THE EFFECTS OF d-PROPRANOLOL AND CAPTOPRIL ON POST-ISCHAEMIC ACUTE RENAL FAILURE IN RATS

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Summary

The effect of the combined therapy of d-propranolol and captopril was evaluated in post-ischaemic acute renal failure in rats.

The glomerular filtration rate measured 24 hours after ischaemic insult in the animals receiving no drugs was 54 ± 11μl/min/100g body weight while in animals treated with the combination of d-propranolol and captopril it was 305 ± 35μl/min/100g body weight (p<0.05). The precise mechanism of protection afforded by the combination therapy is not clear, but this approach could be useful in protecting the kidney from ischaemic damage.

Introduction

Since renal transplantation and renal vascular surgery became common procedures in urological practice, post-operative ischaemic acute renal failure has been a problem. Various techniques have been utilised to prevent the deterioration of renal function following ischaemic insult and several drugs have been employed to ameliorate the post-ischaemic acute renal failure [1]. Propranolol, a β-adrenergic blocking agent, has been shown to be effective in post-ischaemic acute renal failure, but it was only partially effective [2–4].

We previously reported the value of propranolol in post-ischaemic acute renal failure in animal models, and demonstrated that the d-isomer of racemic propranolol was the active compound in improving renal function following ischaemia. However, the efficacy of d-propranolol was also limited, and the glomerular filtration rate (GFR) measured 24 hours after ischaemia had only recovered to 50 per cent of a non-ischaemic kidney [5]. Several mechanisms can be speculated to account for the lack of total protection with a single drug treatment against post-ischaemic acute renal failure. First, the adverse effect of taking one drug at a high dose could be a problem, and secondly, there may be various mechanisms of pathogenesis of post-ischaemic acute renal failure, including the activation of the renin-angiotensin (R-A) system, tubular obstruction, cell swelling and metabolic factors.
Recently, a newly developed drug for the treatment of hypertension, the converting enzyme inhibitor captopril, has been reported to have some action in the kidney, such as increasing renal blood flow, urine volume and urinary sodium excretion. This study evaluates the effect of the combined therapy of d-propranolol and captopril in experimentally induced post-ischaemic acute renal failure in the rat.

Method

Experiments were performed on male Sprague-Dawley rats and anaesthesia was induced by sodium pentobarbital (50mg/kg/IP).

An external jugular vein was cannulated for the infusion of fluids and drugs. Both kidneys were exposed through a mid-line incision and the left renal artery was occluded with microvascular clip to induce 45 min ischaemia. Subsequently, a contralateral nephrectomy was done. At the end of the experiment, the catheter was removed and the rats were allowed to recover. In the drug-treated group, an infusion of d-propranolol (16μg/kg/min), captopril (16μg/kg/min) or a combination of the two was started 30 minutes prior to renal artery occlusion and continued throughout the entire experiment for a total of 195 minutes. Twenty-four hours later, the rats were anaesthetised again by sodium thiopental (Inactin, 100mg/kg/IP). The carotid artery was cannulated for the measurement of blood pressure and collection of blood samples, and the jugular vein was cannulated for the infusion of fluids and inulin. Three 30-minute urine collections were obtained for inulin and electrolyte excretion. A blood sample (0.4ml) was drawn at the beginning and the end of the experiment for inulin and electrolyte determinations. Inulin concentrations were estimated by colorimetric analysis and sodium was analysed by flame photometry. The data were subjected to analysis of variance, and the 0.05 level of probability was used as the criterion of significance.

Results

The alteration of the renal function measured 24 hours following 45-minute renal artery occlusion is presented in Table I. The values shown represent a mean determination of the three periods. In the untreated animals, the GFR was significantly reduced to 54 ± 11μl/min/100g body weight. In contrast to this, in the animals treated with either d-propranolol or a combination therapy of d-propranolol and captopril, the GFR significantly improved to 173 ± 22 and 305 ± 35μl/min/100g body weight, respectively (p<0.05). Furthermore, the GFR value in the animals treated with the combination was significantly higher than in the animals treated with d-propranolol alone, and its value was also about six times that observed in the untreated control.

