Effect of Sodium Fluoride on Calcium, Phosphorus, and Nitrogen Balance in Patients with Paget's Disease

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Prolonged exposure to increased quantities of fluoride, either in industry or in drinking-water, is likely to cause sclerotic changes in bones (Roholm, 1937). It has been suggested that this action could be of great benefit in the treatment of certain metabolic bone diseases. Accordingly Rich and Ensink (1961) studied the effects of sodium fluoride 60 mg./day on the calcium balance of seven patients with osteoporosis and one with Paget's disease, and found a more positive balance in every case. A later report from these authors stated that the drug also produced a positive phosphorus balance (Rich and Ensink, 1962). Purves (1962) treated 14 patients with Paget's disease with sodium fluoride 60 mg./day and reported considerable relief of pain in four to six weeks. Calcium balance studies were made before and during treatment on eight patients, and in six of them the balance became more positive. Bernstein, Guri, Cohen, Collins, and Tamvakopoulos (1963) studied an unspecified number of patients with various types of osteoporosis and Paget's disease before and after fluoride therapy (NaF 50-200 mg./day). They state that "fluoride initiates a grossly positive calcium balance mainly through increased gastric intestinal absorption of calcium."

We present below the results of calcium, phosphorus, and nitrogen balance investigations carried out on three patients suffering from Paget's disease during treatment with sodium fluoride 60 mg./day under full metabolic control.

Material and Methods

The study was made at the metabolic unit of the Royal National Orthopaedic Hospital. The subjects were three patients with Paget's disease of bone who were suffering from symptoms of their disease and had a raised plasma alkaline phosphatase (greater than 12 K.A. units).

Calcium, phosphorus, and nitrogen balance studies were carried out according to the principles of Reifstein, Albright, and Wells (1945). The patients were fully mobilized and given a diet of constant calcium, phosphorus, and nitrogen content, but with a three-day variation of the menu. Six-day collection periods were used, the faecal collections being separated by carmine markers (0.5 g.). Details of the metabolic routine and biochemical methods used in this unit have been published elsewhere (Walker and Collins, 1963). Blood was taken weekly before the midday meal for routine biochemistry (plasma

calcium, phosphorus, alkaline phosphatase, and blood urea). Sodium fluoride was given as a plain solution, 20 mg. in 15 ml. of distilled water, three times daily except in part of the first study, where orange flavour was added.

Results

The results of the preliminary biochemical and radiological investigations are given in Table I, and the calcium, phosphorus, and nitrogen balances in Figs. 1, 2, and 3. A summary of the metabolic data appears in Table II.

TABLE I.—Results of Preliminary Investigations

Case No.	Age and Sex	Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (K.A. Units)	Blood Urea (mg./100 ml.)	Affected Bones on X-ray Film
1	60 M	9.8	3.2	59.0	20	L. humerus; L. scapula; R. pelvis; femora; 1st metatarsal
2	63 F	8.9	3.7	79.5	20.4	Pelvis; sacrum; femora; tibia; bodies L1, 4, 5; skull
3	67 M	10.1	4.0	35.3	25.5	Pelvis; body L4

Case 1

A man aged 60 was suffering from a great deal of pain in the hips and back at the time of admission. Sodium fluoride therapy brought considerable relief of his pain and discomfort, although his symptoms never actually disappeared. The control periods of his balance (Fig. 1) were uneven, but when averaged to make a 12-day period they showed a zero balance for calcium, phosphorus, and nitrogen. The urine calcium was normal (117 mg./day). After six periods on sodium fluoride 60 mg./day there was virtually no change in the balance. At the end of period 8 nandrolone phenylpropionate (Durabolin), 25 mg. intramuscularly twice weekly, was added. No change in the calcium balance occurred, but a positive nitrogen and phosphorus balance was produced, due to the protein anabolic action of the drug. The plasma calcium, phosphorus, and alkaline phosphatase were unchanged. After the conclusion of the balance test the patients continued to take sodium fluoride 60 mg./day for a further six weeks. After four months of treatment (total intake of sodium fluoride 7.2 g.) his plasma calcium was 9.1 mg./100 ml., phosphorus 3.6 mg./100 ml., alkaline phosphatase 64 K.A. units, blood urea 24 mg./100 ml., and daily urine calcium output 128 mg.

