Catheterization and Cardiovascular Interventions 68:89–96 (2006)

Basic Science Review

Irinotecan-Eluting Stents Inhibited Neointimal Proliferation in Hypercholesterolemic Rabbit Aortas

Daniel H. Berrocal,[1] MD, Germán E. González,[2] MD, Celina Morales,[2] MD, Ricardo J. Gelpi,[2*] MD, and Liliana R. Grinfeld,[1] MD, FACC

Objective: To assess the effect of irinotecan-eluting stents (IS) on neointimal growth in the aortas of hypercholesterolemic rabbits and to determine other local histopathological effects such as necrosis, fibrin, and inflammatory reaction. Methods: Phosphorylcholine-coated stents were deployed in the aortas of hypercholesterolemic rabbits. Group 1 (control; $n = 8$) received unloaded stents, group 2 ($n = 7$) and group 3 ($n = 9$) received IS with 0.046 mg and 1.29 mg of irinotecan, respectively. Eight weeks after implantation the rabbits were killed. Neointimal thickness (NT) was assessed by morphometry. Semiquantitative injury score (from 0 to 3+) was used to analyze inflammatory infiltrate, fibrin deposits, and necrosis in the stented segments. Results: NT was reduced only in high-doses IS (G1, 167.4 ± 20.8 μ; G2, 170.24 ± 21.2 μ; G3, 111.56 ± 12.7 μ; $P < 0.05$, G3 vs G1 and G2). Necrosis decreased significantly with IS [1.00 ± 0.10 in G1 to 0.33 ± 0.07 and 0.02 ± 0.01 in G2 and G3, respectively] only in the media layer. The inflammatory infiltrate was present in the three layers of aortas from G1, but only decreased significantly in the intimae layer of the high-dose group [1.50 ± 0.15 in G1 vs 1.00 ± 0.18 in G3, $P < 0.05$]. Conclusion: Stents loaded with high-dose irinotecan inhibit NT in the aortas of hypercholesterolemic rabbits. This effect was accompanied by decreased inflammatory infiltrate and media necrosis.

Key words: rabbits; drugs eluting stents; irinotecan; restenosis

INTRODUCTION

During the last decade, the use of endoluminal stents has become a routine procedure for the treatment of coronary disease, particularly after multicenter studies showed a significant reduction in restenosis compared with results obtained with balloon angioplasty [1–3]. The rate of restenosis decreased significantly with the use of stents to approximately 20–30% [1–3]. However, restenosis continues to be high. To further decrease the rate of restenosis, new stent technologies, most prominently the drug-eluting stents, have been developed in the past years. Because of the pharmacokinetic characteristics of the antirestenotic agent, which is slowly and gradually released, these stents are inhibitors of intimal hyperplasia. Thus, a dual action is exerted on the plaque—the mechanical effect of the stent and a biological activity of the drug to prevent intimal hyperplasia. The agents tested so far include antithrombotics such as heparin, anti-inflammatory drugs, e.g., corticosteroids [4–6], or cell proliferation inhibitors, e.g., paclitaxel [7–10] or rapamycine [11,12]. In many instances, these agents adhere to the stent via a synthetic polymer that plays a role as drug reservoir, like phosphorylcholine. Irinotecan or camtotheca is an antineoplasic drug that blocks cell division [13,14] and so far it has not been tested as an inhibitor of the neointimal proliferation associated with stent implantation.

The objective of the present study was to evaluate qualitatively and quantitatively, the neointimal hyperplasia in response to phosphorylcholine-coated stents loaded with two different irinotecan doses, in a rabbit

[1]Interventional Cardiology Department, Hospital Italiano de Buenos Aires, Argentina
[2]Department of Pathology, Faculty of Medicine, Cardiovascular Pathophysiology Institute, University of Buenos Aires, Argentina

*Correspondence to: Ricardo J. Gelpi, Cardiovascular Pathophysiology Institute, Department of Pathology. Faculty of Medicine, University of Buenos Aires, Argentina. E-mail: rgelpi@fmed.uba.ar

Received 11 October 2005; Revision accepted 19 January 2006

DOI 10.1002/ccd.20694
Published online 8 June 2006 in Wiley InterScience (www.interscience.wiley.com).

model of restenosis utilizing the abdominal aorta and hypercholesterolemic diet. An additional objective was to determine whether the effect on hyperplasia is accompanied by other local effects such as necrosis, fibrin, or any type of inflammatory reaction.

