SHORT COMMUNICATION

LITHIUM ACCUMULATION IN BONE
AFTER ORAL ADMINISTRATION IN RAT AND IN MAN

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SUMMARY

1. The concentration of lithium in bone was determined after various periods of lithium administration in rats of differing ages and also after discontinuation. Lithium content was determined in human bone of three lithium-treated and two control subjects.

2. There was an inverse relationship between age at commencement of treatment and the final bone lithium content. This suggests that lithium is incorporated into the mineral of rapidly growing bone.

3. The loss of lithium from bone after discontinuation of medication indicates that one fraction is lost rapidly, and a large fraction remains and is lost very slowly.

4. Analysis of human bone from three subjects after lithium discontinuation shows that concentrations exist similar to those of rat bone. Control human bone had a lithium concentration which was similar to that of control rat bone.

Key words: lithium pharmacokinetics, bone drug effects, psychoses, manic depressive drug therapy.

After oral administration, lithium is distributed throughout the body (Schou, 1968) but is concentrated in bone (Birch & Jenner, 1973), where some of it is retained after discontinuation of medication (Birch & Hullin, 1972). In studies of weanling rats it was suggested that the immature state of the bone might account for lithium binding (Birch, 1971). However, a post-mortem sample from a patient who had received prophylactic lithium therapy up to 9 months before his death indicated that lithium was retained in adult human bone (Birch & Hullin, 1972).

The present experiments were designed to determine (a) the time-course of loss of lithium from bone in rats after discontinuation of lithium administration, and (b) the relation of lithium accumulation to the age at start of treatment.

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METHODS

Female Wistar rats were housed in groups of up to four. Lithium was administered in drinking water to the treated groups as aqueous 10 mmol l\(^{-1}\) lithium chloride (LiCl). The control groups received tap water. Food was available ad libitum. The post-mortem sampling of blood and femur was carried out and tissues were analysed by atomic absorption techniques previously described by Birch & Jenner (1973).

Four experiments were carried out with treatment regimes as follows.

Experiments G and K. In each experiment, twelve weanling animals were divided into two groups of six and treated with either 10 mmol l\(^{-1}\) LiCl or tap water for periods of 18 months (Expt. G) or 15 months (Expt. K).

Experiment H. Twenty-four animals, approximately 9 months of age, were divided into two groups and allowed access to either 10 mmol l\(^{-1}\) LiCl or water. These animals were all killed after 28 days.

Experiment J. Forty animals, approximately 5 months of age, were divided at the start into six groups. Of two groups of eight animals one was given drinking water and acted as control. The other group of eight animals, and the four remaining groups of six, were treated for 28 days with 10 mmol l\(^{-1}\) LiCl. The groups of eight were then killed and the tissues sampled. Two of the animals were found to have abdominal tumours and were discarded. The remaining groups of six animals had water substituted for the lithium drinking fluid and were killed at intervals of 3, 7, 14 and 42 days respectively and their tissues sampled as before.

In addition to these experiments, data are presented from experiments previously described (Birch & Jenner, 1973). In experiment A seven female Wistar rats of 150 g (approximately 7 weeks old) received 8 mmol l\(^{-1}\) lithium chloride in drinking fluid for 28 days and were killed immediately after treatment.

Data are presented from human bone obtained by cylinder biopsy of the iliac crest (Nordin & Smith, 1965), taken for diagnostic purposes from one patient who developed osteoporotic symptoms. This patient (A.B.) had received lithium intermittently for several years, the last course of lithium terminating 10 months before the bone biopsy. Data are also presented from analysis of transverse sections of femur, taken post mortem from a point one-fifth of the length of the femur from the epicondyl to the greater trochanter. These samples were taken from one male patient aged 47 who had received lithium up to 9 months before death and from one female patient aged 70 who had received lithium up to 4½ months before death. In neither case was lithium toxicity apparent. Two age- and sex-matched control samples were also obtained from non-lithium-treated subjects. The samples were digested and analysed as described above.

RESULTS

The effect of discontinuation of lithium in the rat after 28 days of treatment (Expt. J) is shown in Fig. 1(a). The previous finding of release of lithium is confirmed and the rapid time-course of its loss demonstrated. The presence of a more strongly bound fraction is also confirmed.