Captopril treatment brought better GFR (102±16μl/min/100g body weight) values than the untreated control group, but this value did not reach statistical significance. Likewise, the sodium reabsorption rate was significantly higher in the d-propranolol treated group (97.3 ± 0.7%) than in the untreated group.
TABLE I. Renal function obtained 24 hours after release of renal artery occlusion†

<table>
<thead>
<tr>
<th></th>
<th>GFR (µl/min/100g/BW)</th>
<th>UV (ml/min/100g/BW)</th>
<th>UNaV (µEq/min/100g/BW)</th>
<th>Per cent sodium reabsorption</th>
<th>Heart rate (beats/min)</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. untreated control (n=9)</td>
<td>54 ±11</td>
<td>3.8 ±0.8</td>
<td>0.22 ±0.06</td>
<td>92.7 ±1.5</td>
<td>332 ±10</td>
<td>110 ±4</td>
</tr>
<tr>
<td>2. d-propranolol 16µg/kg/min for 195 min (n=7)</td>
<td>173 ±22*</td>
<td>5.0 ±0.4</td>
<td>0.36 ±0.04</td>
<td>97.3 ±0.7*</td>
<td>337 ±9</td>
<td>111 ±3</td>
</tr>
<tr>
<td>3. captopril 16µg/kg/min for 195 min (n=6)</td>
<td>102 ±16</td>
<td>8.0 ±1.9*</td>
<td>0.6 ±0.16*</td>
<td>93.9 ±2.4</td>
<td>338 ±6</td>
<td>102 ±5</td>
</tr>
<tr>
<td>4. d-propranolol 16µg/kg/min plus captopril 16µg/kg/min for 195 min (n=7)</td>
<td>305 ±35*,***</td>
<td>9.1 ±1.7*,**</td>
<td>0.6 ±0.14*</td>
<td>94.1 ±3.9</td>
<td>352 ±18</td>
<td>113 ±1.9</td>
</tr>
</tbody>
</table>

† Values are mean ± SEM. Abbreviations are defined as: GFR=glomerular filtration rate; UV=urine volume; UNaV=sodium excretion; BW=body weight; n=number of rats.

* Significantly different from untreated control (p<0.05)
** Significantly different from untreated control and d-propranolol (p<0.05)
*** Significantly different from untreated control, d-propranolol and captopril (p<0.05)

(92.7 ± 1.5%) and the animals treated with the combination had better sodium reabsorption (94.1 ± 3.9%) than the untreated group, but this was not significant. There was a significant increase of urine volume and sodium excretion in the animals which received captopril.

No significant difference was observed in the blood pressure or heart rate between these groups.

Discussion

We previously reported that the β-blocking agent propranolol was effective in ameliorating the deterioration of renal function after ischaemic insult in the rat model. Furthermore, we demonstrated that the d-isomer of racemic propranolol, which lacks β-adrenergic blocking properties, was the active compound in protecting the kidney from ischaemia and speculated that the so-called membrane stabilising properties of d-propranolol could be significant. However, complete
recovery was not observed even in the animals treated with d-propranolol with the GFR returning only to 30–50% of the non-ischaemic kidney measured two hours and 24 hours after ischaemic insult. The present study clearly demonstrated that the recovery of the GFR obtained 24 hours following ischaemia was significantly enhanced by the combined therapy of d-propranolol and captopril than when d-propranolol was used alone, and its value was six times higher than the untreated control group.