MATERIALS AND METHODS

Experimental Model

Twenty four New Zealand rabbits that weighted 1.8–2.0 kg were fed with 1% cholesterol enriched-diet during 8 weeks, and randomly assigned to the different experimental protocols. This diet was continued throughout the follow-up period after stent implant, and each animal was treated with aspirin at a dose of 5 mg/kg/day. The animals were killed after 8 weeks following stent implant.

The present study complies with the guide for the Care and Use of Laboratory Animals, published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996).

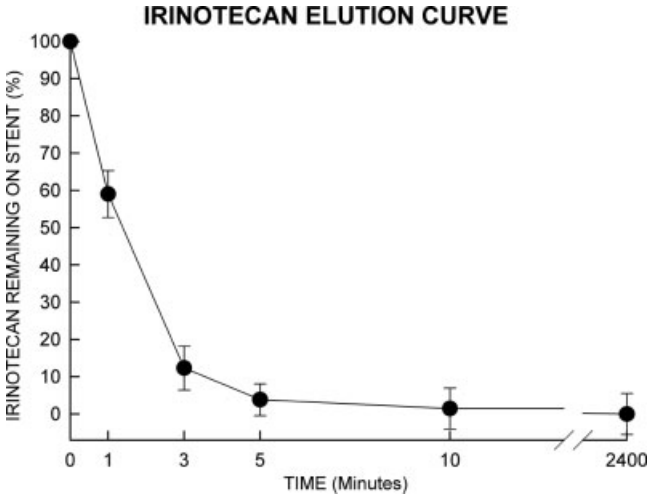

Fig. 1. Elution graph of irinotecan from phosphorilcholine-coated stents. Note the exponential decay of the release showing a biphasic pattern, a very early elution phase, followed by a slower phase of release. A similar elution pattern has been previously shown for paclitaxel polymer-coated stent (see Ref. 15).

Stent Design

The laser cut BiodivYsio® stent was used. It was built of a biocompatible 316L stainless steel material, and a balloon expandable stent that can reach 3.0–4.0 mm diameters. In this case, the stent was coated with phosphorylcholine as a drug carrier polymer. Stents 15-mm in length with a loading of 0.046 mg and 1.29 mg of irinotecan (CPT-11) or [Campto ((+)-7-ethyl-10-hydroxy-camptothecin 10-14′-bipieridine-1′carboxylate hydrochloride, trihydrate)] per stent were used. Figure 1 shows the elution graphs for irinotecan-coated stents. The elution characteristics of the stents were obtained in vitro (data reported from the company, Biocompatibles, UK).

This compound is a semisynthetic derivative from the alkaloid camptothecin that is obtained from a tree called *Camtotheca acuminata*. Its effect is due to the interruption of cell division via the topoisomerasa I inhibition, which leads to the blocking of DNA duplication at the S phase of the cellular cycle [16]. The rationale for the two doses was to have as wide a spectrum as possible in order to establish the efficacy of irinotecan. The reason for the higher concentration was that irinotecan is metabolized to its active form (SN-38) in the presence of hepatic and gastrointestinal carboxylesterase. Given that the blood levels of carboxylesterase are likely to be lower, and with less conversion, it is probable that the higher dose may provide a better chance of irinotecan working over a longer period. We acknowledge that this may not be the best rationale when the proximity of the stent or drug to the vessel wall or lesion is being considered, but it is a reasonable way to determine irinotecan's activity.

At present, irinotecan is used as main therapy, associated to 5-fluroracyle, in the treatment of rectal and colon cancer. It is also being tested in uterine, breast, prostate, both of small and nonsmall cell lung cancer, in leukemia, and lymphoma [17].

Stents were mounted on 3.0-mm diameter by 20-mm length balloons. All systems were sterilized with γ radiation and coded per unit.

Experimental Protocol

Procedures were carried out at the cath lab. All standard hospital aseptic procedures for human stent implantation were followed to avoid infection hazards that could endanger animal lives and/or alter findings.

Rabbits were randomized in three groups in a blind fashion: group 1 ($n = 8$), phosphorylcholine-coated stents without drug (control group); group 2 ($n = 7$), phosphorylcholine-coated stents loaded with 0.046 mg of irinotecan per stent (low-dose group); group 3 ($n = 9$), phosphorylcholine-coated stents loaded with 1.29 mg per stent of irinotecan (high-dose group).