An iliac-crest bone biopsy before treatment and at the end of the four months showed no detectable histological change. The radio-

TABLE II.—Figures Represent an Average of 2-6 Six-day Collection Periods on Each Regime

Case No.	Regime	No. of 6-Day Periods	Calcium (mg./Day)				Phosphorus (mg./Day)				Nitrogen (mg./Day)			
			Intake	Urine	Faeces	Balance	Intake	Urine	Faeces	Balance	Intake	Urine	Faeces	Balance
1	Control	2	978	117	855	+6	1,177	760	347	+70	11.65	9.46	1.61	+0.58
	NaF 60 mg./day	6	978	125	871	-18	1,177	783	385	+9	11.65	10.28	1.59	+0.22
	NaF 60 mg./day + nand. phenylpropionate 25 mg. 2x weekly		978	106	919	-47	1,177	672	445	+60	11.65	8.68	1.80	+1.17
2	Control	3	880	102	660	+118	1,194	674	450	+70	11.61	9.23	1.88	+0.50
	NaF 60 mg./day	4	880	96	717	+67	1,194	595	487	+112	11.61	8.03	1.98	+1.60
3	Control	2	860	254	677	-71	1,055	842	381	-168	11.43	10.75	1.57	-0.89
	NaF 60 mg./day	6	860	259	679	-78	1,055	801	388	-134	11.43	10.84	1.40	-0.81

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logical appearance of the affected bones was also unchanged. The sodium fluoride mixture was taken for three months without trouble, but he then complained of nausea for about 30 minutes after each dose. This disappeared when the mixture was flavoured with orange.

Case 2

A woman aged 63 complained of a persistent dull headache and pain in both hips. After sodium fluoride the hip pain had improved but her headache remained. In the control period she had a positive calcium balance of about 100 mg./day and a slightly positive phosphorus and nitrogen balance. During the four periods on sodium fluoride 60 mg./day there was no significant change in the balance. Treatment was continued for a further three months after the balance investigation was concluded, but no further improvement occurred and the plasma biochemistry remained unchanged (calcium 8.9 mg./100 ml., phosphorus 3.9 mg./100 ml., alkaline phosphatase 76 K.A. units, urea 23 mg./100 ml.). The patient took her medicine without complaint and no toxic effects were noted. Radiologically the appearance of the bones did not alter.

Case 3

A man aged 67 complained of pain and stiffness in the right knee, thigh, and leg, which did not alter after treatment. The balance study (Fig. 3) showed him to have a high urine calcium (254 mg./day) and a slightly negative calcium, phosphorus, and nitrogen balance. Sodium fluoride 60 mg./day was given for six periods, without causing any change. A slight increase in plasma alkaline phosphatase was noted. During the study he was on a weight-reducing diet, which accounts for the negative nitrogen and phosphorus balances. No radiological change was seen. The medicine caused no toxic symptoms.

Discussion

In our cases sodium fluoride caused no change in the calcium, phosphorus, or nitrogen balance. These results do not support

the findings of Rich and Ensinn (1961), Purves (1962), and Bernstein *et al.* (1963). The report of Rich and Ensinn (1961) is brief and contains details of only two balances; both were interrupted during fluoride therapy and thus are not a continuous record. Their later report (Rich and Ensinn, 1962) and that of Bernstein *et al.* (1963) are abstracts and contain no metabolic data. The methods of Purves (1962) do not comply with the usual accepted standards of accuracy for calcium-balance techniques (Reifenstein *et al.*, 1945). The patients were not given a steady calcium intake, four-day collection periods were used, and the balances were not continuous.

The alleviation of pain in two of our patients could be due to the placebo effect of admission to hospital with rest from their usual activities and the use of a new drug.

Fluoride acts as an enzyme system-poison (Waldrott, 1963). The lethal dose may be as low as 4 g. (Sollman, 1957), but survival following 50 g. has been recorded (Peters, 1948).

Fluoride has been implicated in abnormalities of blood coagulation, anaemia, and impairment of thyroid and renal function (Cannell, 1960). Geall and Beilin (1964) have reported the development of optic neuritis in a man being treated with 100 mg./day, and Sorsby and Harding (1960) found retinal damage in 17 out of 94 rabbits given fluoride.

In view of these facts and the questionable metabolic response we do not feel that long-term treatment with this drug is at present justified.

