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NOTE

Effect of Lithium on Serum Calcium Level and Parathyroid Function in Manic-Depressive Patients

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Abstract. The purpose of this study is to find out whether hypercalcemia and hyperparathyroidism are rare or not in manic-depressive patients taking lithium carbonate. The subjects were 13 patients receiving lithium and 19 healthy subjects not receiving it as normal controls. Serum ionized calcium (Ca^{++}), serum parathyroid hormone (PTH), urinary calcium and cyclic AMP (cAMP) were measured. Cervical ultrasonographic examination was also performed. The mean serum Ca^{++} level in the lithium administered group was significantly higher than that in the control group ($P<0.02$). There was no significant difference between the serum PTH levels in the two groups. The mean urinary calcium level in the lithium administered group was below the normal range, but the mean urinary cAMP level was within the normal range. Although a parathyroid cyst was found in one lithium administered patient on ultrasonographic examination, no swelling of the parathyroid gland was observed in the other patients in the lithium administered group or in any of the control subjects. In the present study, no distinct hyperparathyroidism was found in the patients in the lithium administered group. Lithium administration affects calcium metabolism in manic-depressive patients and hypercalcemia seems to be one of the complications needing attention at the time of lithium administration.

Key words: Lithium, Hypercalcemia, Hyperparathyroidism, Hypocalciuria

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LITHIUM CARBONATE is mainly used in the treatment of manic depression. Hypercalcemia and hyperparathyroidism are side effects of this drug and have been reported several times in Europe and America. Their incidences in patients taking lithium carbonate are said to be relatively higher than expected at 10–40% [1–3]. In Japan, on the other hand, only one case of the disease has been reported by Takami *et al.* [4] and there were no patients with a history of lithium administration among 145 patients treated surgically due to primary hyperparathyroidism at Shinshu University Hospital, Matsumoto, Japan in the 20 years from January, 1974 to December, 1993. In view of this, we investigated the serum calcium level and parathyroid function to find out whether hypercalcemia and hyperparathyroidism are rare or not patients taking lithium carbonate in Japan.

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Materials and Methods

The subjects were 13 (3 male and 10 female) patients receiving lithium and 19 (4 male and 15 female) healthy subjects not receiving it as controls. The mean ages of the two groups were 36

(18–59) and 42 (26–59) years, respectively. Control subjects were sex- and age-matched to patient subjects. The mean duration and dosage of lithium administration in the lithium administered group were 50 (2–108) months and 623 (400–800) mg/day. The mean serum lithium level in the lithium administered group was 0.49 (0.13–0.79) [mEq] (therapeutic dose: 0.60–1.20). Serum urea nitrogen and creatinine were measured in all the subjects to confirm that they were within the normal range. Informed consent was obtained from each subject.

Serum ionized calcium (Ca^{++}) [mEq/*l*] (normal range: 2.27–2.63), measured by SERA 252 (Horiba, Tokyo, Japan), was assessed in all the subjects. Serum parathyroid hormone (PTH), measured by highly sensitive PTH-RIA kit (Yamasa, Tokyo, Japan) [pg/m*l*] (normal range: 150–500), consisting of PTH antiserum (CH9), ^{125}I labeled Tyr^{42} hPTH (43–68) and synthetic hPTH (1–48) as standard, was assessed in all the subjects. Blood for determination of serum Ca^{++} levels was collected into vacuum tubes containing paraffin. Urinary calcium [g/day] (normal range: 0.1–0.3) and cyclic AMP (cAMP) [μmol/day] (normal range: 1.8–6.3) were measured in 5 out of 13 patients in the lithium administered group. Moreover, in 10 out of 13 patients in the lithium administered group and all the control subjects, cervical ultrasonographic examination was performed by means of a real-time electronic scanner with a 7.5 MHz transducer (TOSHIBA SSA-260A, Tokyo, Japan) to detect swelling of the parathyroid gland.

