

PHARMACEUTICAL TOXICITY AS A FUNCTION OF BIODEGRADABILITY

In the December 1972 issue of the *Journal of Nuclear Medicine* Subramanian and his colleagues inferred that the diphosphonate bone-seeking compound may be toxic because it is not biodegraded after intravenous administration (1). To prematurely equate the toxicity of diphosphonate to its lack of biodegradability is bias since the opposite is often true with other compounds. There are many examples in which metabolic conversion (or biodegradability) of a chemical results in the formation of products that are more toxic than the original compound (2), such as those listed in Table 1. Such a process is called metabolic toxication. For example, it is apparent that metabolic alteration resulting from

the conversion of the organic phosphorus compound parathion to paraoxon is very significant since the the metabolic product is an effective poison whereas the parent compound is not.

Our laboratory has reported on the acute intravenous toxicity of 1-hydroxy-ethylidene-1, 1-disodium phosphonate and found it to be nontoxic (3). To date we have scanned approximately 1,000 patients with <sup>99m</sup>Tc-diphosphonate (<sup>99m</sup>Tc-HEDSPA) without adverse effects where the carrier dose of diphosphonate was approximately 0.5 mg/patient (4,5). Diphosphonates are also used in large amounts over extended periods of time for the therapeutic treatment of metabolic bone disorders such as Paget's disease (6).

FRANK P. CASTRONOVO, JR.  
Massachusetts General Hospital  
Boston, Massachusetts

TABLE 1. INCREASED TOXICITY RESULTING FROM METABOLIC CONVERSION

Compound	Product
Sulfanilamide	Acetylsulfanilamide
Ethylene glycol	Oxalic acid
Methanol	Formaldehyde
Fluoroacetate	Fluorocitrate
Parathion	Paraoxon
Tremorine	Oxytremorine
Tri- <i>o</i> -cresyl phosphate	Cyclic phosphate
Dimethyl nitroso amine	Diazomethane
Schradan	Schradan-N-oxide
Heptachlor	Heptachlor epoxide
Pyridine	n-methyl pyridinium chloride
Chloral hydrate	Trichlorethanol chloride
Nitrobenzene	Nitrosobenzene, phenylhydroxylamine
Acetanilid	Aniline
Pentavalent arsenicals	Trivalent arsenicals
Selenate	Selenite
2-naphthylamine	2 amino-1-naphthol
Codeine	Morphine
Phenylthiourea	Hydrogen sulfide

REFERENCES

1. SUBRAMANIAN G, MCAFEE JG, BLAIR RJ, et al: <sup>99m</sup>Tc-EHDP: A potential radiopharmaceutical for skeletal imaging. *J Nucl Med* 13: 947-950, 1972
2. SCHUSTER L: Metabolism of drugs and toxic substances. *Ann Rev Biochem* 33: 590-595, 1964
3. CASTRONOVO FP, CALLAHAN RJ: New bone-scanning agent: <sup>99m</sup>Tc-labeled 1-hydroxy-ethylidene-1, 1-disodium phosphonate. *J Nucl Med* 13: 823-827, 1972
4. PENDERGRASS HP, POTSAID MS, CASTRONOVO FP: The clinical use of <sup>99m</sup>Tc-diphosphonate (HEDSPA): A new agent for skeletal imaging. *Radiology* 107: 557-562, 1973
5. CASTRONOVO FP, CALLAHAN RJ, POTSAID MS, et al: A new skeletal imaging radiopharmaceutical: 1-hydroxy-ethylidene-1, 1-disodium phosphonate <sup>99m</sup>Tc complex: In *New Developments in Radiopharmaceuticals and Labelled Compounds*, Vienna, IAEA, 1973
6. SMITH R, RUSSELL RG, BISHOP M: Diphosphonate and Paget's disease of bone. *Lancet* vol 1, 945-947, 1971

THE AUTHORS' REPLY

Dr. Castronovo's letter has not questioned the validity of the data presented or the discussion which followed, but rather the conclusions which might be inferred from the discussion. In our paper, no correlation between biodegradability and toxicity was stated or intended. Many radioactive agents which have been used in relatively small doses in nuclear medicine are not biodegradable, such as colloids of gold or sulphur or polyvinyl pyrrolidone. We contend, however, that when several agents are available for a particular clinical study, those which are metabolized or not retained for prolonged peri-

ods should be preferred to nonbiodegradable agents which exhibit biological retention if other radiopharmaceutical properties of the agents (toxicity, physical characteristics and tissue localization) are similar. We completely agree that many drugs which undergo metabolic breakdown may be toxic: indeed, pharmacological action is often attributed to drug metabolites rather than the parent compound (1).

