DEVELOPMENTS OF IN VIVO NEUTRON ACTIVATION ANALYSIS AND PHOTON ABSORPTIOMETRY IN EDINBURGH

by

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ABSTRACT

Systems for measuring calcium in the forearm and spine using sources of ^{252}Cf have been developed. Whole-body calcium is measured using neutrons from a cyclotron. Dual photon absorptiometry is used to measure bone mineral in the lumbar spine. All the systems are used in clinical research, both absolute levels and changes being studied.

1. INTRODUCTION

The development of in vivo neutron activation analysis in Edinburgh began in 1974, when a californium-252 facility for part-body assays was transferred from East Kilbride for clinical evaluation. Dr. Keith Boddy and his team had devised a storage and pneumatic delivery system and carried out studies demonstrating the feasibility of activation analysis of calcium in the limbs and iodine in the thyroid gland(1).

Michael Smith was appointed as a research physicist and set about optimising the irradiation and detection conditions for measuring calcium in the forearm and spine and applying the system clinically.

Subsequently whole-body activation became possible and developments of dual photon absorptiometry of bone mineral in the lumbar spine were undertaken. A series of clinical research assistants has served the project.

2. FOREARM CALCIUM MEASUREMENTS

2.1 Instrumentation

The apparatus has been described at a number of conferences(2,3,4,5) and in more detail in references(6 and 7). At the time of transfer there were two ^{252}Cf sources, each of about 50 mCi. Large wax cylinders are used as neutron reflectors and wax or water as moderator (see Appendix). Detection is by two opposed 6 in x 4 in NaI crystals in a lead shield. It was found possible to measure forearm calcium with a precision of 2.6% and a dose of 1.6 rem to the bone and 6 rem to the skin per measurement. The second irradiation geometry, using a water bath as partial moderator, eliminated the effect of variation in soft tissue thickness and allowed the determination of "absolute" levels of forearm calcium. Measurements on subjects with no likely bone disease

allowed normalisation for size and provided a basis for assessing calcium levels in disease, the coefficient of variation being 12%(4).

2.2 Clinical applications of part-body calcium measurements

2.2.1 Renal osteodystrophy Patients undergoing haemodialysis for renal failure were followed for a period of 2½ years(4,8,9,10). Their levels of forearm calcium at the beginning of the study were significantly lower than in normal controls, with an inverse correlation between calcium content and period on dialysis. Different concentrations of calcium in the dialysis bath did not affect changes in forearm calcium, but increases were promoted by treatment with 1 α-hydroxycholecalciferol.

2.2.2 Anti-convulsant therapy An attempt was made to assess the osteopenia which may result from treatment with anti-convulsant drugs. The initial forearm calcium of a group of 30 epileptic patients was found to be normal and no effect of vitamin D treatment was found(4,11). The patient selection procedure had probably eliminated those likely to benefit from vitamin treatment.

2.2.3 Lithium therapy 11 patients suffering from manic depressive illness had forearm calcium determinations before and six months after commencing treatment with lithium carbonate. A significant loss of calcium was demonstrated.

2.2.4 Post-gastrectomy study More than 80 patients who have had stomach operations have recently been studied in conjunction with some whole-body calcium measurements. The data are still being analysed.

2.3 Comparison with photon absorptiometry

As far as possible determinations of bone mineral in the distal radius have been made on patients investigated by neutron activation analysis. In the renal and anti-convulsant patients a highly significant correlation was demonstrated between changes recorded by the two techniques(12,13).

3. SPINE CALCIUM MEASUREMENTS

3.1 Instrumentation

The development of the apparatus is described in reference(6). The original ^{252}Cf sources had decayed to only 25 mCi each, and were replaced by two new 100 mCi sources to permit spine activation. From many different irradiation geometries that were tried, the best used a source-skin distance of 6 cm and no pre-moderator or reflector (see Appendix). Detection is by a whole-body counter with four 6 in x 4 in NaI crystals. In a pilot study on control subjects a precision of 3% was obtained with a bone dose of 0.7 rem and a skin dose of 6 rem per measurement.

3.2 Osteoporosis

The clinical indicator for osteoporosis was taken to be a fractured neck of femur and this choice led to difficulties of measurement and a worsening of reproducibility to about 5%. Fewer patients than had been hoped were suitable for investigation. Nevertheless a statistically significant difference was established between patients receiving a combination of oral calcium, oestrogen and 1 α-hydroxycholecalciferol and those receiving a placebo(14).

4. WHOLE BODY NAA

The installation by the Medical Research Council of a cyclotron in Edinburgh for a trial of neutron therapy offered the possibility of whole body activation. The programme was initiated in January 1978 with the appointment of Norman Kennedy as research physicist. Most attention has been paid to the measurement of total body calcium.

4.1 Instrumentation

An irradiation chamber has been designed which minimises the variation of activation efficiency throughout the body (see Appendix). Bilateral irradiation at 5.5 metres from the target is used. The mean neutron energy is 6.1 MeV. Induced radioactivity is measured in a scanning shadow shield whole body counter. The transfer time is approximately 5 minutes. Repeated measurements on anthropomorphic models have demonstrated a coefficient of variation of total body calcium of 1.8% with an absorbed dose of 1.3 rem(15). Corrections to compensate for the effects of patient size have been developed.

