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Original article

Treatment of carvedilol for refractory hypertension in patients with renal diseases: A multicentre, prospective clinical trial

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ABSTRACT

Hypertension is one of the main risk factors for cardiovascular diseases. In this study we aimed to evaluate efficiency and safety of carvedilol treatment in refractory hypertensive patients with renal diseases, including chronic kidney disease (CKD), polycystic kidney disease (PKD), dialysis and post-transplantation population. A multicentre, prospective, open label, self-compared trial was conducted in the east area of China in 2005. Two hundred and seventeen patients were enrolled in this study. Mean arterial blood pressure (systolic/diastolic) at 4 weeks significantly reduced in comparison with that before the use of carvedilol ($142.6 \pm 14.4/84.2 \pm 10.1$ mmHg vs $166.2 \pm 18.1/90.4 \pm 11.0$ mmHg, $P < 0.05$), and then it continued to drop to 136.9 ± 12.4 mmHg/80.1 ± 10.6 mmHg at the completion of trial (week 8). Total efficiency (subjects with a BP less or equal to 130/80 mmHg or having a fall of greater or equal to 10 mmHg in DBP or greater or equal to 30 mmHg in systolic blood pressure) was 57.1% at 4 weeks and 79.7% at 8 weeks, and dominant efficiency (subjects with a BP of less or equal to 130/80 mmHg and those showing a fall of greater or equal to 10 mmHg in diastolic blood pressure) was 11.5% and 26.7%, respectively. Mean heart rate declined from 79.3 ± 10.2/min to 75.9 ± 7.6/min at 4 weeks and 75.0 ± 8.5/min at 8 weeks ($P < 0.05$). Plasma norepinephrine level decreased from 38.7 pg/mL before this trial to 17.6 pg/mL ($P < 0.05$). The total number of patients experiencing at least one adverse event was 13. None resulted in withdrawal of the patient from study. This study suggests that carvedilol is an efficient and safe drug in treatment of refractory hypertensive patients with renal diseases.

1. Introduction

It is well known that hypertension is one of the main risk factors for cardiovascular diseases (CVD) [1–3]. Various large-scale clinical studies have shown that treatment of hypertension with medication can prevent onset of CVD and reduce mortality and morbidity [4,5], and treating hypertension has been associated with an approximately 40% reduction in the risk of stroke and an approximately 15% reduction in the risk of myocardial infarction [6].

The pathogenesis of hypertension in patients with renal diseases has been classically considered to be due to the combined result of volume overload/sodium retention and inappropriate activation of the renin–angiotensin–aldosterone system (RAAS). There is an emerging, strong body of evidence to indicate that the sympathetic nervous system in general also plays an important role in the development of hypertension [7,8]. Human studies examining muscle sympathetic nerve activity (MSNA) have unequivocally shown elevated sympathetic nerve activity in patients with renal failure [9,10]. This appears to be driven by the impaired kidneys, because patients who had bilateral renal nephrectomy had both correction of blood pressure and MSNA [11–13]. In addition to showing increased MSNA, renal failure patients also demonstrate increased plasma catecholamines, whether measured as plasma levels or total body noradrenaline spillover. In experimental animal models of renal failure, renal denervation has also been shown to attenuate or even reverse increased blood pressure. This includes established models of renovascular hypertension [14], autosomal

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dominant polycystic kidney disease [15] and a model of neurogenic hypertension caused by renal phenol injection [16].

The β-blockers have a mild antihypertensive effect; they are widely used in the treatment of essential hypertension [17–19]. However, they are rarely used alone in patients with renal hypertension because they decrease the cardiac output, thus reducing the renal perfusion pressure and potentially leading to worsening of renal function [20]. Carvedilol is a new β-blocker possessing a vasodilating action and has been reported to increase the renal blood flow [21]. This drug is metabolized in the liver and is excreted mainly in the faeces [22]. Hence, its nephrotoxicity is likely to be low, even in patients with impaired renal function, and it is unlikely to accumulate. In 2006, Weber et al. carried out a multicentre study, this randomized controlled trial suggest that carvedilol has a clinically meaningful defined dose-dependent antihypertensive effect [23]. Carvedilol is thus a potentially useful agent for patients with renal hypertension.