The rabbits (2.0–2.3 kg) were anesthetized with subcutaneous solution of ketamine (75 mg/kg) and xylazine (0.75 mg/kg). A 5% dextrose solution was infused (3 ml/min) through a marginal ear vein. The anesthesia was supplemented using the same vein to administer additional doses of ketamine, according to surgical requirements. Both groins were shaved, disinfected with povidone iodine, and sterile fields were placed. When

anesthesia was stable, the femoral artery was exposed via plane dissection. Upon reparation of the artery with linen, an intra-artery, 1.3 mm diameter (Abbocath 22^{TM}) teflon cannula was inserted. Intravenous heparin 50 UI/kg was administered previously. A control angiography was performed via the cannula and before stent implantation by injecting 5 ml of iodine, low osmolarity (ioxaglate) contrast. After the anatomy was visualized, a segment of infrarenal abdominal aorta of about 2.8 mm diameter placed underneath the kidney arteries was selected. The stent system was placed over a 0.014-in. wire. One 15-mm BiodivYsio OC^{TM} was implanted by inflation of the delivery balloon at no less than 10 atmospheres. Only one stent was implanted in each rabbit.

Upon conclusion of the procedure, the femoral artery was ligated and the injury was cleaned with povidone iodine. Suture was carried out with separated linen stitches. Aspirin 5 mg/kg/day were administered during complete follow-up period.

Histopathological and Morphometric Examination

Eight weeks after the implant and after blood samples were obtained, the animals were sacrificed with an overdose of sodium thiopental (35 mg/kg).

The aorta segment containing the stent was embedded in methyl methacrylate and cut into three sections at predetermined points (cephalic, medial, and caudal levels). Stained sections with hematoxilin–eosin (H&E) and Masson's trichrome were evaluated by a cardiovascular pathologist.

The following histopathology findings were evaluated at the intima, media, and adventitia layers according to description from Makkar et al. [18]: inflammatory cells (lymphocytes or macrophage seen on high power), fibrin deposits (peristrut deposits of acelullar purple-stained material), and necrosis (loss of nuclear staining). The histopathology features were semiquantitatively graded as follows: (0) absent, (+) mild, (++) moderate and (+++) severe [18].

The morphometric study of the histological sections was performed using digital image analyzer software (Image Pro® Plus 3.0) and maximum and minimum interstruts neointimal thicknesses (NT) were measured. A pathologist blinded to the group assignment performed the analysis. The thickness was expressed as mean value of maximum and minimum thickness.

Statistical Analysis

Variable comparisons were performed among the three groups. For the continuous variables the distribution type was determined. In those that showed normal distribution, means with their standard deviations were used and subjected to variance analysis (ANOVA) and the Bonferroni test. Those variables with non-Gauss distribution were analyzed via nonparametric tests (Kruskal–Wallis). Statistical tests were two-tailed performed, where $P < 0.05$ was considered statistically significant.

TABLE I. Hemogram Performed After 2 Months of Stent Implant

	Control ($n = 8$)	Low doses ($n = 5$)	High doses ($n = 9$)
Hemoglobine (g/dl)	8.7 ± 0.6	7.7 ± 1.3	9.2 ± 0.3
Hematies (mill/mm^3)	3.9 ± 0.4	3.4 ± 0.7	3.9 ± 0.2
Leucocytes (per mm^3)	11,366 ± 1,825	14,440 ± 3,016	17,862 ± 6,206

RESULTS

All the stents were successfully implanted. In two rabbits, transient respiratory support with oxygen was necessary because of pharmacological respiratory depression in both animals that fully recovered. No other complications during the implant procedure were noted. There were six premature deaths—three animals from the control group, one from the low-dose group, and two from the high-dose group. Thus, the follow-up period was completed in 24 rabbits. The implant pressure and the balloon/artery relationship were similar in all the animals and did not show differences in the three groups.

Biochemical Analysis

No differences were found in hemoglobin, hematies, and leukocytes (Table I) after 2 months of stent implants.

Table II shows cholesterol plasma levels in all groups. There was a statistically significant increase in total cholesterol, HDL-cholesterol, and LDL-cholesterol levels in animals fed with cholesterol enriched diet compared with the values from rabbits fed on a normal cholesterol diet ($P < 0.05$). At the end of the study, there were not significant differences noted among the groups.

No stent thrombosis was observed in any of the cases, and all stents showed good angiographic permeability at the end of the follow-up period.