4.2 Absolute measurements of total body calcium

20 women and 20 men normal volunteers between the ages of 40 and 70 have been measured and the data normalised using height or span and where appropriate the years post-menopause. The coefficient of variation of normalised whole body calcium in normal women is 6.5% and in men 7.8%. A highly significant correlation between total body calcium and years post-menopause was found, with a loss of 1.4% per annum(15).

4.3 Clinical applications of total body calcium measurements

4.3.1 Osteoporosis 12 women with vertebral crush fractures were studied. Their mean calcium was 68% of that of pre-menopausal controls. When menopausal status was taken into account, their total body calcium was 16% below normal ($P < 0.01$). Treatment with 1 α-hydroxycholecalciferol, ethinyloestradiol and calcium led to a significant increase in 6 months (16,17).

8 women with Colles fracture of the wrist had a mean total body calcium 84% of the normal pre-menopausal level, but this deficit could be accounted for by the time since menopause.

4.3.2 Renal osteodystrophy 15 patients with chronic renal failure had a mean total body calcium 13% below the control group. Following renal transplantation there was no significant continuing loss.

4.3.3 Post-gastrectomy osteomalacia The mean total body calcium of 44 patients who had undergone various forms of gastric surgery was slightly lower than that of matched controls but no differences relating to alternative types of operation were observed and no changes resulted from vitamin D_2 treatment.

4.3.4 Rheumatoid arthritis Total body calcium was significantly reduced by 6% ($P < 0.01$) in 63 patients with rheumatoid arthritis, with a further reduction (13% below normal, $P < 0.001$) in 31 patients receiving corticosteroid therapy(18). Sequential studies have shown that no further loss occurs over an 18-month period in the steroid treated group, but does in the patients managed without steroids.

4.3.5 Miscellaneous diseases Absolute levels and changes of total body calcium are being studied in hyperparathyroidism, thyrotoxicosis, osteomalacia and paraplegia. Numbers of patients are at present too small to draw conclusions.

4.4 Other elements

Values of whole body sodium and chlorine are available from the same irradiations and the precision of determination is 2.2% and 4.3% respectively. After normalisation using lean body mass the coefficient of variation of total body sodium was 5.9% for men and 6.4% for women; the corresponding figures for total body chlorine were 9.5% for men and 10.7% for women(19).

Our irradiation conditions are unfavourable for the determination of phosphorus, due to low neutron energy, patient transfer time and uncertainties of irradiation timing.

5. PHOTON ABSORPTIOMETRY

As most of our NAA applications have been concerned with calcium, they need to be compared with alternative measures of bone mineral, particularly photon absorptiometry, especially as the radiation dose from the latter is very much lower.

5.1 Forearm absorptiometry

For many years we have measured bone mineral in the distal radius using a rather crude home-made scanner. Early work used a source of ^{241}Am, but improvements have been obtained by substituting ^{125}I. A water bath for the arm also improved precision. Scanning is still manual, but a data logger allows computer processing. A comparison between forearm absorptiometry and NAA has already been mentioned in section 2.3.

5.2 Spine absorptiometry

As there is more interest in the mineral content of trabecular bone and particularly that of vertebrae, we have been developing a system of dual photon absorptiometry(20, 21). A dual-headed rectilinear scanner is used, with off-line computer processing of data. Two pairs of photon energies have been compared, 60 keV from ^{241}Am plus 660 keV from ^{137}Cs, and the 44 and 100 keV radiation from ^{153}Gd. Greater precision has been obtained with a 200 mCi source of the latter, reproducibility of the bone mineral content of three lumbar vertebrae in patients being 1% when the operator was experienced, falling to 2.4% for less experienced operators(21).

Measurements on 50 normal volunteers, aged 20-61 years, demonstrated a highly significant inverse correlation between spine bone mineral and age in women ($r = -0.56$, $P < 0.001$) but no correlation in men(21). A higher activity (1 Ci) ^{241}Am source has now been installed for spine absorptiometry and is leading to a precision not far short of that obtained with ^{153}Gd.

6. FUTURE PLANS

Our programme of total body calcium analysis is continuing with an emphasis on rheumatoid arthritis and renal failure patients. The small biological variation of normalised results encourages us to make more use of single measurements, but longitudinal studies are also in progress. We are particularly examining prophylactic measures designed to reduce the bone loss associated with rheumatoid arthritis and its treatment with corticosteroids.

We are establishing an assay for total body nitrogen, using a prompt gamma technique with a ^{252}Cf source.

In the field of photon absorptiometry we plan to devote more attention to the problem of fat, as we believe this imposes the biggest limitations on accuracy and precision. A single-photon absorptiometry system has been developed for measuring bone mineral in the whole hand and is being applied to study peri-articular bone changes in rheumatic patients.

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