Effect of propranolol on secondary hyperparathyroidism in chronic renal failure (CRF) patients on iterative hemodialysis (HD)

F. Carrera, A. Vaz, I. Rodrigues, J. Vinhas*

Resumen

Se han estudiado 47 pacientes en programa de hemodiálisis para evaluar el efecto del propranolol sobre el hipoparatiroidismo secundario. Se han comparado dos grupos: Grupo 1, de 13 pacientes bajo tratamiento con propranolol, y Grupo 2, de 34 pacientes a los que nunca se había prescrito tratamiento con betabloqueantes durante su estancia en hemodiálisis. Ambos grupos fueron estudiados con respecto a las siguientes variables: Edad, duración de la hemodiálisis, calcio, fósforo, aluminio y calcitonina. A todos los pacientes se les practicó una radiología de las manos. Se encontró que los valores de parathormona (PTH) y fosfatasa alcalina (AP), así como el grado de resorción endo y perióstica no tenían diferencias estadísticamente significativas entre los dos grupos. Concluimos que la medicación con propranolol no parece ser una forma de tratamiento efectiva en el hipoparatiroidismo secundario.


Introduction

In addition to the extracellular calcium concentration, many other factors may affect parathyroid gland secretion. These include a variety of cations and anions, bioamines, prosta glandins, peptic hormones and vitamin D metabolites (1).

Direct evidence of B-adrenergic receptors in bovine parathyroid cells (2) and the increase in parathormone secretion experimentally induced by sympathomimetic agents (2, 3) have led various authors (4) to investigate the possible beneficial effects of B-blockers in secondary hyperparathyroidism.

The present study evaluates secondary hyperparathyroidism in 2 groups of dialysis patients. Thus, the hormonal expression (serum levels of immunoreactive parathyroid hormone), the biological activity (serum levels of alkaline phosphatase) and the radiological evidence (periosteal and endosteal resorption) of secondary hyperparathyroidism were assessed in these two groups of uraemic patients. The first group was treated with propranolol and the second one used as control had never been submitted to any B-blocking medication.
Subjects and methods

47 uremic patients (creatinine clearance < 3 ml/min) undergoing maintenance hemodialysis (HD) were studied. These patients had a mean age of 46.0 ± 13.2 years and a mean permanence under HD of 40.2 ± 23.6 months.

They were dialyzed from 12 to 15 hours a week. Hollow fiber dialyzers (1 m² area), dialysate containing 1.75 mmol/l of calcium and a mean dose of 6.000 U of heparin per HD session were utilized.

No patient was treated either with cimetidine of vitamin D metabolites. No patients had parathyroidectomy or bilateral nephrectomy. The oral dose of aluminum hydroxide prescribed was depend on the monthly serum levels of phosphorus and calcium.

Pre-dialysis blood samples were taken for the following biochemical determinations:

- By the colorimetric method: calcium (2.0-2.6 mmol/l); phosphorus (0.8-1.6 mmol/l); alkaline phosphatase (18.38 U/l).

- By radioimmunoassay utilizing an antibody which primarily recognized the carboxylic terminal fragment: Parathyroid hormone (0.4-1.5 ng/ml); calcitonin (< 80 pg/ml).

- By flameless atomic absorption spectrophotometry: Aluminum (< 20 mcg/l).

(Figures in brackets represent laboratory reference values).

Every patient had X-ray of the hands on standard conditions, i.e. with the same focus-object distance, the same type of X-ray film and using the same developing technique. The assessment of endosteal resorption was done by the measurement of the metacarpal index (5) of the second metacarpal bone of the hand not affected by vascular access; in the event of a history of accesses in the both limbs, the right hand was selected. The radiological evaluation, at midshaft, of total bone width and marrow-cavity width was conducted by three different observers; the final result being the mean value of the observations made. For periosteal resorption three observers analyzed the outlines of the middle phalanges of the II, III and IV fingers of the both hands utilizing an optical lens which had a magnifying rate of about 3 times the natural X-ray image. Classification of resorption was graded, in accordance with Meema (5) as follows:

- Grade 0 normal: smooth middle phalangeal outlines, including slightly undulating surfaces.

