POSTER SESSION

1139

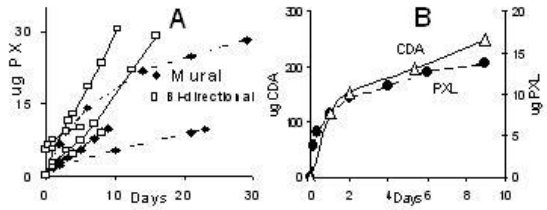
Drug-Eluting Stents: Bench to Bedside

Tuesday, March 09, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1139-47 Drug-Eluting Stent With Multidimensional Programmable Pharmacokinetics

Colin T. Watanabe, Joseph Aragon, Saibal Kar, Ted Parker, Frank Litvack, Neal L. Eigler, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Our objective was to evaluate the range of programmable parameters of the Conor Medsystems MedStent™ loaded with lipophilic paclitaxel (PXL) in an *in vitro* elution experiment. We examined: 1) spatial homogeneity, 2) the breadth of multiple temporal and directional kinetic profiles, and 3) simultaneous combination of PXL with water soluble 2-chlorodeoxyadenosine (CDA), a potent macrophage inhibitor.
Methods: Stents (9 formulations of 4 stents each) were immersed in aliquots of agitated N, N-diethylnicotinamide, and released drug was measured by HPLC for up to 30 days.
Results: Spatial homogeneity for PXL varied by <3.5%. Graph A shows cumulative release curves for 100% of the loaded PXL over 5-30 days. Seven unique first and zero order temporal profiles were achieved with doses from 10-30 μg released either at the vessel wall or at the wall and lumen. Graph B shows cumulative simultaneous release from stents containing PXL and CDA.
Conclusions: This stent's layered multi-drug/polymer inlay technology permits precise control of spatial and temporal first and zero order pharmacokinetic elution profiles. A novel feature is the ability to simultaneously deliver water soluble and lipid soluble combination chemotherapy from a simple polymer carrier structure. These capabilities are undergoing further investigation in animal and human clinical trials.



1139-48 Comparative Efficacy of Everolimus and Sirolimus Delivered via Polymeric Drug-Eluting Stents in the Porcine Coronary Model

Andrew J. Carter, Chi-An Wang, Jeff Royal, Leslie Coleman, Lori Gibson, Anastasia Rossi, Julie Booth, Russ Jones, Renu Virmani, Providence Heart Institute, Portland, OR, Armed Forces Institute of Pathology, Washington, DC

Background: Rapamycin and its analogs are now being coated on different stent platforms, using different polymer matrices to prevent restenosis by impairing vascular smooth muscle cell proliferation and neointimal formation.
Methods: We evaluated the feasibility and compared the efficacy of biostable polymeric everolimus eluting stents and sirolimus eluting stents (Cypher™, Cordis, Inc.) in a porcine coronary model at 28 days. Cobalt chromium balloon expandable stents were coated with a polymer containing everolimus (200 $\mu g/cm^2$). Twelve pigs underwent placement of 36 oversized (1.1:1) sirolimus (n=12), everolimus (n=12) and bare metal (cobalt chromium, n=12) stents in the coronary arteries.
Results: Histological analysis revealed a similar mean percent stenosis between the everolimus and sirolimus coated stents (20.8 ± 6.9% and 20.8 ± 7.6%, respectively). The bare metal stents had a greater % area stenosis (26.8 ± 7.8), compared to both the everolimus and sirolimus coated stents (p = 0.05). Neointimal thickness for vessels with both the everolimus (0.13 ± 0.07 mm) and sirolimus (0.13 ± 0.08 mm) stents was also reduced versus the bare metal stents (0.20 ± 0.07 mm, p < 0.04). There were no significant differences in injury score between any of the groups.
Conclusion: Stent-based delivery of sirolimus and everolimus delivered via polymeric matrices are equally effective in the suppression of neointimal formation at 28-days in the porcine coronary model. Further study is necessary to document dose response and long-term comparative effects of these drug eluting stents.

1139-49 Sirolimus-Eluting Stents: Pharmacokinetics in Blood, Vessel, and Myocardium in a Porcine Coronary Model

Fumiaki Ikeno, Lynn Bailey, Clark Willard, Gregory A. Kopia, Fermin Tio, John Dooley, Cordis Corporation, Warren, NJ, University of Texas, San Antonio, TX