The major conclusions reached in our paper are similar to those of Yano (2,3) and Castronovo (4)—i.e., ethane-1, hydroxy-1, 1-diphosphonate (often called EHDP) as a <sup>99m</sup>Tc-Sn complex appears to be

an excellent agent for skeletal imaging. The diphosphonate is a stable chemical in aqueous solutions, and there is still no evidence that it is metabolized in vivo, unlike linear polyphosphates. Despite the increasing number of publications on the pharmacology and toxicity of diphosphonates, most of these have reported results of oral or subcutaneous administrations, and there is still a paucity of information on intravenous toxicity. In our laboratory, the  $LD_{50/30}$  for EHDP administered intravenously as a tin complex was 45–50 mg EHDP/kg body weight in albino mice and 40–45 mg/kg in New Zealand adult rabbits compared with 100 mg/kg in both mice and rabbits for linear polyphosphate. Recent measurements of the long-term retention of  $^{99m}\text{Tc}$ -EHDP in beagles by total-body counting and radioassay of excreta have revealed a slow component with a biological half-time of 72 days for 15% of the administered activity (5). Although the effects of subcutaneously administered diphosphonates on ionizable serum calcium and the histological appearance of bone have been studied in dogs (6), similar information following intravenous injection has not been reported. The human experience on the administration of large doses of EHDP for the treatment of Paget's disease and other skeletal lesions is probably not closely related to single or repeated intravenous administrations since only about 3% of these therapeutic doses administered orally are absorbed. The small quantities of diphosphonates currently used for radioisotope imaging studies appear to be considerably below levels of demonstrable toxicity; however, the evidence to date suggests that their skeletal concentration depends on the degree of dilution, the diphosphonate-to-tin molar ratio,

and the chemical dose administered. Therefore, more experimental data are needed to define better the optimal diagnostic dose and the minimal dose for undesirable effects following intravenous administration.

Since the introduction of the  $^{99m}\text{Tc}$ -Sn complex of linear polyphosphate (MW 5,000), other polyphosphates, pyrophosphate, and several diphosphonates have been developed recently as successful skeletal imaging agents at various centers. More experience will be needed to determine which of these will be the most satisfactory agent; at the present time, it is the authors' opinion that one of the labeled diphosphonates may prove to be "the best".

GOPAL SUBRAMANIAN  
JOHN G. McAFEE  
RICHARD J. BLAIR  
Upstate Medical Center  
Syracuse, New York

## REFERENCES

1. GOLDSTEIN A, ARONOW L, KALMAN SM: *Principles of Drug Action: The Basis of Pharmacology*. New York, Harper & Row, 1968
2. YANO Y, McRAE J, VANDYKE DC, et al:  $^{99m}\text{Tc}$ -labeled Sn(II)-diphosphonate: A bone scanning agent. *J Nucl Med* 13: 480, 1972
3. YANO Y, McRAE J, VANDYKE DC, et al:  $^{99m}\text{Tc}$ -labeled stannous ethane-1-hydroxy-1-diphosphonate: a new bone scanning agent. *J Nucl Med* 14: 73–78, 1973
4. CASTRONOVO FP, CALLAHAN RJ: New bone scanning agent:  $^{99m}\text{Tc}$ -labeled 1-hydroxy-ethylidene-1, 1-disodium phosphate. *J Nucl Med* 13: 823–827, 1972
5. KALLFELZ FA, et al: Unpublished data
6. KING WR, FRANCIS MD, MICHAEL WR: Effect of disodium ethane-1-hydroxy-1, 1-diphosphonate on bone formation. *Clin Orthop* 78: 251–270, 1971

## FREQUENCY OF EARLY SKULL METASTASIS IN BREAST CANCER

Since we began using  $^{99m}\text{Tc}$  as our bone-imaging agent, we have noted a high frequency of skull metastases in breast cancer patients. In 31 patients studied so far, 16 (53%) have had skull involvement in addition to other bone metastases, principally in the axial skeleton. In ten (32%) patients with early bone metastases, i.e., those with positive scintiphotos and negative roentgenograms, the skull was the first site of involvement. In each case the scintiphoto findings were confirmed by subsequent roentgenographic changes. We had not noted a similar frequency of skull metastases when using  $^{18}\text{F}$  (1,2) and have attributed its appearance to the superior scintiphotos obtained with  $^{99m}\text{Tc}$ . Our limited experience suggests that the frequency of early skull metastasis in breast cancer may be greater than heretofore recognized (3) and stresses the need for rou-

tine skull views. We would be interested in knowing if others have made a similar observation.

G. BRUCE HOPKINS  
KAI A. B. KRISTENSEN  
Scripps Memorial Hospital  
La Jolla, California

## REFERENCES

1. HOPKINS GB, KRISTENSEN KAB, BLICKENSTAFF DE: Fluorine-18 bone scans in the detection of early metastatic bone tumors. *JAMA* 222: 813–814, 1972
2. HOPKINS GB, KRISTENSEN KAB: Whole body skeletal scintiphotos in the detection of occult metastatic breast carcinomas. *Calif. Med*: to be published
3. HAAGENSEN CD: *Diseases of the Breast*. Philadelphia, WB Saunders, 1971, pp 426–449