BLOCKERS OF BETA AND H₂ RECEPTORS AND SECONDARY HYPERPARATHYROIDISM OF URAEMIA

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Summary

The suppressive effect on PTH secretion of propranolol, a β1 and β2 blocker, and that of atenolol a specific β1 betablocker was compared in 24 uraemic patients not yet on dialysis in a cross over study. Although plasma PTH concentrations were comparable, plasma bicarbonate was higher with propranolol suggesting that the initial suppression of PTH secretion by propranolol was greater as a higher bicarbonate should lead to lower ionised calcium.

The suppressive effect of cimetidine on PTH secretion was assessed in 12 patients on chronic haemodialysis. In the seven compliant patients there was no change in N and C terminal plasma PTH values but plasma calcitonin concentrations significantly decreased with cimetidine and returned to initial values after cimetidine was discontinued.

Introduction

Ionised calcium and magnesium are the major determinants of parathyroid hormone (PTH) secretion. Recent studies have indicated that beta-receptors and H₂ receptors are also involved [1–3]. On the basis of the two following independent studies, their role will be discussed mainly from the point of view of the treatment of the secondary hyperparathyroidism of uraemia.

Therapeutic value of cardioselective and non-cardioselective betablockers in uraemic hyperparathyroidism

The presence of beta-receptors on parathyroid cells has been demonstrated by radioligand studies [1]. Their pathophysiological role in secondary hyperparathyroidism of uraemia is suggested by the fact that chronic oral administration of the betablocker propranolol is effective in lowering increased PTH concentrations in both retrospective [4–6] and prospective studies [7,8]. However,
while acute suppression of PTH hypersecretion in uraemic patients is readily obtained with intravenous administration of propranolol, a $\beta_1$ and $\beta_2$ beta-blocker, it is not obtained with intravenous administration of metoprolol a specific $\beta_1$ blocker [9]. Therefore the question arises as to whether or not there is a difference in chronic suppression of PTH secretion by cardioselective and non-cardioselective betablockers. Therefore in this study we compared plasma PTH in a randomised cross over study in uraemic hypertensive patients while they were alternatively treated by propranolol and by atenolol a specific $\beta_1$ blocker.

Patients and methods

Twenty-four uraemic hypertensive patients not yet on dialysis (SCr = 3.5mg/dl) were selected because of their willingness to co-operate and because they had no overt bone disease (normal bone X-rays and normal alkaline phosphatase). In a randomised cross over study, they received alternatively for two months, propranolol (155 ± 75mg/day) and atenolol (125 ± 53mg/day) to achieve the same control of their hypertension. During the study there was no other change in their treatment (diuretics, diet, 3g calcium carbonate supplement, phosphate binders). None received simultaneously cimetidine or vitamin D.

At the end of each therapeutic period the following parameters were measured: blood pressure, heart rate, plasma concentrations of propranolol or atenolol, PTH (with N and C terminal specific antibodies, methods of, respectively, Desplan [10] and Gueris [11]) 25 OH vitamin D, calcium, phosphate, electrolytes, urea and creatinine.

Results

Table I shows that the control of hypertension and heart rate was comparable during the two periods and that the drug concentrations obtained were in the

| TABLE I. Comparison of propranolol and atenolol in the control of hyperparathyroidism in uraemic (mean ± SEM) |
|---------------------------------------------------------------|--------------------------|--------------------------|
| Plasma concentrations of                                    | Propranolol              | Atenolol                 |
| PTH C terminal ng/ml                                          | 18 ± 4.5                 | 18.5 ± 4.5               |
| PTH N terminal ng/ml                                          | 0.14 ± 0.04              | 0.12 ± 0.04              |
| 25 OH vit D ng/ml                                              | 35 ± 18                  | 29 ± 14                  |
| Calcium mg/dl                                                  | 9.5 ± 0.2                | 9.4 ± 0.2                |
| Phosphate mg/dl                                                | 3.7 ± 0.4                | 3.7 ± 0.4                |
| Bicarbonates mEq/L                                             | 29 ± 1.3                 | 27 ± 1.8*                |
| Protein g/L                                                    | 71 ± 2                   | 70 ± 1.5                 |
| Drug μg/L                                                      | 129 ± 25                 | 722 ± 120                |
| Supine BP mmHg                                                 | 144 ± 5/95 ± 5           | 141 ± 5/93 ± 5           |
| Supine heart rate beat/mn                                       | 68 ± 10                  | 65 ± 10                  |

* p < 0.05

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usual therapeutic range suggesting good compliance. There was no significant
difference between the two drugs as regards the plasma concentrations of all
the parameters measured except bicarbonate which was significantly higher
with propranolol.

Discussion

The concentrations of plasma PTH were not different with the two drugs indi-
cating that chronic control of hyperparathyroidism in uraemic patients not yet
on dialysis is comparable with atenolol and propranolol. However, since the
plasma bicarbonate was higher with propranolol this suggests that, initially,
propranolol more efficiently suppresses PTH secretion. This would lead to an
increase in bicarbonate reabsorption and therefore to the higher plasma bicarbo-
nate concentrations. This would decrease ionised calcium since there was no
difference in plasma calcium, phosphate and protein there must have been a
secondary stimulation of PTH secretion to bring the PTH concentrations to
their initial values, i.e. a value comparable to that observed on atenolol.

Stronger initial suppression of PTH with propranolol is compatible with the
presence of both β1 and β2 receptors. Although there is no in vitro study of beta-
receptors in uraemic parathyroid glands, Brown has shown that there are both
β1 and β2 receptors on parathyroid adenoma cells [2].

