after s.c. injection of 200 mg/kg of a 8 % creatinine solution. Urinary pH and osmolality were also studied.

The dogs were sacrificed immediately after the function tests and both kidneys were weighed.

RESULTS

All dogs were healthy throughout the observation period except for wet radiation epidermitis (only after total doses of 24 and 36 Gy) and minor wound infections.

Phantom dosimetry with Victoreen thimbles gave a dose rate of 11.6 Gy/min at the skin, 5.8 Gy/min in the rear capsule of the kidney and 3.2 Gy/min in the renal pelvis. The midplane dose rate was estimated as 4.0 Gy/min. The 95% and 90% isodoses at the skin had diameters of 84 and 124 mm, respectively, without the extra lead shield.

All irradiated kidneys weighed less than the contralateral ones (Table). No trends with dose or protection could be discerned in kidney weight or urinary pH.

Urinary osmolality decreased in all but one irradiated kidney to 10-20% of that in the unirradiated, contralateral kidney. The exception was a protected kidney (24 Gy) in which the decrease was only 50%.

Creatinine clearance was significantly lower in the irradiated kidneys than in the unirradiated ones. In the groups irradiated with 25 Gy (total midplane dose) there was a clear difference with a higher GFR in the protected kidney.

DISCUSSION AND CONCLUSIONS

This study was performed in order to evaluate the possibility of kidney radioprotection by repeated, selective injection of degradable microspheres prior to but in conjunction with the irradiation.

Repeated injection of these spheres into the same renal artery has been shown not to inflict on the renal function. This is true also when the injections are spaced by one day (12).

As recognized by previous investigators (11) it was found, that the animals had to be re-catheterized before each irradiation. Chronically indwelling catheters invariably slipped out of the renal artery.

Urinary pH, urine osmolality and kidney weight are probably not good measures of radiation damage in the type of study attempted here. Compensatory hyperplasia in the unirradiated kidney may to some extent explain the lower relative weight

of the irradiated kidneys.

Table I. Dogs in which the left kidney was irradiated with three consecutive, daily fractions without (A) or with (B) hypoxic protection achieved through injection of starch microspheres into the renal artery. The midplane kidney dose, kidney weight, interval between irradiation and sacrifice of the dogs and the exogenous creatinine clearance values are given. For weight and clearance data the percentage values of irradiated versus non-irradiated kidney are given in brackets.

Dog	Total midplane dose Gy	Interval between irradiation and sacrifice (weeks)	Kidney weight (g)		Exogenous creatinine clearance (ml/min)	
			right	left (%)	right	left (%)
A. (not protected)						
1	15.6	7	55	39(71)	55	5(9)
2	15.6	11	56	33(58)	21	2(10)
3	24.0	10	71	37(52)	87	0(0)
4	24.0	11	99	61(61)	80	3(3)
B. (protected)						
5	24.0	13	41	21(52)	39	7(19)
6	24.0	8	43	31(72)	45	7(15)
7	24.0	9	44	33(75)	35	4(11)
8	36.0	12	43	19(43)	65	1(2)
9	36.0	12	56	38(68)	78	2(3)

A better measure of kidney damage is probably the relative creatinine clearance (RCC) of the irradiated kidney. From the data in the Table one may estimate a dose modification factor of about 0.7 since RCC is similar in the 16 Gy unprotected and 24 Gy protected groups as well as in the 24 Gy unprotected and 36 Gy protected groups.

The fairly inhomogeneous dose distribution in the irradiated kidney (maximum 145%, minimum 80% of the midplane dose) may have contributed to the substantial experimental errors and should be ameliorated in future studies.

The results demonstrate clearly that multifractionated unilateral irradiation of dog kidneys is feasible under selective, transient hypoxia, induced by degradable microspheres, and that a protective effect is achieved by the microspheres.

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