

RADIOZINC UPTAKE AND SCINTISCANNING IN PROSTATIC DISEASE

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Zinc radioisotopes have been used to study the tissue distribution of zinc in the rat and human and to obtain scintigraphic images of the prostate in man. Two hours after administration of ^{65}Zn into the rat most of the radioactivity was found to be in kidney, liver, pancreas, and prostate. However, after 20 hr the uptake of ^{65}Zn by kidney, liver, and pancreas decreased whereas the uptake of radioactivity in the prostate, seminal vesicle, and bone continued to increase. The uptake of ^{65}Zn by prostate, bladder, and muscle was measured in patients with benign prostatic hypertrophy (BPH) by injecting ^{65}Zn at different periods prior to open prostatectomy. There was a continuous increase in the concentration of ^{65}Zn by the prostate whereas the concentration in muscle remained constant. The greatest contrast between prostate and surrounding muscle was found to be between 12–24 hr after administration. Using ^{67}Zn , prostate images were obtained in patients with BPH and carcinoma of the prostate. The scintiscan showed only an indefinite outline of the prostate in BPH. The results demonstrate the limitations of these radioisotopes in the study of prostatic disease.

The presence of considerable amounts of zinc in human tissues and biological fluids has been reported by many investigators and it is now well established that the concentration of this metal is highest in prostatic tissue and seminal fluid (1). It has also been shown that prostatic tissue is able to accumulate and retain radioactive zinc, both in experimental animals (2–5) and in humans (6). More recent interest in the uptake of this metal by prostatic tissue has been due to the potential use of radioactive zinc as an agent for prostate imaging (5,6).

Various zinc radioisotopes are available and have been used to study the differences between benign and malignant tissue (6–8). In this paper we report our experience using ^{65}Zn for uptake studies in rat and human prostate and discuss this information in relation to scanning of the diseased prostate using ^{67}Zn .

MATERIALS AND METHODS

Zinc radioisotopes and radiation dosimetry. The decay characteristics of ^{65}Zn (1–120 keV gamma-ray, 245-day physical half-life) and evidence of long biological half-life (9) make it unsuitable as an in vivo imaging agent and restrict its use to tracer studies. The two other zinc radioisotopes suitable as possible imaging agents are $^{69\text{m}}\text{Zn}$ (6), and ^{67}Zn both of which have a more suitable gamma-ray emission and physical half-life. Reactor-produced $^{69\text{m}}\text{Zn}$ (440-keV gamma-ray, 13.8-hr physical half-life) was not readily available but ^{67}Zn (510 and 590-keV gamma-rays, 9.3-hr physical half-life) was produced in the M.R.C. Cyclotron Unit by the (alpha, 2n) reaction on ^{60}Ni (10). The relatively short physical half-life of ^{67}Zn poses the problem of the optimum time following administration for obtaining a prostatic image. Radiation dosage was estimated using the 6-hr distribution of $^{69\text{m}}\text{Zn}$ chloride in dogs reported by Gold and Lorber (5). At 6 hr liver, pancreas, and prostate showed approximately equal concentration of radiozinc and kidneys showed about half this concentration. Uptake in other organs was low compared with these and for the purpose of estimating radiation, dose is assumed to be negligible. Radiation dose (D) has been estimated using

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the relationship $D = 2.13 \times C \times [\sum_{\beta} E_{\beta} + \sum_{\gamma} E_{\gamma} \times \Delta_{\gamma} \times \rho_{\gamma}] \times 1.44 \times t_E$ rads, where C denotes organ concentration in microcuries per gram, E_{β} beta-ray or locally absorbed radiation energies in MeV, E_{γ} gamma-ray energies in MeV, Δ_{γ} absorbed fractions for gamma rays, ρ_{γ} abundance of particular gamma-ray emission, and t_E effective half-life in hours (11). In these calculations, masses for whole-body (70 kg), liver (1700 gm), pancreas (70 gm), prostate (30 gm), and kidneys (300 gm) were assumed. The biological half-life of the ^{65}Zn was assumed to be long compared with its physical half-life. The whole-body radiation was calculated to be 0.4 rads/mCi dose administered with approximately 12 rads to each of liver, pancreas, and prostate and 6 rads to the kidneys.