These results were analyzed by Student's *t*-test. All values were expressed as the mean ± SD.

Results

Mean serum Ca^{++} levels were 2.66 ± 0.09 mEq/*l* in the lithium administered group and 2.57 ± 0.08 mEq/*l* in the control group. The former value was significantly higher than the latter ($P<0.02$) (Fig. 1). Mean serum PTH levels were 324.4 ± 88.9 pg/m*l* in the lithium administered group and 297.5 ± 115.2 pg/m*l* in the control group. There was no significant difference (Fig. 2). Lithium administered and control groups were not clearly divided in plotting the serum PTH *vs.* Ca^{++} levels (Fig. 3).

We next divided the patients in the lithium administered group into two groups consisting of those given lithium for less than 36 months and

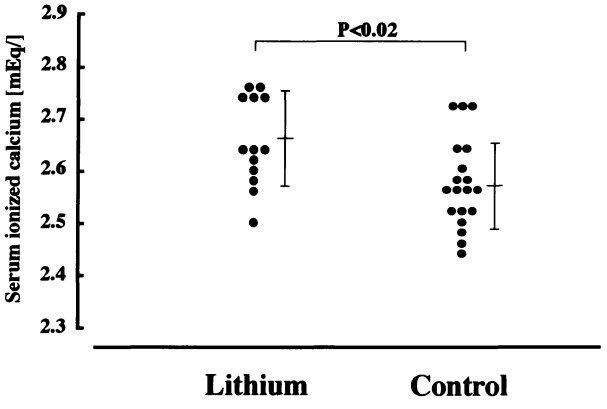

Fig. 1. Serum ionized calcium (Ca^{++}) levels in lithium administered and control groups. Values are the mean ± SD. The mean serum Ca^{++} level in the lithium administered group is significantly higher than that in the control group ($P<0.02$).

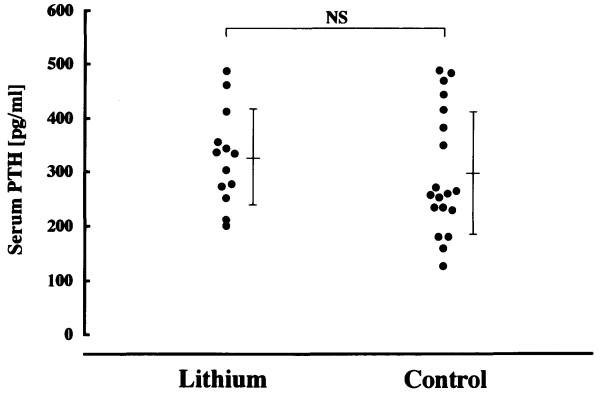

Fig. 2. Serum PTH levels in lithium administered and control groups. Values are the mean ± SD. There is no significant difference between the two groups in the serum PTH level.

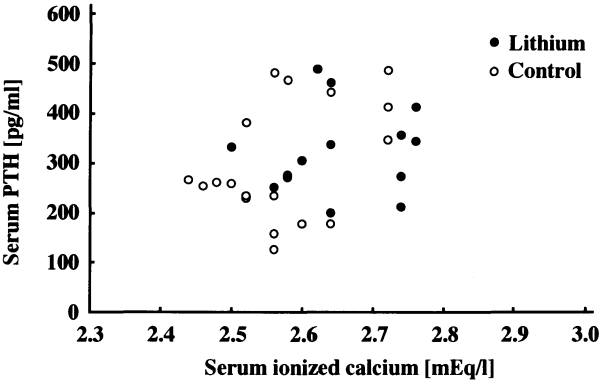

Fig. 3. Plot of serum PTH *vs.* ionized calcium (Ca^{++}) levels in individuals with lithium administered (closed circle) and control (open circle) groups. The two groups were not clearly divided.

those given the drug for 36 months or longer. Mean serum Ca^{++} levels were 2.68 ± 0.07 and 2.63 ± 0.09 mEq/*l*, respectively, while mean serum PTH levels were 325 ± 97.5 and 323.9 ± 88.7 pg/m*l*, respectively. Neither parameter showed any significant difference (Fig. 4). There was no correlation between the duration of lithium administration and the serum Ca^{++} or PTH level (Fig. 5).