From a practical point of view, in uraemic patients not yet on dialysis
there is no reason to prefer propranolol to atenolol for the control of hyper-
parathyroidism. In patients on chronic haemodialysis with negligible renal
function, differences in bicarbonate reabsorption are unlikely. Therefore a
possible greater initial suppressive effect of propranolol on PTH secretion
compared with a cardioselective betablocker would not be masked by higher
bicarbonate values and would lead to lower plasma PTH. A less marked effect
of cardioselective betablockers on PTH secretion in haemodialysed patients
would explain why we have found no significant difference in plasma PTH
between sequential treatments with metoprolol, alphamethyldopa and clonidine
whereas plasma calcium was higher with clonidine [12].

The clinical significance of PTH suppression by betablockers in uraemia has
been suggested up to now only by retrospective studies comparing two groups of
patients on chronic haemodialysis which differed only by the use of propranolol
[4, 5]. The propranolol group had not only lower PTH values but also lower
alkaline phosphatase and less severe bone disease. In the study of Surian [6] the
PTH concentrations were comparable but the alkaline phosphatases were lower
in the propranolol group.

In summary prospective studies are still needed to prove the clinical usefulness
of controlling hyperparathyroidism in uraemia by betablockers in addition to the
other important measures aimed at overcoming the trend to decreased ionised
calcium (control of hyperphosphataemia, correction of negative calcium balance
by high dialysate calcium, and/or CaCO₃ supplements, and/or active vitamin D
metabolites).
Therapeutic usefulness of cimetidine in uraemic hyperparathyroidism

H₂ receptors have been demonstrated by in vitro studies on dispersed parathyroid cells culture [2]. Their pathophysiological role in the secondary hyperparathyroidism of uraemia has been suggested by decrease of C terminal PTH, in uraemic patients [13–15]. These results have however not been confirmed by Vanherweghem [16]. When N terminal PTH assays were used, either no change [17] or even an increase [15] in PTH concentrations were reported. Plasma calcium has been reported to remain unchanged although Lanier [18] has reported correction by cimetidine of two cases of hypercalcaemia due to hyperparathyroidism.

Because of these discrepancies, possibly explained by variability in PTH assay specificity, we have studied the effect of cimetidine on PTH in patients on chronic dialysis by using two PTH assays, C terminal [11] and N terminal [10]. Furthermore compliance of the patients was confirmed by measuring plasma concentrations of cimetidine. Plasma calcitonin was also measured since lack of calcitonin has been implicated in the pathogenesis of uraemic osteitis fibrosa [19] and since IV cimetidine in normals has been reported to decrease plasma calcitonin [20].

Patients and method

Twelve patients (six males, six females, aged 21 to 71 years) on chronic haemodialysis for more than 12 months received 200mg of cimetidine orally twice daily for one month. One month before and after cimetidine as well as during cimetidine there was no change in their treatment (dialysis schedule, phosphate binders, Ca supplement) and no vitamin D or betablockers were given. During the study the following parameters were measured every two weeks, before the first dialysis of the week: plasma cimetidine (HPLC method [21]) PTH with N and C terminal specific antibodies [10, 11], calcitonin [22], calcium and phosphate.

Results

Plasma cimetidine concentrations were measurable in only seven patients with individual values of 0.30 to 4.1mg/L (mean ± SEM: 1.50 ± 0.50mg/L) but undetectable in the five others.

In the group of the seven patients with good compliance there was no significant change in either C terminal or N terminal PTH values nor in plasma calcium. Plasma phosphate increased slightly during cimetidine and decreased after cimetidine discontinuation. Plasma calcitonin was initially undetectable in one case and remained so with cimetidine. In the six others it decreased significantly by 75 per cent with cimetidine and returned to initial values after cimetidine discontinuation (Figure 1).

In the group of the five non-compliant patients, none of the parameters changed significantly during the period of cimetidine prescription. The two groups of patients differed only as regards the variations of their plasma phosphate and calcitonin during cimetidine administration and discontinuation.
Discussion

At the dosage used, cimetidine does not decrease PTH concentrations in patients on chronic haemodialysis whereas it significantly decreases calcitonin. Since lack of calcitonin has been implicated in the pathogenesis of renal osteodystrophy, these results do not lead us to recommend cimetidine in the treatment of uraemic secondary hyperparathyroidism.

The response of PTH may be dose related according to Jacob [17] who achieved suppression by increasing cimetidine dosage from 600 to 900mg or even 1200mg/day. However Vanherweghem did not obtain PTH suppression at the dose of 1000mg/day. Although these dosages did not induce side effects in their studies, they are not recommended on a pharmacological basis since Larsson et al [23] have shown that in patients on chronic haemodialysis, 200mg twice daily resulted in persistent plasma concentrations above 0.5mg/L, a concentration which adequately suppresses gastric secretion in healthy subjects. We did not feel justified in giving doses higher than 400mg daily since mental confusion has been related to plasma concentrations above 1.25mg/L in uraemic patients treated with 1200mg daily [24].

The decrease in calcitonin is still more remarkable as cimetidine increases gastrin secretion and it is known that gastrin stimulates calcitonin secretion.

General conclusion

Whereas beta blockers, and more particularly non selective blockers such as propranolol, may have a clinical usefulness in the control of hyperparathyroidism in uraemia and may be therefore the drug of choice to treat hypertension in uraemic patients, cimetidine does not appear to be useful in this respect.
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References