ACUTE EFFECTS OF PROPRANOLOL AND METOPROLOL ON PLASMA CONCENTRATIONS OF PARATHYROID HORMONE AND CALCITONIN IN URAEMIC PATIENTS


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Summary

Nine uraemic patients not yet on dialysis received IV 1μg/kg/min of propranolol for 85 min after a priming dose of 1mg. Fifteen days later six of them received IV 1.2μg/kg/min of metoprolol after a priming dose of 1.2mg. Plasma concentrations of PTH and calcitonin decreased significantly with propranolol but not with metoprolol. No change was observed with either drug as regards plasma concentration of total and ionised Ca and PO₄. Heart rate was decreased similarly with both drugs.

We conclude that (i) propranolol acutely suppresses PTH and Calcitonin secretion in uraemic patients. This warrants further studies to assess its long term effects on the secretion of these hormones and on renal osteodystrophy; (ii) the contrast between the significant effect of propranolol and the lack of effect with metoprolol supports the concept that PTH and CT secretion are moderated through specific β2 receptors.

Introduction

Most uraemic patients suffer two potentially serious complications: hypertension and renal osteodystrophy. In about 20% of the hypertensive patients, the hypertension persists in spite of ultrafiltration, and hypertensive drugs must be added [1]. Renal osteodystrophy in patients on chronic haemodialysis is mainly due to osteitis fibrosa secondary to parathyroid hormone hypersecretion [2]. Deficient secretion of calcitonin has however also been recently incriminated [3].

Interactions between beta-adrenergic receptors and secretion of parathyroid hormone and calcitonin have been demonstrated. Thus, in vitro studies with radiolabeled hydroxybenzylpindolol [4] have clearly demonstrated the existence of beta adrenergic receptors in the parathyroid tissue. Furthermore since stimulation of PTH secretion and cyclic AMP was greater with isoproterenol than with epinephrine and greater with this latter than with norepinephrine, these receptors are of
beta 2 type [4]. Finally it has also been shown that propranolol prevents the increase of PTH secretion by catecholamines but not the increase induced by hypocalcaemia. The results of these in vitro studies were confirmed by in vivo studies in animals [5, 6]. Studies in man have however given inconsistent results [7–11]. As regards calcitonin secretion, direct evidence of beta 2 adrenergic receptors has not yet been given, but stimulation of calcitonin secretion by isoproterenol, epi-nephrine or salbutamol and the blockade of this stimulation by propranolol have been shown in vitro [12] as well as in vivo studies in animal [13, 14] and in normal man [15, 16]. In uraemic patients Heynen et al [16] have shown that propranolol could prevent the increase of calcitonin secretion induced by alcohol ingestion.

Thus in man, the data are contradictory and concern only propranolol but not the newer cardioselective betablockers. Because these latter may offer a few advantages over non selective ones (shorter titration duration, less frequent hypoglycaemia on dialysis and less bronchoconstriction [17]) their use is more and more often considered in the treatment of hypertension in uraemic subjects. Since uraemic patients also have secondary hyperparathyroidism, the effects of these two types of betablockers on PTH and calcitonin secretion may be of clinical relevance in the choice of antihypertensive therapy. We compared the acute effects of propranolol and metoprolol, a newer cardioselective betablocker, on the plasma concentrations of PTH and calcitonin in uraemic men.

Patients and Methods

Patients

Nine patients not yet on dialysis, with a mean serum creatinine (± SD) of 5.0 ± 2.6mg/dl, were chosen because of the absence of contraindications to the use of betablockers (asthma, cardiac-failure, PR interval > 0.20 sec, heart rate < 60/min) and their willingness to cooperate. Their mean age (± SD) was 29 (± 10) years. They were five men and four women. The nature of the nephropathy was chronic glomerulonephritis in five cases, congenital interstitial nephropathy in three cases and nephroangiosclerosis in one case. The patients had not taken betablockers for at least three weeks.