In the work reported here, ^{65}Zn as zinc chloride in 0.1 M HCl (specific activity 600 mCi/gm) was used for the animal studies and radiopharmaceutical-grade zinc chloride (^{65}Zn) (pH 2–3, specific activity 800 mCi/gm) was used in the human tracer studies.

Animal studies. Albino Wistar male rats of 200-gm body weight were used. Each rat received 50 μCi of ^{65}Zn chloride intravenously at either 2, 8, or 20 hr before sacrifice. The prostate and other tissues were removed, weighed on a torsion balance, and the radioactivity counted in a liquid scintillation counter to give a standard error of counting of less than 1% by the method of Ashcroft (12). The results were expressed as a percentage of dose administered per gram wet tissue.

Human studies. A group of 12 patients with benign prostatic hypertrophy (BPH) each received 20 μCi of ^{65}Zn chloride i.v. prior to open prostatectomy. Each dose had been counted in a fixed geometry above a well scintillation counter for subsequent comparison with a standard. After injection, the syringe residue was counted in the same geometry.

The patients were injected at varying times (0–24 hr) before operation at which time samples of prostatic tissue were obtained as well as bladder and abdominal muscle. Each sample was blotted and weighed (wet weight) and then counted in the well counter. The results were expressed as a percentage of the dose administered per gram of tissue.

A group of six patients with BPH and three patients with prostatic carcinoma were studied by prostate scanning. Each patient received an intravenous dose of 1 mCi of ^{65}Zn chloride. Scans were performed at selected times based on the results of the ^{65}Zn tracer studies. A Picker Dual-Detector scanner (3 \times 2 in. NaI(Tl) crystals) was used with $\frac{5}{8}$ -in. resolution high-energy focusing collimators

(Picker 2107A) on the detector heads. Additional Pb shielding was mounted on both heads to reduce further the effect of side-wall penetration due to gamma radiation from the significant fraction of the radioactivity in parts of the body outside the scan area. Pulse-height analyzer settings were such as to include both the 510-keV and 590-keV photopeak energies of ^{65}Zn . Under these conditions the average counting rate in the scan area was about 10,000/min (12-hr scan) for the summed output from the two detectors. Scan presentation was on photographic film and each scan took between 30 and 40 min to complete at a scan speed of 30 cm/min and line spacing of 0.4 cm.

RESULTS

Animal studies. Uptake of ^{65}Zn by the tissues of the adult male rat showed that the highest radioactivity occurred in kidney, liver, pancreas, and prostate (Table 1). The uptake at 2, 8, and 20 hr shows that the relative amount of radioactivity changes in some of these tissues during this period. Therefore, the concentration of ^{65}Zn in kidney, liver, and pancreas decreased while the concentration in prostate, seminal vesicle, testis, and bone increased during the period of study (Fig. 1).

Human studies. *^{65}Zn tracer studies.* The uptake of ^{65}Zn by the prostate, bladder, and abdominal muscle in 12 patients with BPH is shown in Table 2. These results indicate an increasing concentration in the prostate and the bladder although absolute levels are low. The concentration in abdominal muscle remained approximately constant over the 24-hr period of study. The ratio of prostate-to-muscle con-

