nm/PRELIMINARY NOTE

POTENTIAL VALUE OF TOLUIDINE BLUE ANALOGS AS PARATHYROID SCANNING AGENTS

Guprem S. Kang and Walter DiGiulio

Veterans Administration Hospital and University of Michigan Medical School, Ann Arbor, Michigan

Although ^{75}Se-selenomethionine parathyroid photoscans can localize abnormal parathyroids weighing 1 gm or more, smaller tumors or those in the mediastinum cannot be regularly visualized. The demonstration (*1*) that toluidine blue (T.B.) administered intravenously to dogs resulted in a blue coloration of parathyroids led us to investigate the quantitative distribution of T.B. in dogs to evaluate the potential value of gamma-emitting analogs of this or similar dyes.

METHODS

T.B. (Catalog Number C 175 G, certified grade, E. H. Sargent Co., Detroit, Mich.) was administered intravenously (10 mg/kg body weight) to eight mongrel dogs. Two hours after the 45-min infusion, 0.5 ml of blood and 0.5-gm specimens of tissues listed in Table 1 were obtained for assay of T.B. content. Parathyroids from two groups of three and five dogs, respectively, were pooled. The weight of parathyroids in these two pools was 78 and 192 mg. The tissues were homogenized in 2 ml ethanol and centrifuged. Two additional ethanol extracts of the residue (each with 2 cc of ethanol) were combined with the original supernatant. The optical density of the extracts was measured at a wave length of 625 mu in a Bausch and Lomb Spectronic-20 spectrophotometer, and concentrations of T.B. were read from a standard curve of alcohol solutions of known concentrations (0.08–8 μg T.B./ml). More than 90% of known quantities of T.B. added *in vitro* were recovered by the method described above from each of the tissues in Table 1.

TABLE 1. DISTRIBUTION OF T.B. IN DOG TISSUES

Organ	T.B. μg/gm (mean of 8 dogs)	Standard deviation
Parathyroid	91.9*	——
Thyroid	9.0	3.8
Muscle	8.2	4.8
Lymph node	17.7	6.6
Salivary gland	26.9	15.1
Spleen	28.2	19.7
Pancreas	50.3	23.0
Liver	3.4	1.9
Kidney	48.2	28.0
Stomach	36.6	41.8
Duodenum	12.5	5.1
Heart	60.3	32.5
Lung	8.1	3.1
Blood	1.5	0.8

* One pool of parathyroids had 93.8 μg/gm concentration of T.B. and the other pool had 90.0 μg/gm.

RESULTS

The distribution of T.B. in dog tissues 2 hr after a 45-min infusion of T.B. is given in Table 1.

The uptake of T.B. per gram of parathyroid tissue was 0.92% of the kilogram dose. The mean concentration of dye in parathyroids was 10 times greater than thyroid, 11 times the concentration in muscle and 63 times the concentration in blood. These concentrations of T.B. show greater specificity of T.B. for parathyroid tissue than has been observed with ^{75}Se-selenomethionine in humans. The highest concentration of ^{75}Se-selenomethionine that we observed in 14 patients with hyperparathyroidism was 0.04 μCi ^{75}Se/gm parathyroid tissue*. This concentration was observed in two patients at 0.5 and 6.0 days after the administration of ^{75}Se-selenomethionine. The average concentration ratios in these 14 patients were as follows: parathyroid to thyroid—2.7 (range

Received June 5, 1968; revision accepted Sept. 3, 1968.

For reprints contact: Walter DiGiulio, Radioisotope Service, Veterans Administration Hospital, 2215 Fuller Rd., Ann Arbor, Mich. 48105.

* Dose of ^{75}Se-selenomethionine was 250 μCi per patient (approximately 4 μCi/kg).

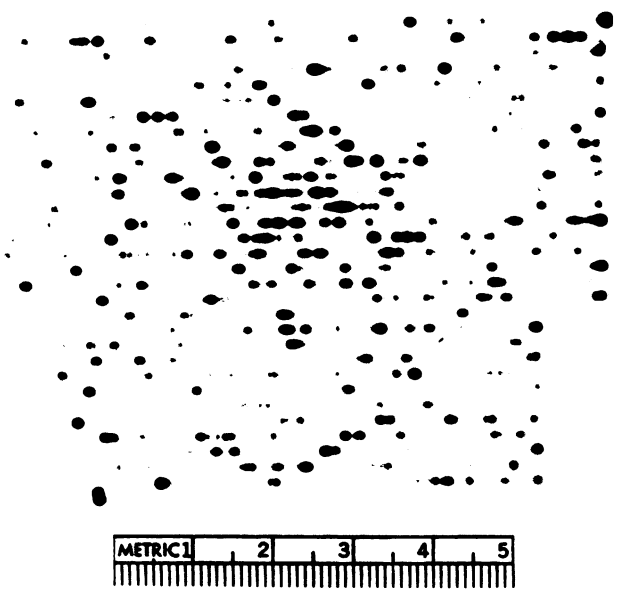

FIG. 1. Scan of 0.3 ml mock tumor (0.015 μCi). Target-to-nontarget ratio = 20:1. Maximum counts per minute = 1,200. Scan speed = 7 cm/min. Time constant = 0.1 sec. Collimator has 3 in.-coarse focus, 31 hole. Density is 25.

1.0–6.7); parathyroid to blood—2.4 (range 1.3–4.3); and parathyroid to muscle—4.3 (range 2.2–12.0).

If a distribution similar to that of T.B. could be obtained in humans with an ^{131}I-labeled analog of T.B., approximately 0.05 μCi would be concentrated in a 1-gm adenoma following a dose of 5 μCi/kg. Extrapolating from Table 1 the target-to-nontarget ratio of radioactivity in surrounding neck tissue would be between 10-to-1 (parathyroid-to-thyroid) and 63-to-1 (parathyroid-to-blood).

Studies in phantoms (Fig. 1) indicate that a 0.3-ml mock tumor with a concentration of radioiodine of 0.05 μCi/ml and a target-to-nontarget ratio of 20-to-1 (7 μCi ^{131}I in 2,800 ml water is background) can be clearly visualized at a depth of 2 cm with a 5-in. crystal scanner (Picker Magnascanner).

The concentration of T.B. was also high in the heart, pancreas and kidney. A suitable gamma-emitting analog of T.B. may also have clinical applications for scanning of these organs. Of particular note is the very high pancreas-to-liver ratio.

CONCLUSIONS

While the uptake of T.B. per gram of dog parathyroid tissue 2 hr after its intravenous infusion is similar to the percent uptake of ^{75}Se-selenomethionine in some humans, the ratios of parathyroid concentration to that in thyroid, muscle and blood are greater than with ^{75}Se-selenomethionine. These data suggest that radiolabeled analogs of this dye may be excellent scanning agents, particularly for parathyroid-gland photoscanning. Obviously, to incorporate a useful gamma-emitting isotope such as ^{75}Se or ^{125}I into the T.B. molecule, some chemical modification will be required. The effects of such modifications cannot be assessed until these agents have been synthesized and are available for study.

REFERENCE

1. KLOPPER, P. A. AND MOE, R. E.: Demonstration of the parathyroids during surgery in dogs, with preliminary report of results in some clinical cases. *Surgery* **59**:1,101, 1966.