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CIRC - 10b
(H-64)

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: Feb. 20, 1968

REPOSITORY Records Holding Area, Bldg. 494
COLLECTION Committee-Clinical Investigations and Uses of Radioisotopes
BOX No. 4
FOLDER CIRC #10B

TO: Clinical Isotope Committee

FROM: Drs. S.H. Cohn, W. Hauser and H.L. Atkins

SUBJECT: Approval for clinical tracer study

Permission is requested to perform an addition to the study on osteoporosis described in memo of February 3, 1967 and in H-64 protocol.

The general protocol will be exactly as described with the exception that sodium fluoride will be fed in place of Ca supplements.

A number of studies have indicated that fluoride at appropriate levels has a beneficial effect on the calcium metabolism of osteoporotic patients. Relatively low doses of fluoride act to depress the resorption of bone. The overall results suggest that F has a profound effect on calcium balance manifested by a decreased rate of urinary Ca excretion. The object of this study is to quantify the underlying kinetic effect of F in osteoporotic patients and to measure subtle beneficial changes.

Sodium fluoride administered orally in divided doses of 60 mg/day of F for 14 weeks was shown to have no untoward effects (2). Black, Kleiner and Bolker also found no evidence of toxicity in 60 human subjects treated for as long as 6 months with an average daily dose of 320 mg NaF (2.4 mg F/kg/day) for a 60-kg subject (4). Rich (3) reported no evidence of nonskeletal effect (chemical, clinical or roentgenographic) at 1 mg F/kg/day. In one patient epigastric pain was initially observed. This was ameliorated by measures which reduce gastric acidity and by the use of enteric coated tables. There was pain in joints observed in three patients which could be ascribed to the exacerbation of existing degenerative arthritis symptoms by the NaF, but this is not clear. There were no other symptoms and no biochemical evidence of toxic effects in any patients. Very high levels of fluoride in man can lead to fluorosis with excessive bone formation (6,7). Levels of 4000-5000 ppm in bone have been shown to have deleterious effects on bone (6). The toxicity of F is largely a function of a high dose rate and an extended duration of the intake of from 5-20 years (6).

The proposal for the present study is to administer NaF to 8 osteoporotic patients at the dose described by Rich, 60 mg/day for 6 weeks maximum. The tracer kinetic study with ^{47}Ca will be performed before and after the F feeding.

Following this study and pending successful results, the combined effects of NaF and Ca supplementation will be studied on a group of osteoporotic patients. The results of the high Ca diet study indicates a beneficial effect in terms of Ca deposited in bone. The mechanism of F action appears to differ from that of Ca supplementation, and therefore the effects of the combined treatment should be additive.

Note: This memo attached to back of CIRC 10 C

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REFERENCES

1. D. M. Hegsted. Beneficial and detrimental effects of fluoride in the environment. Proc. Ann. Conf. on Trace Elements in Environmental Health, Univ. Missouri, 1967.

2. G. Rich and J. Ensinck. Effect of sodium fluoride on calcium metabolism in human beings. Nature 191, 185, 1961.

3. C. Rich, J. Ensinck, and P. J. Ivanovich. The effects of sodium fluoride on calcium metabolism of subjects with metabolic bone diseases. J. Clin. Invest. 43, 545, 1964.

4. M. M. Black, I. S. Kleiner, and H. Bolker. The toxicity of sodium fluoride in man. N. Y. State J. Med. 49, 1187, 1949.

5. D. S. Bernstein, N. Sadowsky, D. M. Hegsted, C. D. Guri, and F. J. Stare. Prevalence of osteoporosis in high and low fluoride areas in North Dakota. J.A.M.A. 198, 499, 1966.

6. H. C. Hodges and F. A. Smith. Fluorine Chemistry, Vol. IV., J. H. Simons, Ed., Academic Press, New York City, 1965, p. 52.

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: February 3, 1967

TO: Clinical Isotope Committee

FROM: Dr. S. H. Cohn

SUBJECT: Approval for clinical tracer study

We would like to perform further clinical studies as described in clinical isotope request H-64 which permits the use of ^{47}Ca in tracer amounts. Since there have been several modifications in the original protocol, we would appreciate your review.

The other investigators involved in the present study include Dr. H. L. Atkins and Dr. J. S. Robertson.

The general protocol is the same except that two tracer doses of ^{47}Ca (20 μc) will be administered to each patient one month apart, and each patient will receive supplemented diets of Ca gluconate (2.5 g/d) during this interval. A compartmental analysis involving the use of the computer is used for the determination of the various parameters of skeletal metabolism, as described in Cohn, S. H. et al., "Formulation and testing of a compartmental model for Ca metabolism in man," Radiation Res. 26: 319, 1965.

In the specific study planned, the therapeutic effects of a high Ca diet on patients with senile osteoporosis will be evaluated clinically, radiographically, by bone density measurements, hydroxyproline excretion, whole-body counting measurements, and by the use of the ^{47}Ca kinetic study described.

Our hypothesis states that the basic defect in senile osteoporosis, i.e., loss of bone mass, results from an increased bone resorption rate with the accretion rate into bone remaining normal. The high Ca diet, therefore, should act to diminish the bone resorption rate without affecting the accretion rate leading to an increased bone mass or density and a diminution of the osteoporosis.

To accomplish these objectives, 8 patients, 60-70 years old, with advanced senile osteoporosis will be selected from the Suffolk Infirmary (under the same arrangement set up by Dr. Jesseph three years ago). After the patient undergoes a period of equilibration on the standard BNL diet (0.8 g/day) of Ca, 20 μc of ^{47}Ca will be administered and the above kinetic study will be carried out over a 10-day period.

Note: This experiment became base for CIRC 10 A [illegible]

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Once the base line for the various parameters of Ca metabolism is established for each patient, they will be placed on a Ca gluconate supplemented diet (2.5 g/day) for 20 days. At the end of this time the patients will receive a second tracer injection of ^{47}Ca (20 μc) and the kinetic study will be repeated for a 10-day period.

The alteration in the values of the parameters of skeletal metabolism, compartment sizes and intercompartmental fluxes resulting from the high Ca diet should test the above hypothesis. Following the high Ca diet the balance between bone resorption and accretion should be shifted to one more closely resembling non-osteoporotic patients of the same age. Presumably this study would provide a more sensitive test of the value of a high Ca diet in the treatment of osteoporosis than can be obtained by balance studies or radiography alone.