MEDICAL APPLICATIONS OF CYCLOTRON PROCEDURES: TOTAL BODY CALCIUM AS DETERMINED BY NEUTRON ACTIVATION ANALYSIS

C.H. Chesnut III, W.B. Nelp and J.D. Denney
Division of Nuclear Medicine, University Hospital,
University of Washington, Seattle, Washington 98195

Knowledge of the pathophysiology and treatment of various metabolic bone diseases is enhanced by accurate measurement of total bone mineral mass and precise estimation of bone mass change. Such measurements of total body calcium (TBC) and calcium balance are possible utilizing the technique of total body neutron activation analysis. A 60 inch cyclotron yields 22 Mev deuterons which produce neutrons between 4-12 Mev upon striking a beryllium target. Patients are irradiated with a 200 millirad dose over a 1.5 minute period; ^{48}Ca is converted to ^{49}Ca through a n,γ reaction and the ^{49}Ca is subsequently quantitated in a whole body counter.

This technique detects absolute levels of TBC with a $\pm$ 5.2% accuracy and plots serial net changes (calcium balance) with $\pm$ 2% precision. To date 230 measurements have been performed in 115 patients with bone mineral metabolism disorders, including osteoporosis, osteomalacia, renal osteodystrophy and multiple myeloma.

Recently the technique of <u>in vivo</u> total body neutron activation analysis (NAA) has been introduced to measure certain bulk elements in the body such as sodium, chlorine, nitrogen, phosphorus and calcium. At the University of Washington methods have been established measuring total body calcium (TBC) by NAA with a high degree of precision and accuracy. Since 98-99% of the body's calcium is normally in the skeleton such measurements are most pertinent to the study of bone mass and calcium balance and consequently to bone wasting diseases. The methodology represents an outstanding example of the application of a cyclotron based procedure to medical problems.

The technique's basic principle is as follows: stable calcium-48, of .18% natural abundance, is uniformly activated by neutron capture and converted to calcium-49, a radioactive gamma emitter of 8.8 minutes half-life easily quantitated in a whole body counter. The amount of radioactivity (Ca-49) induced is proportional to the amount of stable calcium (Ca-48) present in the patient.

For neutron activation 22 Mev deuterons from a 60 inch cyclotron are directed through an external beam tube to an adjoining room where they strike a 1/8 inch thick beryllium target. Neutrons averaging 8 Mev in the forward direction are consequently produced. Patients are irradiated 14 1/2 feet in front of the beryllium target where the neutron flux is uniform within $\pm$ 7% over an area 7 feet high and 3 feet wide.

Activation of Ca-48 occurs primarily at neutron energies below 0.4 ev; consequently high energy neutrons entering the body must be slowed (by collisions with hydrogen) to low energy before they can activate calcium. It is necessary, however, to irradiate with high-energy neutrons so that penetration of the bone can occur. If low-energy or thermal neutrons were used for irradiation almost all activation would occur near the body surface. To slow the high energy neutrons, and to partially compensate for variable tissue thickness in the skull and extremities, various moderating fixtures have been devised. These include a lucite helmet covering the head and neck, lucite cylinders covering each arm to the axilla, and a lucite boot covering the lower extremities to the mid-thigh level; the arm and leg fixtures are filled with water to provide additional hydrogenous moderator. In addition both front and back irradiations are performed by these procedures. Uniformity of calcium activation throughout the skeleton varies by only ± 5%.

A 1.5 minute controlled exposure of the patient yields a maximum total body dose of 200 millirads as neutron irradiation and 100 millirads as gamma irradiation, or 2.10 rem. Immediately following irradiation the Ca-49 induced in the patient is quantitated in a whole body counter containing an annular array of four 4 by 9 3/8 inch sodium iodide crystals. Serial, net change is determined by a repetitive comparison of induced Ca-49 activity in the patient to that induced in a liquid calcium standard, always simultaneously activated and counted under identical conditions. The precision of measurement is such that a 2% net change in TBC is detectable.

Variations in body geometry pose a problem in determining the absolute amount of calcium present in grams, since the amount of tissue thickness surrounding the skeleton from patient to patient will variably attenuate thermal neutron flux entering the skeleton. Heavy individuals will receive slightly less activation per gram of body calcium than thin individuals. To compensate for these differences a series of cadavers of varying body size and thickness have been activated and counted, followed by chemical analysis of the calcium content of the ashed skeleton. This permits the establishment of a relationship between induced Ca-49 activity in skeletons of various body builds to the actual chemical value. In essence any patient activated can then be compared to a cadaver standard of similar body form. TBC in grams can subsequently be determined with an accuracy of ± 5.2%.

