EFFECTS OF ACUTE AND CHRONIC RANITIDINE ADMINISTRATION ON RENAL FUNCTION AND PARATHYROID ACTIVITY IN CHRONIC RENAL FAILURE

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Summary

In 11 patients with advanced renal failure, chronic treatment with ranitidine decreased plasma immunoreactive parathormone (PTH) without affecting phosphate reabsorption or urinary excretion of cyclic AMP. No significant changes in glomerular filtration rate and in urinary excretion of electrolytes were evident.

Introduction

Secondary hyperparathyroidism is a frequent complication of advanced renal failure. If calcium is the major factor involved in the regulation of parathyroid secretion, the influence of other factors such as histamine has been established in vitro. Controversy exists as to whether cimetidine reduces PTH secretion [1]. This study addresses the question of the influence of acute and chronic administration of ranitidine, a new H₂ antagonist with few side effects [2], on renal function and PTH release in advanced renal failure.

Methods

Eleven stable patients (mean age: 53 ± 11, BW = 62.2 ± 10.5) were given ranitidine, 150mg twice a day for 28 days, without other changes in treatment. Renal failure (creatinine clearance: C Cr = 0.45 ± 0.29ml/sec) was due to chronic glomerulonephritis (n = 3) interstitial nephritis (n = 2) or polycystic disease (n = 6). The patients were studied before (study A) and on the last day of treatment (study B). After a control period, ranitidine 150mg was given orally with 300ml of water, and urine was further collected during period I (0 to 90 min) and II (90 to 180 min). Blood was drawn at 0 and 180 min. The following parameters were measured: urinary excretion of Na, K, Ca, P, uric acid, urea, creatinine, cyclic AMP (normal values: 2.95 ± 0.48mM%/ml GFR), osmolality; blood electrolytes, creatinine, osmolality, ranitidine (HPLC) and immuno-
reactive PTH (iPTH, using a 'C terminal' antibody and MRC standard, CEA – IRE kit, normal range: 450–1450ng/L). Blood calcium was corrected for protein content according to Parfitt and the renal threshold concentration for phosphate (TmP/GFR) calculated from Walton's nomogram. The influence of treatment was assessed by comparing (non parametric tests on paired values) identical periods in study A and B (chronic administration) or the two consecutive periods on the same study (acute effects).

Results

Chronic administration

After 28 days of treatment, no significant changes were observed for weight, mean arterial pressure, blood creatinine, urea, electrolytes, for the values of creatinine, uric acid and osmolar clearances and urinary excretion rates of electrolytes. Blood iPTH was significantly decreased (p<0.05) while urinary cAMP and TmP/GFR showed no significant changes (Table 1).

<table>
<thead>
<tr>
<th>TABLE 1. Effects of chronic treatment with ranitidine</th>
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<tr>
<td>Plasma</td>
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<td>Creatinine mmol/L</td>
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<td>Urea mmol/L</td>
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<td>Calcium mmol/L</td>
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<td>Phosphorus mmol/L</td>
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<td>iPTH ng/L</td>
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<td>Ranitidine microg/L</td>
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<td>Creatinine clearance ml/sec</td>
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<td>U cAMP mmol % ml GFR</td>
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<td>TmPO4/GFR mmol/L</td>
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(*) p<0.05; (**) p<0.01

Acute studies

In study A, Cr remained stable in period I and decreased in period II (0.45 ± 0.31 and 0.39 ± 0.28ml/sec). The urinary excretion of all electrolytes (either expressed as excretion rates or as the concentration ratio to creatinine) showed no consistent changes. Blood levels of iPTH did not vary (2759 ± 1798 and 2758 ± 1705ng/L. Urinary cAMP and TmP/GFR remained stable. Similar findings were obtained in study B with a 16 per cent decrease in C Cr and no significant variations in other parameters.
Plasma ranitidine values were lower in study A (0 at 0 min and 895 ± 293 μg/ml at 180 min) than in study B (330 ± 221 and 1082 ± 400μg/ml), (p<0.01).

Discussion

In this study, chronic treatment with ranitidine decreased plasma iPTH without affecting the commonly used indexes of PTH action on the kidney. Interference of ranitidine with the assay can be excluded from the unchanged values of PTH at 180 min when plasma ranitidine is markedly elevated. Such a discrepancy is common [3] and relates to the well known problems of PTH measurements in uraemia [4]. The ‘C terminal’ immunoreactivity is a better index of the parathyroid activity than a single determination of the intact hormone even given the prolonged half life of ‘C fragments’ in renal failure. Assaying samples from patients given cimetidine with two different assays, Jacobs et al found no decrease with an assay measuring ‘intact hormone’ and a significant decrease in ‘C terminal immunoradioactivity’ [5]. An increase in the clearance of ‘C fragments’ or a decreased generation of these fragments from intact PTH is conceivable [6] but remains speculative. On the other hand, the reliability of urinary cAMP and phosphate transport in advanced uraemia as index of parathyroid activity is questionable: plasma cAMP is elevated in this setting and urinary cAMP (even expressed as % ml GFR) does not reflect perfectly nephrogenic cAMP [7]: several factors other than PTH can influence phosphate transport in uraemia. However the issue is not yet settled since Cunnighan et al, using three different assays found no decrease in iPTH in dialysed patients treated with ranitidine [1]. The absence of acute effect on PTH in our patients is in contrast with results obtained in subjects with normal renal function but could be explained either by the prolonged half life of C terminal fragments in renal failure or by the use of different routes of administration [8]. As already reported no dramatic changes occurred in plasma calcium or phosphate, data consistent with a direct effect of the H₂ antagonists on parathyroid cells [1].

The assessment of drug action on kidney function is mandatory in renal failure. Cimetidine reduces creatinine clearance, without affecting glomerular filtration rate, an effect due to inhibition of its tubular secretion [9]. Ranitidine has no such effect [2]. Our results confirm the lack of effect of a chronic treatment on renal function. Therefore, the slight decrease in creatinine clearance observed in period II in studies A and B may be non specific. An alternative explanation could be that a decrease in creatinine clearance can be observed only for the high values of plasma ranitidine obtained at 180 min. We were however unable to find any correlation between the plasma ranitidine at 180 min and the decrease in creatinine clearance between periods I and II. There might be however a time dependent effect with an early fall, followed by complete recovery, as reported with cimetidine.

High plasma values of ranitidine were obtained in this study without side effects. Ranitidine accumulates in renal failure [10] and the plasma ‘trough’ values obtained were above therapeutic levels. Further trials using lower doses, and including other parameters of parathyroid activity such as bone resorption are therefore needed.
References