Since Goormaghtigh first suggested the involvement of the R-A system in the pathogenesis of acute renal failure [6], a number of studies have been employed to elucidate the relationship between GFR and RBF in acute renal failure. Several investigators reported the efficacy of propranolol against post-ischaemic acute renal failure in animal models but they failed to clarify the precise mode of action of propranolol. Some studies suggested that the effectiveness of propranolol against post-ischaemic acute renal failure was not mediated through the improvement of renal blood flow in the recovery phase [3,4]. On the other hand, Solez et al did find a significantly better renal blood flow value immediately after reflow which resulted in a significantly higher GFR [7]. We have shown previously the beneficial effect of propranolol on post-ischaemic acute renal failure, but we did not see any relationship between GFR and renal blood flow. Furthermore, from our previous observation, if the R-A system is primary in the pathogenesis of the initial deterioration of renal function after ischaemia, the l-isomer of propranolol, which is a potent β-adrenergic blocker, and also captopril should be effective, which was not the case. It was an interesting observation that the combined treatment could enhance significantly the recovery of GFR observed 24 hours after ischaemia over that of d-propranolol alone.

It is known that captopril has various actions in the kidney such as increase of RBF, urine volume and sodium excretion [8,9]. But the mechanism of the above action in the kidney is controversial. We observed similar captopril actions in non-ischaemic kidneys in our study. Diuretics, such as mannitol and frusemide which increase renal blood flow, solute excretion, and water excretion have been shown to be effective on post-ischaemic acute renal failure [10]. These clearance studies do not show why the combination is so beneficial. The precise mechanism of better protection afforded by a combined therapy on post-ischaemic acute renal failure in our model is not clear at this time, but synergistic actions of d-propranolol which stabilise the membrane and captopril which alters renal haemodynamics may attenuate more effectively the renal damage from ischaemia.

Acknowledgments

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References

1. Tiller DJ, Hudge GH. Kidney Int 1980; 18: 700

Open Discussion

IAINA (Israel) In the past we have tried to use d-propranolol in a dose of 1mg per Kg body weight per minute and I could not obtain any beneficial effect. When I used 30mg d-propranolol there were some changes. What do you mean when you say “beneficial membrane stabilising effect of beta adrenergic blocker”?

ISHIGAMI I think your group reported about two years ago a 70 minute ischaemic model* instead of 45 min ischaemia which I used this time and also the timing infusion of d-propranolol was different. You used infusions just 50 minutes after releasing occlusion. I used a 30 minute prior to renal occlusion and continued to infuse through our entire experiment which was about 180 minutes. For your second question I cannot give you any explanation for that, but from a pharmacological understanding and from the literature some studies suggest d-propranolol preserves more ADP activity in the cell and may affect some ion movement such as calcium and potassium. When we look at the literature nobody can explain the meaning of membrane stabilisation, but when we use d-propranolol we are just speculating from the pharmacological characteristics that a major action is membrane stabilisation.

CHAIRMAN We have recently shown that some of the renal effects of captopril are accounted for by increased prostaglandin secretion such as the natriuretic effect and the increasing renal blood flow. This suggests that the protective effect afforded by captopril in acute renal failure may be mediated by increased prostaglandins.

ISHIGAMI Well it may be possible but we never measured the urinary prostaglandins, but in the literature in an ischaemic occlusion model where prostaglandin was used there was no improvement of renal function.

CHAIRMAN It has been argued that captopril when given to patients with bilateral renal artery stenosis or unilateral renal artery stenosis in a single kidney may precipitate acute renal failure. † It is being postulated that this is due to an effect on the efferent arterioles. How can you reconcile with your explanation?

† Farrow PR, Wilkinson R. Br Med J 1979; 1: 1680
ISHIGAMI Well I don't know. It has been shown by some that captopril blunts autoregulation which is very important in cases of high renin activity. After ischaemia, as in our model, we have high renin activity but we didn’t measure renin or angiotensin II.

CHAIRMAN If I may comment upon this point. The reason for acute renal failure precipitated by captopril in patients with a single kidney with renal artery stenosis has been attributed to decreased constriction of efferent arterioles. Actually, we have given evidence in a recent paper which has been presented in the International Congress in Los Angeles that at least some cases of acute renal failure can be accounted for by increased urinary salt excretion and by volume depletion. We had six patients in which acute renal failure was promptly reverted by giving salt, simply giving salt while continuing therapy with captopril.