In the management of hypertension, it is critically important to lower blood pressure to levels of less than 140/90 mmHg in the general population, and even lower in the chronic kidney disease (CKD) group. Unfortunately, data from NHANES – demonstrated that only 27% of individuals actually achieved a blood pressure of less than 140/90 mmHg [24]. Five separate trials (UKPDS, HOT, MDRD, ABCD, and AASK) showed that renal disease progression was reduced by an additional 30–50% and the cardiovascular disease risk was reduced by an additional 40–70% over the higher blood pressure control groups [25–29]. Hypertension occurs commonly and early in renal disease and is paralleled by increases in sympathetic nerve system (SNS) activity [7,10]. Especially in patients with polycystic kidney disease (PKD) or dialysis, increased BP is always hard to control and increased MSNA have been demonstrated [12,30], but few trials have conducted in this group, so in the present multicentre trial at 12 sites in East China, we gave carvedilol to refractory hypertensive patients with kidney diseases and investigated its efficacy, safety, and optimal dose.

2. Subjects and methods

2.1. Subjects

The subjects were 217 refractory hypertensive patients with chronic kidney diseases who fulfilled the conditions in Table 1. They were selected from patients attending 12 participating institutions. Informed consent was obtained from each subject after a full explanation of the study. These patients were divided into four groups according to their therapy style: (1) maintenance dialysis (MD) group (including hemodialysis and peritoneal dialysis), measured Kt/V greater or equal to 1.2 or URR greater or equal to 65% for hemodialysis patients or weekly Kt/V greater or equal to 1.8 for peritoneal dialysis patients; (2) kidney transplantation (KT) group, all patients must receive cyclosporin A or tacrolimus therapy, and the renal function is stable in the last 8 weeks without any rejection phenomenon; (3) CKD group (including various kinds of primary and secondary kidney diseases), having not entered dialysis yet and not receiving any hormone or immunosuppressive drugs in the last 8 weeks; (4) PKD group, patients with an established diagnosis of PKD and had not entered dialysis yet.

2.2. Study design

This was a multicentre, prospective, open label, self-compared clinical trial (stage 4). Film-coated tablets containing 25 mg carvedilol were used. Approval of the local hospital (Huashan Hospital, Fudan University) ethics committee was obtained prior to the start of the study. The nature of the trial was fully explained to all patients prior to receiving their consent to participate. All patients were free to withdraw from the study at any time.

Table 1
Criteria for entry and exclusion.

Inclusion criteria
1. Patients with an established diagnosis of refractory hypertensive, patients received a combined antihypertensive drug therapy (at least 3 types of drugs, diuretic agent, calcium-channel blocker [CCB], RAS blocker or others for at least 1 month), the diastolic blood pressure (DBP) was still ≥ 95 mmHg and/or systolic blood pressure (SBP) was ≥ 145 mmHg. This decision was based on the investigator's clinical judgment of the patient's current hypertensive status and history
2. Aged, < 70 years in general
3. Both genders were enrolled
Exclusion criteria
1. Patients with abnormal liver function
2. Patients experiencing sudden episodes of hypotension
3. Unstable heart failure, advanced bradycardia, conduction abnormalities (including sick sinus syndrome and advanced atrial ventricular block), cardiac shock or recent myocardial infarction (within 3 months of study)
4. Patients with chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD)
5. Patients suspected of having pheochromocytoma
6. Pregnant or possibly pregnant women and women who were breast-feeding
7. Hypersensitivity to carvedilol
8. Other patients judged to be unsuitable for this study by the attending physicians

Antiadrenergic drugs (metoprolol) were withdrawn from subjects who received them before the trial, and subjects showing obvious withdrawal symptoms in the 7-day washout qualification period were not selected.

The treatment period was 8 weeks, and the drug was taken once daily after breakfast. The initial dose of carvedilol was 12.5 mg daily, which was increased to 25 mg after 2 days and to 50 mg after a further 4 weeks if the effect was insufficient (if the blood pressure remained greater or equal to 150/90 mmHg or the mean pressure decreased less than 13 mmHg) and the patient could tolerate the higher dose. Other antihypertensive drugs were given without changing the route and dose throughout the trial period. If excessive hypotension, serious side effects, or worsening of renal function developed, the dose was reduced or administration was stopped by the judgment of the attending physician. Throughout the study, patients were required to maintain at least 75% compliance in taking study medication over the period preceding each visit. Use of other drugs considered likely to affect the blood pressure was prohibited.

2.3. Blood pressure, heart rate

The blood pressure and heart rate were measured with the patient seated at least once every week about 3 h after administration of carvedilol. Blood pressure and heart rate were then measured three times at approximately 3-min intervals on the same arm by the same physician using a standard pressure cuff. At the completion of treatment periods, the presence or absence of orthostatic hypotension was determined by measurement of the blood pressure with the patient in the supine and standing positions (within three rain of standing up).

2.4. Laboratory and other studies

Study eligibility was determined at the initial screening visit on the basis of medical history, a complete physical examination, chest X-ray (taken within the preceding 12 months), 12-lead electrocardiogram (ECG), and routine laboratory studies. The following items