Design of the Study

Propranolol was administered IV using a priming dose of 1mg diluted in 20ml of isotonic glucose and then as a continuous infusion (Harvard pump) at the rate of 1μg/kg/min for 85 mins according to the protocol of Williams [8].

Metoprolol was administered according to the same protocol at a comparable betablocking dose of 1.2mg for the priming dose and 1.2μg/kg/min for the infusion. The two drug administrations were performed on the same patients 15 days apart in order to prevent any interference. Metoprolol was administered to six patients only.

Venous blood samples were taken into vacutainers before (TO) and 15 (T15), 30 (T30), 60 (T60) and 90 (T90) minutes after the priming dose for measurement
of plasma concentrations of total and ionised calcium, phosphate, bicarbonate, protein, pH and immunoreactive PTH and calcitonin.

Analytical Methods

Plasma calcium, phosphate, bicarbonate and protein were measured using an auto-analyser. The pH was measured with a radiometer pH meter. Ionised calcium was measured with the flow-through electrode Orion SS20. Our normal mean (± SD) is 2.08 (± 0.13 mEq/L) [18]. PTH was measured by radioimmunoassay using an N terminal specific antibody. This antibody was obtained in goats immunised with the synthetic fragment 1–34 of the PTH molecule according to the sequence of Niall [19]. The upper limit of normal is 0.45ng/ml. Calcitonin was measured with the homologous radioimmunoassay of Moukhtar [20]. The upper limit of normal is 0.70ng/ml.

Statistical Methods

The significance of the changes during betablocker administration was assessed with the Wilcoxon test for paired data. The comparison of the two drugs was made with the Wilcoxon test for non-paired data since complete data were not available for all patients with the two drugs.

Results

Effect on the Plasma Concentrations of PTH

Plasma concentration of PTH was 0.44 ± 0.12ng/ml before the administration of propranolol and 0.53 ± 0.23ng/ml before the administration of metoprolol. This difference was not significant. Figure 1 shows the percent changes of the plasma concentrations of PTH versus time zero (TO) after administration of the drugs. With propranolol there was a significant decrease (p < .02) of −54% ± 19 and −46% ± 15 at T15 and T30 whereas with metoprolol there was no significant change at any time, the greater decrease being −22% ± 27 at T60.

Effect on the Plasma Concentrations of Calcitonin

Plasma concentration of calcitonin was 0.24 ± 0.05ng/ml before the administration of propranolol, and 0.19 ± 0.04ng/ml before the administration of metoprolol. This difference was not significant. Figure 2 shows the percent changes of the plasma concentrations of calcitonin versus time zero (TO) after administration of the drugs. With propranolol, there was a significant decrease of −26% ± 10 at T15 (p < .02) and of −18% ± 15 at T60 (p < .05). With metoprolol there was no significant change at any time. The difference between the two drugs was significant at T60.

651
Figure 1. Percentage changes in PTH levels compared with the PTH level at time zero following the intravenous infusions of metoprolol (---) and propranolol (---). Significance of the difference versus time 0mn: * * p < 0.02. Difference between propranolol and metoprolol: NS

Figure 2. Percentage changes in CT levels compared with CT level at time zero following the intravenous infusions of metoprolol (---) and propranolol (---). Significance of the difference versus time 0mn: * * p < 0.02, * p < 0.05. Difference between propranolol and metoprolol: ◊ p < 0.05

652
Effects on the Other Parameters of Calcium and Phosphate Metabolism

There were no significant changes after administration of either propranolol or metoprolol in the plasma concentrations of total and ionised calcium, phosphate, protein and bicarbonate as well as in the pH. No difference was observed between the two drugs.

Effects on the Heart Rate

Initial heart rate was not different before the administration of either drug and both drugs induced a similar significant decrease in heart rate (75 ± 3 to 64 ± 2 for propranolol; 72 ± 3 to 64 ± 2 for metoprolol).

