Safety and Tolerability of Fast Up-titration of Carvedilol in Patients With Heart Failure

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Background: Although beta-blockers (BB) are now the cornerstone in the treatment of congestive heart failure (CHF), many patients are still receiving inadequate doses, probably due to cautious prescription. We designed this study to evaluate the safety and tolerability of a fast up-titration of carvedilol soon after commencement.

Methods: After commencement, 31 consecutive hospitalized patients (pts) with left ventricular ejection fraction (LVEF) ≥ 0.45 who had never used BB to treat CHF and with no contraindication to BB were selected. Mean age was 55.5 ± 21 years, and in 54.8% (n=17) inotropic support was needed for compensation. Mean LVEF was 32.1 ± 15.0%, mean left ventricular diastolic diameter was 70.0 ± 7.0 cm. The initial dose of 3.125 mg bid was doubled each 2 days until day 8 (target dose of 25 mg bid). Criteria for intolerance to BB were HR >= 55 bpm, systolic blood pressure (SBP) >= 90 mmHg and no worsening of CHF. A 6-minute walk test was performed on day zero, day 5, day 8 and day 30; 24 hours blood pressure continuous monitoring was performed on day zero and day 8. Results: It was possible to reach the daily dose of 25 mg in 23/31 (74.2%) and 50 mg in 19/31 (61.2%) of patients. The dose reached on day 8 was not different between pts who did or did not required inotropic support for compensation. In the patients who reached the dose of 25 mg/day the distance walked did not differ between days zero, 5, and 30 (373 ± 68 ± 65.5 vs. 406 ± 108.8 vs. 396 ± 145.5 vs. 423 ± 168.3 meters; p = 0.18, 0.48 and 0.51 respectively). Mean weight gain was 2.1 kg (±0.52), and SBP tended to be lower on day 30 (83 ± 15.2 vs. 92 ± 17.4 mmHg; p = 0.06). The same tolerability was observed on day 30. The dose could not be increased in 9 patients, had to be reduced in 1, and had to be withdrawn in 2.

Conclusion: Introduction and the fast up-titration of carvedilol can be done even after inotropic support. Rapid titration was safe and can be done on lower intervals than currently recommended.

Carvedilol Improves Myocardial Perfusion in Conscious Dogs With Pacing Induced Dilated Cardiomyopathy

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Background: Both combined (β1, β2, α1, Carvedilol) and selective (β1, Metoprolol succinate) adrenergic blockade have been associated with improved survival and clinical outcome in patients with chronic heart failure (CHF). Although carvedilol (CARV) has been proven effective in clinical trials, there is limited data on its effects on regional myocardial perfusion. We measured regional myocardial blood flow (MBF) using 99mTc-nitroprusside activated microspheres before and after treatment with carvedilol (CARV: 25 mg po BID) and metoprolol (MET: 150 mg po q.d) in conscious dogs.

Methods: Nine conscious left ventricular pacing (240 min-1) conscious dogs were divided into two groups: CARV (n = 6) and MET (n = 3). Before treatment at baseline, the pacing frequency was increased to 240 min-1 and was maintained for 29 days. We measured regional MBF using 99mTc-nitroprusside activated microspheres before and after treatment with carvedilol (CARV: 25 mg po BID) and metoprolol (MET: 150 mg po q.d) in conscious dogs.

Results: In patients who reached the dose of 25 mg/day the distance walked did not differ between days zero, 5, and 30 (373 ± 68 ± 65.5 vs. 406 ± 108.8 vs. 396 ± 145.5 vs. 423 ± 168.3 meters; p = 0.18, 0.48 and 0.51 respectively). Mean weight gain was 2.1 kg (±0.52), and SBP tended to be lower on day 30 (83 ± 15.2 vs. 92 ± 17.4 mmHg; p = 0.06). The same tolerability was observed on day 30. The dose could not be increased in 9 patients, had to be reduced in 1, and had to be withdrawn in 2.

Conclusion: Introduction and the fast up-titration of carvedilol can be done even after inotropic support. Rapid titration was safe and can be done on lower intervals than currently recommended.

Contemporary Dosing of Angiotensin Converting Enzyme Inhibitors and Beta Blockers in Chronic Heart Failure: Report From the Heart Failure: Report From the STAMINA:HFP Registry

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Background: Optimal utilization of angiotensin converting enzyme inhibitors (ACEI) and beta blockers (BB) in heart failure treatment requires treatment of eligible patients and use of proven effective in clinical trials. However, doses commonly given patients with heart failure are not well studied.

Methods: The STAMINA-HFP Registry enrolled randomly selected patients with heart failure from 6/24/02 to 5/19/03 in 12 specialty clinics and 45 community cardiology clinics. Data on 665 return patients with EF < 40 who were taking either ACEI or BB and had information available on doses of these drugs and use of angiotensin receptor blockers (ARB) were analyzed. Doses were converted to milligram equivalents of enalapril or metoprolol CR/XL. Extent of titration in each patient was evaluated as % of ideal target dose in ACEI and BB and mortality trials (%CTTD, 20 mgid for enalapril and 200 mgid for metoprolol CR/XL) and % of the mean doses actually achieved in these trials (%MDA) (16.6 mgid for enalapril and 159 mgid for metoprolol CR/XL).

Results: No patients were taking ACEI + ARB and no BB. Only 2.6% of patients were taking BB + ACEI + ARB. The percentage of patients reaching at least CTTD or MDA and the means SD dose equivalents achieved in other patient groups are shown.

Neutral Endopeptidase Inhibition Augments the Vascular Actions of Bradykinin in Patients With Heart Failure on Chronic Angiotensin-Converting Enzyme Inhibitor Therapy

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Background: Angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP) degrade kinins. ACE inhibition potentiates bradykinin mediated vasodilatation and endothelial release of the pro-lytic factor, tissue plasminogen activator (t-PA) in patients with chronic heart failure (CHF). We investigated whether additional NEP inhibition with thior-