Summary

The effect of sodium fluoride 60 mg./day, on the calcium, phosphorus, and nitrogen balance of three patients suffering from Paget's disease is described. No significant change in the balances was observed. The improvement in the clinical state of two of the patients was probably a placebo effect. Care should be taken in administering sodium fluoride as it may produce long-term toxic manifestations.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 1.—Case 1. Calcium, phosphorus, and nitrogen balance. The balances in this and subsequent figures are plotted according to the method of Reifenshtein *et al.* (1945). The dietary intake is plotted down from the zero line. From the intake line the figures for faeces and, above, urine are plotted back towards the zero line. An area above the zero line represents a negative balance and a gap below a positive balance. Each block represents a six-day collection period. FIG. 2.—Case 2. Calcium, phosphorus, and nitrogen balance. FIG. 3.—Case 3. Calcium, phosphorus, and nitrogen balance.

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Experimental and Clinical Observations Concerning the Neurotoxicity of Ethoglucid

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[WITH SPECIAL PLATE]

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In a recently reported clinical trial of a new alkylating agent, ethoglucid (triethyleneglycol diglycidyl ether; Epodyl), used in the treatment of advanced malignant disease, attention was drawn to the rapidity with which relief from pain occurred after administration of the drug by intravenous or intra-arterial injection (Bond *et al.*, 1964). In addition, the observed toxic effects of the agent included temporary, and occasionally permanent, damage to motor and sensory nerves. A similar account of the neurotoxicity of ethoglucid has been reported by Westbury (1962, 1963). Comparable effects have been observed with the alkylating agent nitrogen mustard. Mahaley and Woodhall (1962) demonstrated that exposure of peripheral nerve tissue to high concentrations of this substance led to neurotoxic changes characterized by destruction of myelin organization and fragmentation of axis cylinders. This neurotoxic property has been utilized by Hanna *et al.* (1963) in the treatment of pain caused by cancer of the head and neck, following several previous observations on its pain-relieving effects (Sholes, 1960; Woodhall *et al.*, 1960).

With these exceptions, the neurotoxicity of alkylating agents has received little attention in the literature, and there is only scant information concerning either their mode of action or their use solely for the relief of pain in advanced malignant disease. It is therefore considered of interest to undertake an experimental study, using ethoglucid, to determine more precisely the nature of this effect and its histopathological basis. The relation of any morphological changes produced to the time of administration of the agent might thus be studied and correlation of the experimental findings with clinical observations made.

Material and Methods

In order to eliminate any effects on the peripheral nervous system which a malignant tumour might produce, the experiments were performed on 10 healthy mongrel dogs weighing between 10 and 15 kg. Of these animals, two served as controls, and from them pieces of normal nerve, muscle, and skin were obtained for comparison with similar material taken from identical sites in the remaining eight receiving the drug.

Each animal for infusion was first anaesthetized, after which the femoral vessels of one hind limb were exposed through a

short incision. A fine-bore polyethylene catheter, or a Seldinger cannula, was then introduced into the femoral artery, the tip being advanced to the bifurcation of the common iliac artery. Ethoglucid in a dose of 100 mg./kg. body weight, diluted in 10 ml. of 0.9% sodium chloride solution, was infused into the artery over a period of three to four minutes. The infusion apparatus was then flushed with normal saline solution, withdrawn, and bleeding from the vessel controlled prior to suture of the skin incision. After injection the animals were sacrificed at intervals of 45 minutes, 24 and 48 hours, and 4, 8, 10, 14, and 28 days. At post-mortem examination the femoral nerve, a section of adductor muscle supplied by the nerve, and the overlying skin were removed from the infused limb for histological examination.

The tissue was embedded in paraffin, prior to which a small amount was used in the preparation of frozen sections. The paraffin blocks were serially sectioned and stained by haematoxylin and eosin, phosphotungstic acid haematoxylin, thionine, Loyez, Gross-Bielschowsky, Scharlach R, and osmic acid. The nerve and muscle were sectioned both transversely and longitudinally.

Results

After operation a limp was detected until the sixth or seventh day in all animals surviving eight days or longer. No evidence of permanent motor-nerve damage was observed and gross sensory disturbances were not detected in any case.

Histology

45 Minutes.—The earliest change detected was an irregular swelling of several of the axis cylinders in the femoral nerve (Special Plate, Fig. 1). The myelin sheaths appeared intact and the Schwann-cell nuclei and vasa nervorum showed no abnormality. The muscle and skin were normal.

24 Hours.—The muscle contained an occasional small group of necrotic fibres with cellular increase due to polymorphs and

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