To date 242 NAA studies have been obtained in 123 individuals, including 115 patients with bone mineral metabolism disorders and 8 normal adult males, age 23-45. In the normal males TBC ranged from 933-1361 grams, averaging 1093 grams. In this group the correlation between TBC and height indicates that TBC varies as 1/5 the cube of skeletal length ($r = .93$). This correlation between height and TBC permits a comparison of normal and abnormal TBC in males in this age range; when compared to five similar aged males with

various bone diseases losses of 25-35% below the expected normal are seen. Utilizing this correlation and its function $y = .203\ x^3$ the grams of calcium predicted for a specific height can be compared to the actual grams of calcium obtained by NAA, and a "% of normal" value calculated. Additional measurements of TBC in normal healthy subjects of both sexes, and of varying ages and body sizes, will provide a range of normal values to which subsequent bone mass measurements can be compared. A single bone mass measurement in any patient can then indicate the degree of bone loss.

Absolute measurements of TBC in various bone wasting diseases included 32 clinically osteoporotic female patients, age 55-75; here TBC varied from 468-895 grams. In 5 clinically osteoporotic male patients, age 35-75, TBC varied from 669-992 grams, a reduction to an average 79% of the expected normal value. TBC determinations in 24 male patients on maintenance renal hemodialysis revealed an average 1070 grams, 96 $\pm$ 12% of that predicted for normals of the same age and height. In 6 individuals with multiple myeloma TBC varied from 450-1105 grams, with good correlation with the extent of radiographic destruction.

Serial TBC measurements essentially provide a determination of calcium balance and are of substantial clinical importance, especially in determining the efficacy of various therapeutic measures in metabolic bone disease. In 5 clinically osteoporotic females, age 45-64, treated with intravenous calcium infusion a continued average loss of 5.2% in TBC was noted over a 13-22 month period. These data clearly establish the ineffectiveness of this form of therapy in patients with osteoporosis.

In the maintenance renal hemodialysis patients calcium balance studies were instrumental in changing the dialysis bath calcium concentration from 3.0 mEq/liter to 4.0 mEq/liter in certain patients; at the beginning of these studies the 3.0 mEq/liter dialysate calcium concentration was associated with a trend toward a negative calcium balance; upon institution of the 4.0 mEq/liter concentration a trend toward stable calcium balance was noted.

In conclusion NAA provides a realistic method of studying absolute body calcium and long term calcium balance, and has become a valuable adjunct in understanding various aspects of calcium metabolism in bone-wasting disease. As a cyclotron-based procedure it is a worthwhile example of the application of cyclotron techniques to medical problems.

REFERENCES

1. J.D. Denney, W.B. Nelp, D.J. Sherrard, Studies of Calcium Balance in Chronic Renal Disease by Total Body Activation, J. Nucl. Med., 13:6, 426 (1972) Abstract.

2. W.B. Nelp, H.E. Palmer, R. Murano, K. Pailthorp, G.M. Hinn, C. Rich, J.L. Williams, T.G. Rudd, J.D. Denney, Measurements of Total Body Calcium (Bone Mass) in vivo with the use of Total Body Neutron Activation Analysis, J. Lab. Clin. Med., 76:1, 151 (1970).
3. W.B. Nelp, J.D. Denney, R. Murano, G.M. Hinn, J.L. Williams, T.G. Rudd, H.E. Palmer, Absolute Measurements of Total Body Calcium (Bone Mass) in vivo, J. Lab. Clin. Med., 79:3, 430 (1972).

DISCUSSION

MINCEY: I wonder if you can tell me something about the uniformity of the field and what is the total absorbed radiation dose to the patient?

CHESNUT: As far as we know, the radiation dose is 200 mrad or 2.1 rem. As I understand it from our physicists, the actual flux is 95% uniform. We feel that we are getting a flux of around about 6.

HARPER: Is this a thermal neutron reaction?

CHESNUT: Yes, it is. The activation of Calcium-48 is actually below 0.7 eV.

HARPER: Do you have any feeling for how your figures could be translated over to a source of neutrons of somewhat lower energy?

CHESNUT: We are currently working on a project using a neutron generator, using argon, which may get us away from the cyclotron. We will be able to manufacture, I think, thermal neutrons although so far we haven't been able to do this. I can't say much more, at least on the technical aspects on that.