BNL--30628

DE83 003217

CONF-820804--4

ENHANCEMENT OF RADIOPHARMACEUTICAL EXCRETION BY CHEMICAL INTERVENTIONS

Z.H. Oster, P. Som, A.B. Brill, D.F. Sacker and H.L. Atkins

Brookhaven National Laboratory, Upton, New York
and
State University of New York, Stony Brook, New York, U.S.A.

INTRODUCTION

We have shown previously that desferrioxamine (DFO) enhances urinary excretion of Ga-67 (Oster and colleagues, 1978, 1980a, 1980b, 1980c, 1981a, 1981b). The present study is an extension of these observations to other compounds that may enhance the excretion of Tc-99m pertechnetate (Tc), Ga-67 citrate (Ga) and Tl-201 chloride (Tl). The purpose of these studies was to find methods of decreasing the radiation dose after radionuclide studies, by giving a compound that will increase the rate of excretion of the radionuclide.

MATERIALS AND METHODS

Groups of 6 Sprague-Dawley rats were given Tc, Ga, or Tl intravenously followed at intervals of 1-24 hrs by one of the following compounds: Desferroxamine (DFO), 2,3-Dimercapto-1-propanol (BAL), Triethylene tetraamine hexaacetic acid (TETHA), Stannous tartarate, Bleomycin (BLEO), 2,3-Dimercaptosuccinic acid (DMSA), Diethylenetriaminepenta acetic acid (DTPA), DTPA+$SnCl_2.2H_2O$, Dihydroxybenzoic acid (DHB) or Ferric-cyanoferrate (II) (Prussian blue, PB). Whole body retention was determined by placing the control or experimental rats over the crystal of a gamma-camera, interfaced to a dedicated minicomputer. The percent of the injected activity was determined by subtracting the background activity and relating the net counts of both the experimental and control groups to a "standard rat." The latter was an animal given the same dose of radiopharmaceutical and sacrificed 5 min after injection. Thus the geometry of the standard was identical and no decay correction was necessary. Tissue distribution studies were performed and organ samples were assayed in a well-type counter. Three dogs were injected with Tl and scintiphotos were obtained at different time intervals. Three other dogs were pre-treated with 0.5g PB orally on the night before and 0.5g PB on the morning of the experiment. Thallium was given one hour after the second PB dose and scans were obtained at same intervals. Animals were sacrificed 24 hrs post injection and activity was determined in stomach, upper small and lower small intestines as well as in the colon. The amounts of all agents given were normalized to the molar equivalents of 50 mg/kg of DFO. All were injected I.V., except BAL which was given I.M. and PB which was given in suspension by intragastric tube to the rats and in capsules to the dogs.

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

OFFICIAL FILE COPY

MASTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

RESULTS

None of the tested agents enhanced Tc excretion significantly. A minimal effect was seen after injections of Sn-DTPA, Sn-Tartarate and PB ($p = 0.05$). Ga excretion was not affected by: DTPA, DMSA, Bleo, PB and DHB. The following agents had a significant ($p > 0.05$) effect on Ga excretion: DFO, BAL and TETHA.

TABLE 1 Effect of BAL on Ga-97 Citrate in Rats

4 hrs 3 hrs
Ga-67-citrate - - - - BAL - - - - Whole Body Counting and Tissue Distribution

	Controls (%/Org)	BAL (%/Org)	p
Whole Body Retention*	85%	56%	<0.001
Blood	19.40±1.10	8.06±1.68	<0.001
Kidneys	1.49±0.04	1.65±0.37	N.S.
G.I. Tract	7.43±1.27	14.40±3.91	<0.001
Liver	9.80±0.42	10.60±3.91	<0.001

*Values are expressed as percent retention compared to "standard rat" (see text).

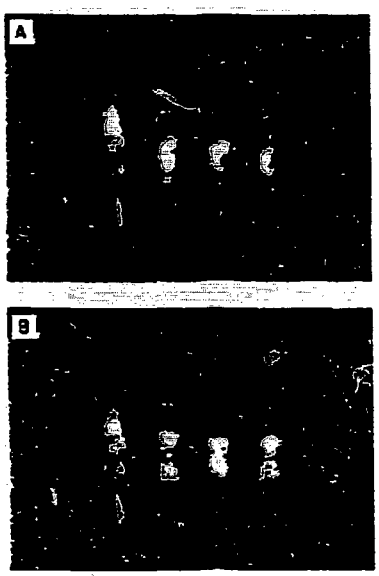

Fig. 1. The effect of BAL on Ga distribution in rats.

As seen in Fig. 1 above, the intestinal Ga activity is much higher in the BAL treated rats (A) as compared to controls (B). Notice that in both A and B the rat on the far left is the "standard rat."

BAL had a minimal affect on Tl excretion ($p = 0.05$) and PB had a significant effect ($p < 0.05$).

Table 2 Effect of PB on Tl Distribution in Rats

Organs	Controls (%/Org)	PB (%/Org)	p
Blood	2.07±0.21	0.96±0.11	0.004
Thyroid	0.14±0.07	0.09±0.02	N.S.
Heart	0.49±0.10	0.33±0.02	N.S.
Kidneys	0.05±0.01	0.04±0.01	0.003
G.I. Tract	13.30±2.48	20.00±4.01	N.S.