The relationship between the age of the animal at the start of treatment and the final lithium content of bone is shown in Fig 1(b). In addition, data are plotted from Hansson, Menander-Sellman, Stenström & Thorngren (1972) showing the normal rate of growth of bone at different ages of female Sprague–Dawley rats.
Lithium accumulation in bone

411

504x719

[Image 0x0 to 504x720]

[175x657]Lithium accumulation in bone

411

1

11

I

I

I

0

10

20

30 40

100

200 300

Period after discontinuation of lithium (days)

Age at commencement (days)

FIG. 1. (a) Effect of discontinuation of lithium after 28 days' treatment on the concentration of lithium in rat femur. (b) Effect of age at which lithium treatment was commenced in rats on the concentration of lithium in femur. ○, Control group; ●, treated groups. The graph of longitudinal bone growth (μm/day) is redrawn from the data of Hansson et al. (1972). All concentrations are given as mmol kg⁻¹ wet weight of bone ± sd.

The lithium determinations on human material showed that the bone biopsy from the 66-year-old female contained 0.38 mmol kg⁻¹ dry weight whereas the post-mortem samples from the 70-year-old female and the 47-year-old male patients contained respectively 0.94 and 0.42 mmol kg⁻¹ dry weight. Their respective controls contained 0.16 and 0.17 mmol kg⁻¹ dry weight. In rats whose lithium had been discontinued for 42 days (Expt. J) the treated group had femoral lithium content of 0.35 mmol kg⁻¹ dry weight and the controls 0.19 mmol kg⁻¹ dry weight. With the exception of the 70-year-old female patient there is thus a marked similarity between rats and humans in bone concentration of lithium in treated and control groups.

DISCUSSION

It is clear from Fig. 1(b) that lithium is laid down in bone at a rate proportional to the rate of bone growth since the growth curve derived from the data of Hansson et al. (1972) parallels closely the lithium concentration found in rats treated from different ages. It should be noted that Hansson et al. used proximal tibia from Sprague–Dawley rats as distinct from the present femora from Wistar rats. However, it is thought that a degree of parallelism exists and that the extrapolation is justified.

The results confirm that lithium is accumulated in bone (Birch & Jenner, 1973) and that a fraction remains in bone even after a considerable period of discontinuation (Birch & Hullin, 1972). However, it is clear (Fig. 1a) that the initial loss of lithium from bone is rapid and that this rapidly exchanging fraction might consist, in part, of ions loosely bound to bone structures.

A quantitative kinetic analysis of the exchange of the different fractions of lithium in bone
was not attempted. However, the two fractions identified could correspond to penetration by
the lithium ion of (a) the rapidly exchanging hydration shell and (b) the much more slowly
exchanging crystal surface or crystal interior (Neuman & Neuman, 1958). The increased
lithium accumulation at the time of rapid bone growth suggests the probable accumulation of
lithium in the latter sites.

Previous work has shown that lithium accumulation in bone is accompanied by a decrease
in bone calcium of approximately 100 times the concentration of lithium (Birch & Jenner,
1973). In addition to any direct exchange with calcium, lithium must therefore have an effect
on the control of bone calcium content.

Lithium has been successfully used in the prevention of recurrent affective psychotic episodes
(Hullin, McDonald & Allsopp, 1972). Since the treatment consists of long-term administration
of lithium salts it is important to determine whether changes demonstrated in rat bone after
lithium are also found after prolonged administration in man. The estimations on human
material confirm that lithium is retained in bone after its prophylactic administration. It is
interesting to note that control human samples contained concentrations of lithium similar to
those in femur samples from control rats.

It is possible that the effects in bone may be a further example of the ‘diagonal relationship’
between lithium and calcium and magnesium (Birch, 1970, 1973) and that bone metabolism
may in some way be involved in the pathogenesis of the manic-depressive syndrome. Other
workers have shown clinical changes in calcium metabolism in depression (Faragalla & Flach,
1970) and in calcium metabolism after experimental lithium treatment in animals (Mellerup,

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