TABLE 1. UPTAKE OF ^{65}Zn BY VARIOUS TISSUES OF THE MALE RAT AT 2, 8, AND 20 HR AFTER INJECTION*

Organs	2 hr	8 hr	20 hr
Kidney	12.6 \pm 1.52	9.10 \pm 0.82	5.73 \pm 0.62
Liver	9.62 \pm 1.58	8.00 \pm 0.58	6.26 \pm 0.77
Pancreas	9.21 \pm 2.10	6.87 \pm 2.39	6.09 \pm 0.76
Prostate	3.99 \pm 0.44	4.39 \pm 0.63	5.66 \pm 0.50
Seminal vesicle	3.34 \pm 0.43	3.96 \pm 1.15	4.92 \pm 0.42
Bladder	2.04 \pm 0.19	4.06 \pm 1.88	3.02 \pm 0.38
Testis	1.93 \pm 0.17	3.67 \pm 0.74	3.52 \pm 0.18
Bone	1.96 \pm 0.34	1.90 \pm 0.19	2.75 \pm 0.48
Upper thigh muscle	1.59 \pm 0.72	1.63 \pm 0.76	1.31 \pm 0.21
Diaphragm	1.48 \pm 0.22	1.62 \pm 0.06	1.90 \pm 0.23
Abdominal muscle	0.60 \pm 0.07	0.74 \pm 0.01	0.96 \pm 0.03
Fat	0.26 \pm 0.26	0.15 \pm 0.00	0.15 \pm 0.03

* Each value represents mean \pm s.e.m. of four separate experiments expressed as % dose administered/gm of wet weight.

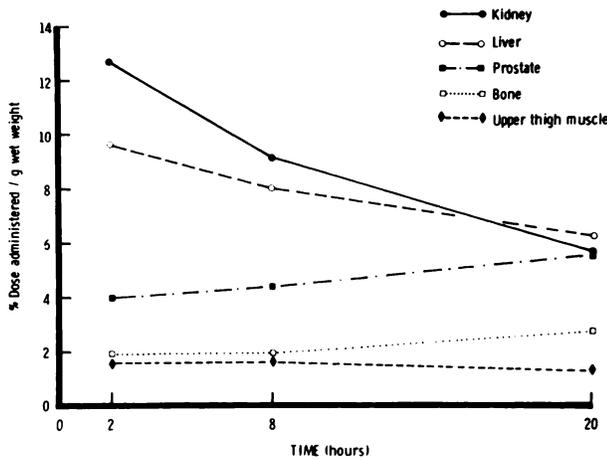


FIG. 1. Changes in concentration with time of ⁶⁵Zn in various organs of male rat.

centration for varying times after administration of ⁶⁵Zn showed that the concentration ratio is significantly higher between 12 and 24 hr than in the period up to 12 hr (Table 2).

⁶⁵Zn prostate scans. On the evidence of the ⁶⁵Zn tracer results (Table 2), four of the six patients with BPH undergoing ⁶⁵Zn prostate scans were studied 12–24 hr after the administration of an i.v. dose of 1 mCi. These scans showed only an indefinite prostatic outline (Fig. 2A, B). Scans were performed on the other two patients at 2 and 4 hr but there was no evidence of increased concentration of radioactivity in the area of the prostate. In the three patients with carcinoma of the prostate scanned at 12–14 hr, there was no significant accumulation of radioactivity in the gland.

DISCUSSION

The results of the uptake of ⁶⁵Zn by the tissues of the male rat showed that although the concentration in the kidney, liver, and pancreas was greater than in the prostate, the prostatic tissues had greater ability to retain ⁶⁵Zn for periods up to 20 hr. The

results also suggested that some other organs of the male rat such as the seminal vesicles, testis, and bone were also capable of accumulating and retaining ⁶⁵Zn for periods up to 20 hr. However, the concentration in the prostate was greater.

Comparison of the uptake of ⁶⁵Zn in various tissues of patients with BPH showed that the uptake by BPH tissue was greater than that of abdominal muscle and the ratio of the uptake in prostate to muscle tended to increase with time. In these studies the greatest ratio of counting rate between prostate and muscle occurred at 12–24 hr.

The studies of uptake of radioactive zinc by tissues of experimental animals reported by other investigators (2,5) suggest a higher uptake of ⁶⁵Zn by the dorsolateral lobe of the prostate compared with other tissues of the male rat. The results reported in this paper as well as by other workers suggest that the binding of radioactive zinc with prostatic tissue is different from that of other tissues. These results demonstrate that there is a higher accumulation of zinc in the prostate with time. This could be explained by the findings of Heathcote and Washington (13), who have isolated a zinc-binding protein in human BPH tissue using electrophoresis and ion-exchange chromatography. Characteristics of this zinc-binding protein are different from that of androgen-binding protein reported by Hansson (14).