The mean urinary calcium level was 0.08 ± 0.03 g/day and this was below the normal range. The mean urinary cAMP level was 2.14 ± 0.78 μmol/day and this was within the normal range.

A parathyroid cyst was found in one of ten patients in the lithium administered group which received cervical ultrasonographic examination. In this case, cystectomy was performed later on for histopathological confirmation. The parathyroid gland excised at the operation as a normal control was histopathologically normal, but no swelling of the parathyroid gland was observed in any of the other nine patients in the lithium administered group or in any of the control subjects.

Discussion

According to Akerstrom *et al.* [5], the incidence of abnormal parathyroid gland in Europe and America was 9.4% (41 out of 422 cases autopsied in Sweden). In contrast, the incidence of abnormal

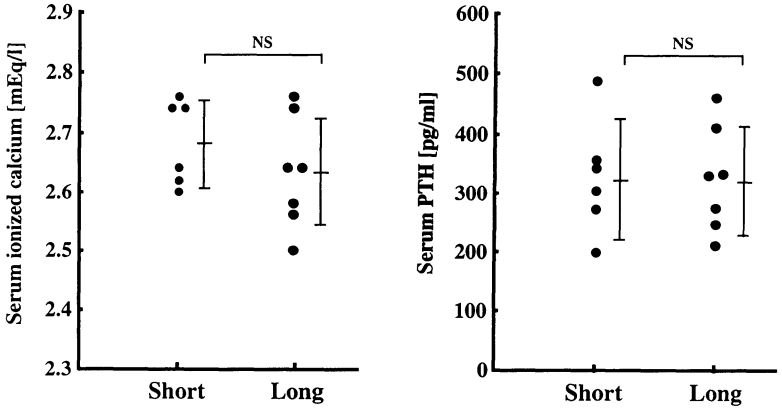

Fig. 4. Serum ionized calcium and PTH levels in the patients given lithium for less than 36 months and those given it for 36 months or longer. Values are the mean ± SD. Neither parameter shows any significant difference.

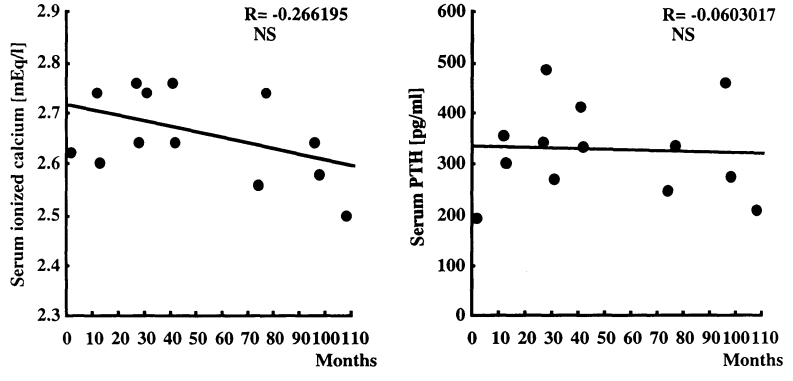

Fig. 5. Correlation between the duration of lithium administration and serum ionized calcium (Ca^{++}) and PTH level. There is no correlation between the duration and serum Ca^{++} or PTH level.

parathyroid gland in Japan was 1.3% (8 out of 614 cases) according to the study by Nobori *et al.* [6] of autopsied cases, and the number was reduced to 0.2% (1 out of 614 cases) when Akerstrom *et al.* reexamined the cases [7]. Nobori *et al.* have been increasing the number of subjects and the latest statistics indicate that the incidence of abnormal parathyroid gland is 0.13% (2 out of 1500 cases) [7]. In any case it is inferred that the incidence of abnormal parathyroid gland in Japan is distinctly lower than that in Europe and America. When the incidence of hyperparathyroidism in patients given lithium in Japan is compared with that found in European or American reports, it seems necessary to take into consideration that background factors in the populations are different, in other words, that the absolute number of hyperparathyroidism cases in Japan is small.

