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Sustained Delivery of a Novel Natriuretic Peptide for Three Weeks with In Situ Polymer Precipitation Delivery System

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Introduction: CD-NP (Cenderitide) is a chimeric natriuretic peptide that acts on both the A and B natriuretic guanylyl cyclase receptors. This differentiated mechanism of action avoids the hypotensive nature of BNP while retaining the cardiac unloading and renal enhancing actions in heart failure (HF) together with direct anti-remodeling actions. CD-NP is being developed as an outpatient therapy for patients following hospital admission for HF, the "post-acute" period, to reduce rehospitalization. Our objective is to design an in situ polymer precipitation delivery system suitable for the chronic and sustained release of CD-NP.

Methods: 0.45% percentage weight/weight (w/w) CD-NP was mixed with 40% Poly (lactic-co-glycolic acid) in 39.55% w/w N-methyl-2-pyrrolidinone and 20% w/w triacetin. Resulting mixture was allowed to homogenize overnight. Three groups of 5 rats (Wistar Male, 250-300g) were injected subcutaneously with the gel. A fourth group (n=5) was injected with blank gels as vehicles. Rats sacrificed at respective time points (1 / 2 / 3 weeks) for plasma and urinary evaluation.

Results: Plasma CD-NP was significantly higher than vehicle $32,700 \pm 2888$ pg/ml, $13,977 \pm 3302$ pg/mol and $7,566 \pm 1115$ pg/mol at 1 / 2 / 3 weeks after gel injection. 24-hr urinary CD-NP excretion was significantly elevated at 107.3 ± 12.7 pg/min, 33.7 ± 29.7 pg/min and 16.5 ± 8.2 pg/min at 1 / 2 / 3 weeks as compared to 2.02 ± 0.10 pg/min pre-injection, while no significant difference was observed before and 3 weeks after gel injection in the vehicle group. Plasma cGMP was significantly elevated at 271.0 pmol/ml ± 41.4 at week 1 with a trend to be higher at weeks 2 / 3 as compared to vehicle. 24-hr urinary cGMP output was significantly elevated to 57.7 ± 2.9 pmol/min and 56.6 ± 7.4 pmol/min at week 1 and 2 as compared to pre-injection.

Conclusion: This study demonstrated that with the appropriate gel formulation, CD-NP release could be sustained over 3 weeks. The use of in situ polymer precipitation delivery system is a feasible and attractive technology for the delivery of the novel chimeric CD-NP in improving patient compliance and quality of life.