In assessing the potential value of ⁶⁵Zn for prostate imaging, it is essential to know the uptake in muscle as well as in the gland in order to determine the “contrast” that might be expected between the radioactivity in the prostate and its surrounding tissues. Data from the ⁶⁵Zn tracer studies on patients undergoing an open prostatectomy provided the means of predicting the scan contrast and gland activity as a function of time after injection of a known amount of ⁶⁵Zn. However, despite the evidence of increasing concentration of ⁶⁵Zn in the prostate with time, the absolute level in the gland is low. Our experience suggests that the injection of 1 mCi of ⁶⁵Zn chloride does not provide an image suitable for diagnostic purposes. The accumulation of zinc in bone

TABLE 2. UPTAKE OF ⁶⁵Zn BY PROSTATE AND OTHER TISSUES IN 12 PATIENTS (4 PER GROUP) WITH BPH*

Time after injection (hr)	% of dose (×10 ⁴)/gm wet wt			Prostate
	Prostate	Bladder	Muscle	Muscle
0–4	6.95 ± 1.52	1.50 ± 0.10	0.77 ± 0.11	11.15 ± 1.45
4–12	10.33 ± 0.52	2.28 ± 0.26	0.88 ± 0.06	11.63 ± 0.29
12–24	16.03 ± 1.35	4.00 ± 1.83	0.77 ± 1.83	21.15 ± 1.22

* Values are mean ± s.e.m. expressed as % of dose administered (× 10⁴/gm of wet wt).

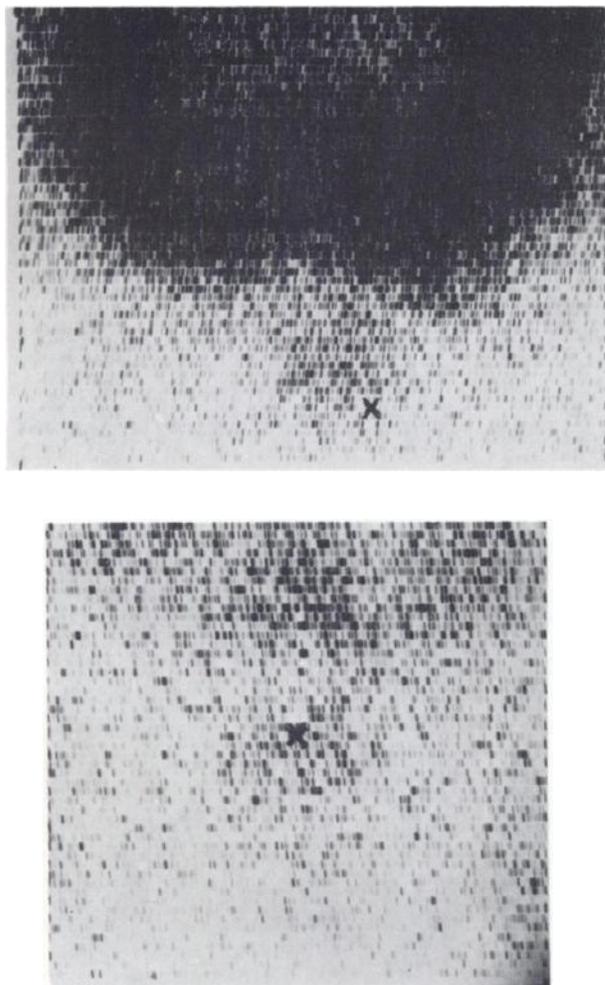


FIG. 2. (Top) Scintigraphic image of prostate of patient with BPH 13 hr after injection of ^{65}Zn . X represents surface marking for prostate. (Bottom) Scintigraphic image of prostate of patient with BPH 14 hr after injection of ^{65}Zn . X represents surface marking for prostate.

and in some of the other tissues presents an inadequate counting rate ratio between these tissues and the prostate. The scans, carried out at the optimum time, confirm the limitations of radioactive zinc chloride for this purpose as suggested by Verrilli, et al (3) and do not support the hopes expressed by Johnston, et al (6). There remains, however, the

possibility that other chemical forms of zinc might prove more suitable.

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