If lithium initiates hyperparathyroidism, its histological type is expected to be hyperplasia but its histological type becomes adenoma provided that lithium promotes hyperparathyroidism [8]. When we consider that adenoma is found in a relatively large number of the cases with the disease in literature [2], lithium is supposed to promote rather than initiate the disease [9]. Provided that lithium promotes proliferation of a nodular lesion originally present in the parathyroid gland leading to clinical hyperparathyroidism [9], it is reasonable to consider that the incidence of hyperparathyroidism accompanying lithium administration in Europe and America is higher than that in Japan due to the originally high incidence of nodular lesions in the parathyroid gland in those areas.

Abnormality in endocrine organs accompanying lithium administration is said to derive from suppression of cAMP by lithium and this fact is in accord with the findings in hyperparathyroidism accompanying lithium administration [2, 10, 11].

In the present study, we selected highly sensitive PTH as an indicator in the parathyroid hormone assay. Plural assays were impossible due to economic circumstances. The intact PTH widely used in recent years is a two-site immunoradiometric assay with antibodies anti-PTH 1–34 and 39–84. Its sensitivity is higher than that of the highly sensitive PTH assay recognizing 43–68. However, it is difficult to measure 1–34 when secretion is low due to its short serum half life, and it has weak points in storage and handling after blood collection as well as in that it is directly influenced by the pulsating nature of PTH secretion [12]. If a PTH assay is chosen for the purpose of ascertaining the difference between normal and hyperparathyroidism, the highly sensitive PTH assay seems to be the most suitable, as the difference is amplified by measuring various fragments provided that renal function is normal.

In the present study, no distinct hyperparathyroidism was found among the patients in the lithium administered group. There was no significant difference between the serum PTH levels in the lithium administered and control groups. The serum Ca^{++} level was significantly higher in the former than the latter group and was therefore worth noting. The mean urinary calcium level in the lithium administered group was below the normal range.

As for hypercalcemia due to lithium administration, the mechanism of its development has not yet been elucidated, but in ordinary primary hyperparathyroidism there is hypercalciuria, and the symptoms caused by lithium administration which accompany hypocalciuria, and therefore, lithium is supposed not only to activate the parathyroid gland but also to affect the renal tubules directly without the intermediation of the parathyroid hormone. The features of the disease are said to be similar to those of familial hypocalciuric hypercalcemia [13, 14].

It was deduced from the results of the present study that one of the causes of hypercalcemia is the direct action of lithium on the renal tubules, because none of the patients developed hyperparathyroidism even though they had hypocalciuria.

Supposing that lithium reacts antagonistically with the calcium sensor, it is considered that the effect of lithium on the calcium sensor in the renal tubules increases the reabsorption of calcium and induces hypocalciuria leading to hypercalcemia, whereas its effect on the calcium sensor in the parathyroid gland raises the set point for calcium and induces an increase in PTH leading to hypercalcemia [11, 15, 16].

It is said that in the initial stage of hypercalcemia, the serum calcium level returns to normal following the withdrawal of lithium administration, but when hyperparathyroidism develops, hypercalcemia becomes irreversible, exceeding a certain point, and surgical excision of the abnormal parathyroid gland becomes unavoidable [1–4, 8, 10, 11].

Although it seems difficult to conclude the present theme in a whole manner, lithium administration does affect calcium metabolism in patients in Japan. Hypercalcemia seems to be one of the complications needing attention at the time of lithium administration and hyperparathyroidism is another. A detailed study on the mechanism of development is necessary.

Acknowledgments

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