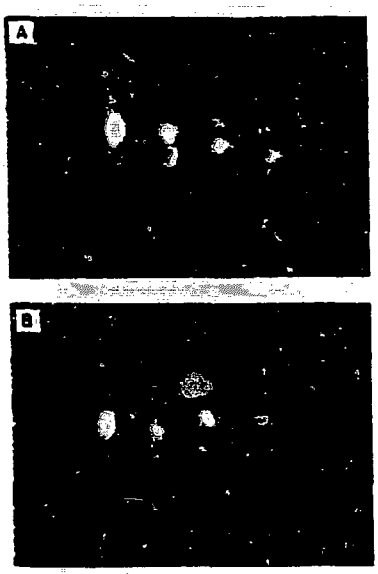

Fig. 2. The effect of PB on Tl distribution in rats. Increased G.I. tract Tl accumulation in the PB treated rats is seen in A as compared to controls, B.

Table 3 Effect of PB on G.I. Tract Content of Tl in Dogs

	(%/Org)	
	PB	Controls
Stomach	14.70	10.20
Upper Small Intestine	12.45	14.20
Lower Small Intestine	11.75	14.20
Large Bowel	39.70	10.80

Fig. 3. Increased G.I. tract accumulation of Tl in PB treated dog is seen in B as compared to control, A.

DISCUSSION

These preliminary results show that with the doses used, none of the tested agents had significant effects on enhancing excretion of Tc. Although Ga excretion was affected by BAL and TETHA, this effect was smaller than observed after DFO (Oster and colleagues, 1980). BAL is still listed in the literature (Grundfeld, 1963) as an antidote for Tl poisoning but our observations add support to the view that it is not very effective (Lund, 1956). PB had a highly significant effect on lowering Tl blood and kidney activity, without decreasing myocardial concentration. Whole body retention as determined in rats was also lowered by PB. Dogs treated with PB show higher accumulation of Tl in the stomach and to a larger extent in the colon.

All the agents used with the exception of PB are chelators. The latter can be divided according to their functional groups as follows: hydroaxamic acid group - DFO, catechol group - DHB, phenol group - BAL, amino carboxylic acid group -DTPA, TETHA. Some of these chelators enhance excretion through the urinary tract (DFO), while most are excreted through the bile. PB was shown to increase Cs excretion through the G.I. tract (Nigrović, 1965) and it presumably acts as an ion exchanger for the ions that are excreted into the gut thus preventing recirculation (Nigrović, 1965). Similar affects were observed by Heydlauf (1969) on Tl excretion. Our findings show that PB treated animals have larger concentrations of Tl in the gut, thus supporting the theory that PB acts as a trapping agent for G.I. excreted thallium, possibly in the same way as bile-salts are trapped by cholestyramine (Oster and colleagues, 1965). These findings suggest that these excretion enhancing agents given following a radionuclide procedure. may reduce the radiation dose.

REFERENCES

Grundfeld, O. (1963). Thallium Poisoning Treated with BAL. New Engl. J. Med. 269: 1138-1140.

Heydlauf, H. (1969). Ferric-Cyanoferrate (II): An Effective Antidote in Thallium Poisoning. Europ. J. Pharmacol. 6: 340-344.

Lund, A. (1956). The effect of various substances on the excretion and toxicity of thallium in the rat. Acta Pharmacol. Toxicol. 12: 260-168.

Nigrović, V. (1965). Retention of radiocesium by the rat as influenced by prussian blue and other compounds. Phys. Med. Biol. 10: 81-91.

Oster, Z.H. (1978). The effect of deferoxamine-mesylate (Desferal) on the biodistribution of Ga-67 citrate. J. Nucl. Med. 19: 732.

Oster, Z.H., P. Som, D.F. Sacker, and H.L. Atkins (1980a). The effects of deferoxamine mesylate on Ga-67 distribution in normal and abscess-bearing animals. J. Nucl. Med. 21: 421-425.

Oster, Z.H., P. Som, D.F. Sacker, and H.L. Atkins (1980b). Time-related Ga-67-citrate concentration in tumor and abscess and the effect of desferrioxamine (DFO). J. Nucl. Med. 21: 24.

Oster, Z.H., P. Som, D.F. Sacker, and H.L. Atkins (1980c). The effect of desferrioxamine (DFO) on Ga-67-uptake in tumor and abscess-bearing animals. Invest. Radiol. 15: 383.

Oster, Z.H., P. Som, H.L. Atkins, and A.B. Brill (1981a). Desferal (DFO) induced Ga-67 washout from normal tissue, tumor and abscess in experimental animals. In: Int. Radiopharmaceutical Dosimetry Symposium. Oak Ridge, TN, Oak Ridge Assoc. Univ. FDA, DOE, BRH, HHS Publication FDA 81-8166, pp. 307-317.

Oster, Z.H., P. Som, D.F. Sacker, N. Cicale, and A.B. Brill (1981b). The use of chelating agents for reduction of radiation dose. J. Nucl. Med. 22: 44.

Oster, Z.H., E.A. Rachmilewitz, E. Moran, and J. Stein (1965). Relief of pruritus by cholestyramine in chronic liver disease. Isr. J. Med. Sci. 1: 599-605.

Research supported under Contract No. DE-AC02-76CH00016 with The U.S. Department of Energy