Preliminary Study of Radioactive Product Obtained from Iodinating Tetracycline. (25709)

ARTHUR L. DUNN, CLEAMOND D. ESKELSON, JOHN F. MCLEAY, RICHARD E. OGBORN AND BENEDICT R. WALSKE* (Introduced by H. P. Jacobi)

Vet. Admin. Hosp., Omaha, and Dept. of Surgery, Creighton Univ. School of Med., Omaha, Nebr.

Rall *et al.*(1) and McLeay(2) reported that tetracyclines localize in tumors and bones. This was learned by observing under ultraviolet light the fluorescence in bones and tumors removed from treated animals. The characteristic yellow fluorescence persists in mouse tumor and bone for 10 to 20 days after last injection of one of the tetracyclines. McLeay observed fluorescence in human cancerous tissue removed from patients pretreated with terramycin. While tetracyclines had no effect on growth of tumors, their accumulation in rapidly growing tissues suggested that they might act as carriers for some antitumor diagnostic agent such as radioactive isotope. This paper deals with a product obtained by chemically labeling tetracycline with I^{131}.

Method. Sprague-Dawley rats weighing 150-300 g and spontaneous mammary tumor mice were used. One % sodium iodide solution to block thyroid uptake of detached iodide was given in drinking water. Animals were treated with I^{131} products obtained from reactions designed to iodinate tetracycline. Details of synthesis and characterization of the product will be published later. Animals were injected intraperitoneally once daily for 3 days with 8 mg/kg of product in 4.4% sodium iodide solution. Control animals were injected similarly with equal amount of radioactivity in a mixture of 4.4% sodium iodide, tetracycline and sodium iodide I^{131}. Twenty-four, 48 and 72 hours after last injection the animals were sacrificed, and thyroid, liver, muscle and femur removed. Tumors were also removed from each tumor-bearing mouse. Radioactivity was determined in each tissue by a well-type scintillation counter. Some tissues were biologically assayed(3) for tetracycline-like qualities and fluorescence of bones was studied under ultraviolet lamp.

* Authors are grateful to Dr. Michael Carlozzi of Chas. Pfizer & Co. for generous supplies of tetracycline.

Results. Table I indicates that the radioactive product was taken up preferentially in bones of the animal. Examination under ultraviolet light of femurs split longitudinally indicated that the material was concentrated in the epiphyseal plate area. In rat No. 2 antibiotic activity (0.48 μg/g of tissue) was detected in femur but not in liver or muscle. Radioactivity was associated usually with antibiotic activity, but no antibiotic activity could be detected in bone with specific activity of less than 0.1 cpm/mg of wet tissue. Snell *et al.*(4) reported that the liver accumulates and excretes tetracycline, and it appears next highest in specific activity in our experiments. No antibiotic activity was detected in liver at any time. Muscle had a

TABLE I. Distribution of Radioactivity in Tissues of Young Rats Following Administration of Radioiodinated Tetracycline.

Rat No.	Tissue	Specific activity, cpm/mg wet tissue
1*	Liver	.012
	Femur	.17
	Muscle	.008
2†	Liver	.055
	Femur	.367
	Muscle	.021
3†	Liver	.15
	Femur	.47
	Muscle	.18
4†	Liver	1.9
	Femur	.12
	Muscle	.05
5*	Liver	‡
	Femur	.20
	Muscle	.045
6*	Liver	.009
	Femur	.19
	Muscle	.043
7*	Liver	4.0
	Femur	1.10
	Muscle	.10
Control* (avg of 2 rats)	Liver	.0009
	Femur	.003
	Muscle	.005

* Sacrificed 24 hr after last inj. † Sacrificed 48 hr after last inj. ‡ Not detectable.

TABLE II. Distribution of Radioactivity in Tissues of Mammary Tumor Mice Following Administration of Radioiodinated Tetracycline.

Mouse No.	Tissue	Specific activity, cpm/mg wet tissue	μg of tetracycline/g
1*	Liver	.91	
	Femur	.98	
	Tumor	1.19	
2†	Liver	.052	§
	Femur	.161	8.95
	Tumor	.062	§
3‡	Liver	.05	§
	Femur	.16	5.81
	Tumor	.09	1.4
4*	Liver	.26	
	Femur	.08	
	Tumor	.63	
5*	Liver	.12	
	Femur	.06	
	Tumor	.08	
6*	Liver	.009	
	Femur	.03	
	Tumor	.19	
7*	Liver	.83	§
(4 inj.)	Femur	.39	3.55
	Tumor	.095	§
Control* (avg of 4 mice)	Liver	.012	
	Femur	.020	
	Tumor	.027	

* Sacrificed 24 hr after last inj. † Sacrificed 48 hr after last inj. ‡ Sacrificed 72 hr after last inj. § Not detectable.

low specific activity, which in most instances is of questionable significance.

Table II indicates that mouse tumor contained a higher specific activity than did mouse femur or liver. Muscle from mice showed a low specific activity. Control animals flushed out most of the NaI^{131} within 24 hours.

These data indicate that the radioactive product is a labeled tetracycline or degradation product and that it is inactivated by liver, since considerable radioactivity was measured in liver specimens, but in no case was antibiotic activity demonstrated. In some animals thyroid became radioactive, suggesting that the product was contaminated with NaI^{131}. This was partly alleviated by giving the product in a solution of nonradioactive sodium iodide and giving animals sodium iodide in drinking water thus blocking the thyroid.

These studies indicate a possible new irradiation tool for detection and treatment of tumors. Bone tumors may offer greatest possibilities in utilizing this new tool.

Summary. Attempts to radioactivate tetracycline by iodination reaction have evolved a product which resembles tetracyclines when injected into rats and mice. It is sequestered in general by fast-growing tissues and in particular by tumor, liver and epiphyseal plate region of bone. Liver appears to inactivate and excrete the material.

1. Rall, D. P., Loo, T. L., Lane, M., Kelly, M. G., *J. Nat. Cancer Inst.*, 1957, v19, 79.

2. McLeay, J. F., *Am. J. Surg.*, 1958, v96, 415.

3. Kucera, L. S., Thesis, Creighton Univ., Omaha, Nebr., 1959.

4. Snell, J. F., Garkuscha, R., Allen, E. L., *Antibiot. Ann.*, 1957, 502.

Received November 16, 1959. P.S.E.B.M., 1960, v104.

Comparison of Effect of Desoxycorticosterone Acetate and Cortisone Acetate on Rat Skeletal Muscle Electrolytes. (25710)

ABBIE I. KNOWLTON

Dept. of Medicine, Columbia University College of Physicians and Surgeons, and Presbyterian Hospital, N. Y.

Recently in a study of differences between hypertensive actions of 2 adrenal steroids, desoxycorticosterone acetate (DCA) and cortisone acetate, the electrolyte composition of eviscerated carcasses of rats injected with one or another of these hormones was determined (1). In animals given the former steroid, while maintained on high sodium intake, an impressive retention of sodium and marked depletion of potassium were noted, findings consistent with previous reports of effects of this compound on skeletal muscle(2,3). In rats injected with cortisone, regardless of sodium content of diet, a severe potassium de-