- Grade 1: Fuzziness of serrations of the periosteal outline at the basal third of the phalanx. This is a normal variant, and although occurring more frequently on chronic renal failure patients than in normals, is not clearly diagnostic of hyperparathyroidism and may be considered a borderline abnormality.

- Grade 2: Fuzziness or serrations involving the middle or distal portions of the middle phalangeal surfaces. This grade represents evidence of hyperparathyroidism. In borderline cases (grade 1 versus grade 2 +), the presence of terminal phalangeal tuft changes, phalangeal periosteal neostosis, or both, favors a grade 2 + classification.

- Grade 3: Involvement of bones other than the middle and distal phalanges by subperiosteal or subchondral resorption.

Of the 47 patients, 13 were under propranolol on an average dose of 80 mg per day and with an average medication duration of 33 months (see the table I).

<table>
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<th>TABLE I</th>
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<td>Group of 13 patients medicated with propranolol due to dialysis-resistant arterial hypertension</td>
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<tr>
<td>Age (years)</td>
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<td>Duration of HD (months)</td>
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<tr>
<td>Daily intake of propranolol (mg)</td>
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<td>Mean time on propranolol (months)</td>
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<th>TABLE II</th>
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<td>Factors that might influence the evolution of secondary hyperparathyroidism</td>
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<tr>
<td>Age (years)</td>
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<td>Duration of HD (months)</td>
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<tr>
<td>Ca (mmol/l)</td>
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<tr>
<td>Pi (mmol/l)</td>
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<td>CT (gg/ml)</td>
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<td>(Al (mcg/l)</td>
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The remaining patients, to whom no B-blockers have been administered during dialysis, formed the control group and were selected out a pool of 150 dialyzed patients to match propranolol-treated patients for mean age, mean duration of HD-treatment and mean serum levels of calcium (Ca), phosphorus (pi), calcitonin (Ct) and aluminium (Al) (table II).

For statistical analysis purposes, the Student test for unpaired data, the Chi-square test and the linear regression analysis have been used.

Results

In the propranolol-treated patients the mean alkaline phosphatase values were within the upper limit of the normal variation (38.0 ± 25.5 U./L). Although control-patients had a higher average (56.7 ± 54.8 U./L) was not statistically different from propranolol-treated patients (t = 1.178; p = n.s.).

In the figure 1, a great scattered of A.P. values can be observed in both groups.

Mean values of iPTH in propranolol-treated patients though higher normal values were not significantly different (t = 0.776; p = n.s.) from control group (figure 1).

An attempt was made to detect any correlation between the iPTH and the propranolol prescribed dose (r = 0.189; p = n.s.) and between iPTH and the medication time with propranolol (r = 0.348; p = n.s.). No significant correlation was noted.

X-ray evaluation revealed neither endosteal resorption (metacarpal index: Group 1 = 0.57 ± 0.11; Group 2 = 0.53 ± 0.11; p = n.s.) nor periosteal resorption (table III) were significantly different between the two groups.

There was a significant correlation between periosteal resorption and iPTH, both in propranolol-treated patients (r = 0.555; p < 0.05) and in control patients (r = 0.452; p < 0.01).

| TABLE III |
| Distribution of patients according to periosteal resorption |
| Grades | 1 | 1+ | 2+ | 3+ |
| Group 1 | 4 | 6 | 2 | 1 | n = 13 |
| Group 2 | 6 | 11 | 11 | 6 | n = 34 |

x² = 2.86; p = n.s.

Discussion

Renal osteodystrophy is usually present in most patients with chronic renal failure. Morphologically it consists of two patterns: osteitis fibrosa and osteomalacia.