Background: Sirolimus-eluting (SRL) stents have been shown to markedly reduce neointimal formation. The purpose of this study was to define the initial in-vivo systemic pharmacokinetics (PK) of SRL stents using the porcine coronary model.
Methods: Juvenile farm pigs underwent placement of SRL stents (153mg/stent) in the LAD coronary artery. For the blood analysis study, SRL stents were implanted and blood samples were drawn both through a catheter placed 1 cm distal to the stent and from the jugular vein at 2, 5, 10, 15, 30, 45 minutes, 1, 2, 3, 4, 5, 6, 8, 24 hours. In a separate study, SRL stents were implanted in each of three coronary arteries of juvenile farm pigs which were sacrificed at 1, 3, 8, 30 days for assessment of sirolimus level in the stented vessel, stent and myocardium and histomorphology. Bare metal stents were implanted as the control.
Result: Both arterial and venous sirolimus levels increased in the first 60 minutes (peak: 3.73ng/ml in the LAD vs. 1.07ng/ml in vein at 60 minutes) and then declined, more rapidly in the arterial samples than in the venous samples (0.84ng/ml in artery vs. 0.61ng/ml in vein at 24 hours). Stent analysis demonstrated that 41±5% and 93±2% of total stent sirolimus was released by 1 day and 30 days, respectively. Tissue sirolimus levels of stented vessel segments peaked at 1 day following stent implantation (14.5±10.9ng/ml) and then declined (1.79±0.90ng/mg at 30 days). The myocardium within and adjacent to the stent borders, proximal and distal vessel and distant myocardium levels were less than 2.0% of stented vessel level. At 30 days, %neointimal area was reduced by 57% with SRL stents when compared with bare metal (48±14% vs. 27±13%, respectively; p=0.0002).
Conclusion: These pharmacokinetic data demonstrate an initial separation between local arterial and systemic blood levels which subsides by 24 hours. The peak sirolimus tissue level occurs at 1 day while the peak blood level occurs at 60 minutes. Arterial and myocardial tissue adjacent to or distant from the stent implanted vessel contains much less sirolimus than the stented vessel. SRL stents can achieve effective local drug delivery to target lesion with minimum drug concentration in surrounding tissue.

1139-50 Effect of Cerivastatin-Eluting Stent on Inflammatory Response, Platelet Deposition and Intimal Hyperplasia in a Porcine Coronary Model

Katsumi Miyauchi, Takayuki Yokoyama, Takatoshi Kasai, Shinya Okazaki, Hitoshi Satoh, Takeshi Kurata, Hiroyuki Daida, Juntendo University, Tokyo, Japan

Drug-eluting stents hold the promise of the dramatically reducing restenosis after coronary intervention. Many experimental studies have shown that statins can inhibit SMC proliferation, inflammation and platelet aggregation. Inflammatory reactions and platelet deposition induced by stent were found to be positively associated with neointimal hyperplasia. We hypothesized that statin-eluting stent might inhibit the early and late inflammatory response, platelet deposition and prevent neointimal hyperplasia in porcine coronary arteries. Fifteen mm long stainless steel balloon expandable tubular stents were coated with a thin layer of a biologic polymer matrix containing 300ug of cerivastatin. Cerivastatin-loaded stents (n=20) and bare stents (n=20) were randomly deployed at a stent to artery ratio of approximately 1.1 to 1.0 in the coronary arteries of 20 pigs. All animals survived without any adverse events. The lipid profile in both groups did not differ. Early inflammatory cell infiltration and platelet doposition was evaluated with scanning electron microscopy at 3 days after stenting and was significantly reduced in the treated vessels compared to bare stent (mean inflammation score 0.45+0.55 vs. 2.88+0.99, p<0.01). Histopathologic assessment after 28 days showed a significant decreased chronic inflammatory cells surrounding the stent filaments and in adventitia of statin-coated stents compared with bare stent. Quantitative intravascular ultrasound revealed that statin-coated stent decreased % diameter stenosis compared to bare stents (19% vs.42%, p<0.01) wheras stent area was similar in both groups. Histomorphometry showed increased lumen (2.66+0.35 vs 1.89+0.22, p<0.01) and reduced neointimal area (0.65+0.22 vs 1.79+0.33, p<0.01) in statin-coated stent versus the bare metal stents despite similar injury scores. **Conclusion:** Cerivastatin-eluting stents results in a significantly decreased neointimal hyperplasia with decreased inflammatory response and platelet deposition in porcine coronary arteries.

1139-51 Optimization of Pharmacokinetic Vectors With a Programmable Paclitaxel Eluting Stent

Joseph Aragon, Saibal Kar, Alexander Parisky, Colin Watanabe, Aamer Jamail, Frank Litvack, Neal Eigler, Cedars Sinai Medical Center, Los Angeles, CA

Background: The Conor MedStent™ loaded with Paclitaxel (PTX) can be programmed from a multiparameter matrix of dose, temporal release profiles (order, duration), and release pathways (lumen, mural (M), or bidirectional(BI)).Any set of parameters determine a unique pharmacokinetic vector (PKV). The goal of this study was to examine the effects of widely differing PKVs on 30 day restenosis in a porcine model of stent injury.
Methods: Stents with 5 PKVs comprising doses 10 or 30 ug, zero order release for 10 or 30 days, and release pathways M and BI, were compared with bare metal and polymer-loaded control stents in 55 coronary segments implanted in 21 pigs.
Results: Late loss (LL) in bare and polymer stents was 0.84±0.63 and 0.96±0.54 mm, respectively (p=NS). There was no difference in balloon/artery ratio between groups, (0.98 +/-0.32 p=NS). All PKVs reduced late loss (LL) vs. controls (Figure). PKV 30 ug PTX, 10 day zero order BI release had the greatest reduction in LL (p<.00001).
Conclusions: We found that a dose, release profile and pathway that performed best among 5 PKVs. Starting with large scale changes, an iterative process can be developed to choose the best PKV.