Discussion

In spite of the fact that all patients had moderate to severe renal failure, the mean plasma concentrations of PTH before administration of the drugs was only at the upper limit of normal. This fact is well known when PTH concentrations are measured with an N terminal specific antibody, whereas they are consistently well above the upper limit of normal when they are measured with a C terminal specific antibody [21]. However only N terminal specific radioimmunoassay is adequate to follow acute decreases in plasma concentrations because of the shorter half life of the N terminal fragments and of the native molecule which are measured by this assay. This is why we have chosen an N terminal specific radioimmunoassay and not a C terminal one, to study the changes of plasma concentrations of PTH during the 90 min following IV administration of betablockers.

The fact that PTH secretion is significantly suppressed by propranolol and not by metoprolol, is in agreement with the in vitro demonstration by Aurbach [4] that only beta 2 adrenoreceptors are found on the parathyroid cells. Similarly, the fact that plasma concentrations of calcitonin are significantly decreased by propranolol and not by metoprolol also suggests that calcitonin secretion is moderated by beta 2 adrenergic receptors. This is in agreement with the finding of Hsu and Cooper that salbutamol, a specific beta 2 adrenoreceptor stimulating agent, is able to stimulate calcitonin secretion.

Since propranolol acutely decreases plasma concentrations of PTH, it is important to assess its long term effect on PTH secretion in uraemic patients with hypertension resistant to volume depletion, and to compare this long term effect with that of other antihypertensive drugs like cardioselective betablockers, clonidine and alphamethylldopa. No such prospective study has yet been done. In a recent study [22] we have only compared in that respect metoprolol, clonidine and alphamethylldopa for six weeks in 13 haemodialysed patients and we have found no significant difference between the three drugs as regards the plasma concentrations of PTH, calcitonin and phosphate. Plasma calcium was however significantly higher with clonidine than with metoprolol suggesting a relatively greater suppression of PTH secretion with metoprolol. In their recent preliminary communication, Caro et al [23] have found that patients on chronic haemodialysis treated with propranolol had lower plasma concentrations of PTH and alkaline
phosphatase and a lower incidence of radiological bone disease than the patients treated in the same centre but not receiving betablockers. Since the doses of dihydrotachysterol and of phosphate binders were comparable in both groups [24], the fact that lower alkaline phosphatase and a lower incidence of radiological bone disease was associated with lower PTH levels, suggests that the probably simultaneous decrease of calcitonin secretion has no serious noxious effect despite the observations of Kanis et al suggesting the contrary [3].

However Caro’s study is a retrospective one and obviously long term prospective studies are needed to assess the clinical relevance of the additional potential suppression of PTH secretion by propranolol or other non selective betablockers in preventing or reversing renal osteodystrophy in uraemic patients. If this appears to be important, non selective betablockers would then be the drugs of choice to treat the hypertension of uraemic men resistant to volume depletion.

References

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Open Discussion

BRANCACCIO (Italy) We should consider the plasma level of propranolol in relation to the pharmacological effect of the drug. In fact you mentioned that the pharmacokinetics of propranolol are very different if you have normal GFR, moderate renal insufficiency or chronic renal failure on dialysis.

The second point is that my experiments performed in uraemic patients on dialysis and with normal volunteers showed in a very acute experiment over 2 hours an unexpected increase of calcitonin in comparison with the propranolol level.

FOURNIER I noticed that your results on CT secretion are in contradiction with ours. I don’t know why. But it is true that you have a significant increase. It would not fit with all the theoretical ideas on CT secretion.

BRANCACCIO Yes, I know that. I know that my results are against the traditional physiological regulation of calcitonin release. Anyway, after 7 days of chronic therapy, calcitonin decreased and probably there is a difference between acute experiments and chronic experiments. I do not know exactly the reason why.

RUMPF (Göttingen) Do you also have measurements of the changes in PTH and calcitonin in patients with renal failure during chronic propranolol treatment?

FOURNIER That is under study. I have not yet the results.