It is believed that most cases of osteomalacia are due to aluminium intoxication (6, 7), whilst the condition of high bone turnover of osteitis fibrosa is due to secondary hyperparathyroidism (8). Generally, renal osteodystrophy consists of combinations in variable percentage of osteitis fibrosa and osteomalacia, the morphological aspect being independent of the bone mass which in a given individual might be reduced, normal or increased (9).

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**Fig. 1.** Blood levels of alkaline phosphatase and immunoreactive parathyroid hormone (carboxil terminal) were not significantly different from one group to the other.
Some authors (10) have suggested that secondary hyperparathyroidism might play an important role on divalent ion homeostasis since the earliest stages of renal failure. Secondary hyperparathyroidism would thus begin with early renal failure and hypocalemia playing a fundamental part on its development.

Another mechanism which may interfere with the secretive activity of the parathyroid gland is its adrenergic tone, made evident by a rich innervation of parathyroid glands by sympathetic nervous system (11). Also, parathyroid hormone secretion increases in response to B-adrenergic catecholamines both in vivo and in vitro (3, 12). In addition, B-adrenergic receptors, type B2, have been identified in isolated bovine parathyroid cells, with an increase in the intracellular production of cAMP in response to adrenergic stimulation (2). Furthermore, in man, stimulus to endogenous epinephrine release, such as a insulin-induced hypoglycemia, has produced increases in serum PTH (1), whilst the i.v. administration of B-blockers is associated with a decrease in those levels (12).

Nevertheless, the physiological importance of B-adrenergic catecholamines on the regulation of PTH release is still controversial (1, 11), and of lesser importance as compared with the control by serum calcium. Thus, glandular release of PTH induced by B-adrenergic agonists is enhanced by hypocalemia and suppressed by hypercalcemia (1, 3, 11). Also, B-adrenergic blocking of the parathyroid gland doesn’t prevent it from responding.

In contrast to the marked stimulation of hypocalemia, the response of PTH to epinephrine and to isoproterenol is transient suggesting that parathyroid cells become refractory to prolonged administration of catecholamines (11).

Retrospective and prospective studies (4, 13, 14) have shown PTH serum levels significantly lower in dialyzed patients treated with propranolol than in untreated patients. It has also been established that the PTH serum levels inversely correlated with the administered dose. These findings had led some investigators (4, 13, 14) to propose therapeutic trials with propranolol on patients candidates to parathyroidectomy. However, aside from changes in PTH levels induced by B-blockers, it is important to assess its clinical use in renal osteodystrophy. It is equally important to evaluate to what extent the medication can be sustained in hemodialyzed patients (non hypertensive and without angina pectoris), inasmuch as its cardiovascular effects may interfere with the hemodynamic stability needed for a correct maintenance hemodialysis treatment.

In the present study we have evaluated two groups of patients, matched for variables supposedly determinant in the evolution of renal osteodystrophy. These groups only differed in the fact that one group was taking propranolol. After almost three years of HD, the group treated with propranolol has not shown serum levels of PTH and alkaline phosphatase significantly different from those of the control group. Furthermore we were not able to find any difference between the two groups with respect to periosteal and endosteal resorption. We have restricted the radiological evaluation to hand radiography because changes in the hand bones (and soft tissues) frequently suggest the diagnosis of a generalized bone disease long before abnormalities appear in the other skeletal areas (5). In addition, when performed with optical magnification, diagnosis sensitivity is considerably increased. In our study we could also detect a correlation between serum PTH levels and periosteal resorption.

Pizzarelli et al. (16), in a study with a similar methodology, but having performed iliac-crest bone biopsies, have established that histomorphometric indexes of secondary hyperparathyroidism did not differ from one group to another.

Thus, we have to conclude that continued medication with propranolol doesn’t seem to be an effective form of therapy in secondary hyperparathyroidism.

Supposedly this conclusion probably agrees with the physiological idea that the adrenergic tone of the parathyroid gland serves mainly to modulate PTH secretion, which is essentially determined by the extracellular concentration of calcium (1, 3, 11).

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References