Morphometric Analysis

NT (Fig. 2) was 167.4 ± 20.82 μ in the control group, 170.24 ± 21.2 μ in the low-dose group, and 111.56 ± 12.7 μ in the high-dose group ($P < 0.05$, G3 vs G1 and G2). Thus, these results showed that

TABLE II. Biochemical Analysis Performed After 2 Months of Stent Implant

	Cholesterol (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
Before enriched diet	61.6 ± 9.3 (13)	23.7 ± 2.6 (13)	21.5 ± 2.3 (13)
After cholesterol enriched diet			
Control	828 ± 129 (7)*	90.0 ± 11.5 (5)*	559 ± 136 (3)*
Low doses	891 ± 133 (6)*	158.2 ± 50.9 (6)*	612 ± 134 (4)*
High doses	1,042 ± 109 (9)*	128.5 ± 15.7 (4)*	795.0 ± 126.0 (3)*

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol. Values inside parentheses correspond to the number of assessed animals.
*$P < 0.05$ vs before cholesterol enriched diet.

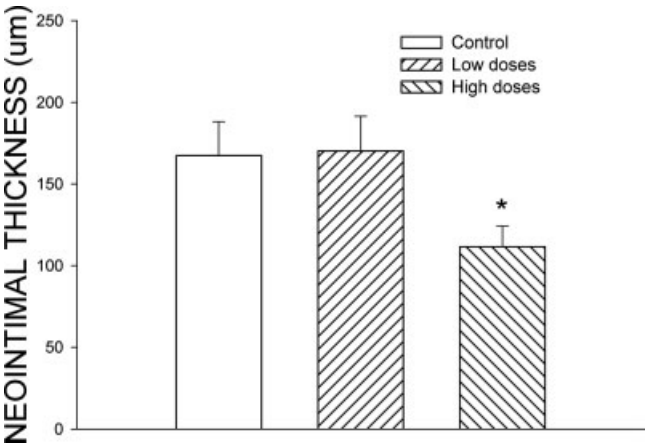

Fig. 2. Bar graph shows the neointimal thickening in the control, low-dose, and high-dose groups. *$P < 0.05$ vs control and low-dose groups.

neointimal proliferation was inhibited in the high-dose irinotecan eluting stents group, when compared with the control group. Representative microphotographs of NT in representative histological sections are shown in Fig. 3.

Histopathology Examination

Figure 4 shows necrosis in the aorta artery at the intima, media, and adventitia layers. With irinotecan therapy, necrosis in the aorta media layer decreased significantly from 1.00 ± 0.10 (+) in G1 to 0.33 ± 0.07 (+) and 0.02 ± 0.01 (+) in G2 and G3, respectively, and was negligible in the intimae and the adventitia.

The inflammatory infiltrate was present in the control group in the three layers of the aorta artery, but decreased significantly only in the intima in the group of rabbits that received high irinotecan dose [1.50 ± 0.15 (+) in G1 vs. 1.00 ± 0.18 (+) in G3, $P < 0.05$] (Fig. 5).

Fibrin deposits peristruts was overall low, i.e., lower than 1(+) in all three groups, and was not modified by local drug elution. This suggests that although there was an activation of the coagulation system to some extent, this activation was mild and also unmodified by the administration of irinotecan.

DISCUSSION

This is the first study to show experimental evidence that phosphorylcholine-coated stents, loaded with irinotecan 1.29 mg, inhibited neointimal hyperplasia in hypercholesterolemic rabbit aortas 8 weeks after the implant. An important finding was that the beneficial effect was obtained without changes in the evaluated hematologic indexes in any of the groups. This would allow assuming that at least the effects of these antineoplasic drugs on the blood cells, were not present in our study and that this drug did not cause adverse systemic effects. An additional and interesting finding was that, besides fibrin, the decrease of intimal hyperplasia was also accompanied by a decrease of the media layer necrosis as well as the inflammatory infiltrate of the intimae. These findings are very important, since the main goal was to attain the benefit of neointimal growth inhibition without causing local damage. A local adverse effect was observed with other drugs such as paclitaxel, which blocks the cellular cycle at the M phase, i.e., at the moment when mitosis occurs. In the study carried out by Farb et al. [8], stents with paclitaxel 20.2 and 42.0 mg inhibited neointimal hyperplasia. However, this effect was accompanied by increased inflammatory infiltrate in both cases, and signs of cytotoxicity in those cases with 42.0 mg.

Irinotecan is a synthetic campothecin-derivated DNA topoisomerase I inhibitor. The inhibitory effect of irinotecan on the cellular cycle is carried out by blocking DNA duplication occurring at the S phase. This phase follows the control point or point of no return. Cells inhibited at this phase would die. The efficacy of irinotecan has been examined mostly against several human tumors. However, inhibition of tumoral angiogenesis is an important new treatment modality for malignancies. Kamiyama et al. [19] have shown in vitro that SN 38 (active metabolite of irinotecan), but not other chemotherapeutic agents, selectively inhibited endothelial proliferation, three dimensional tube and decreased the en-

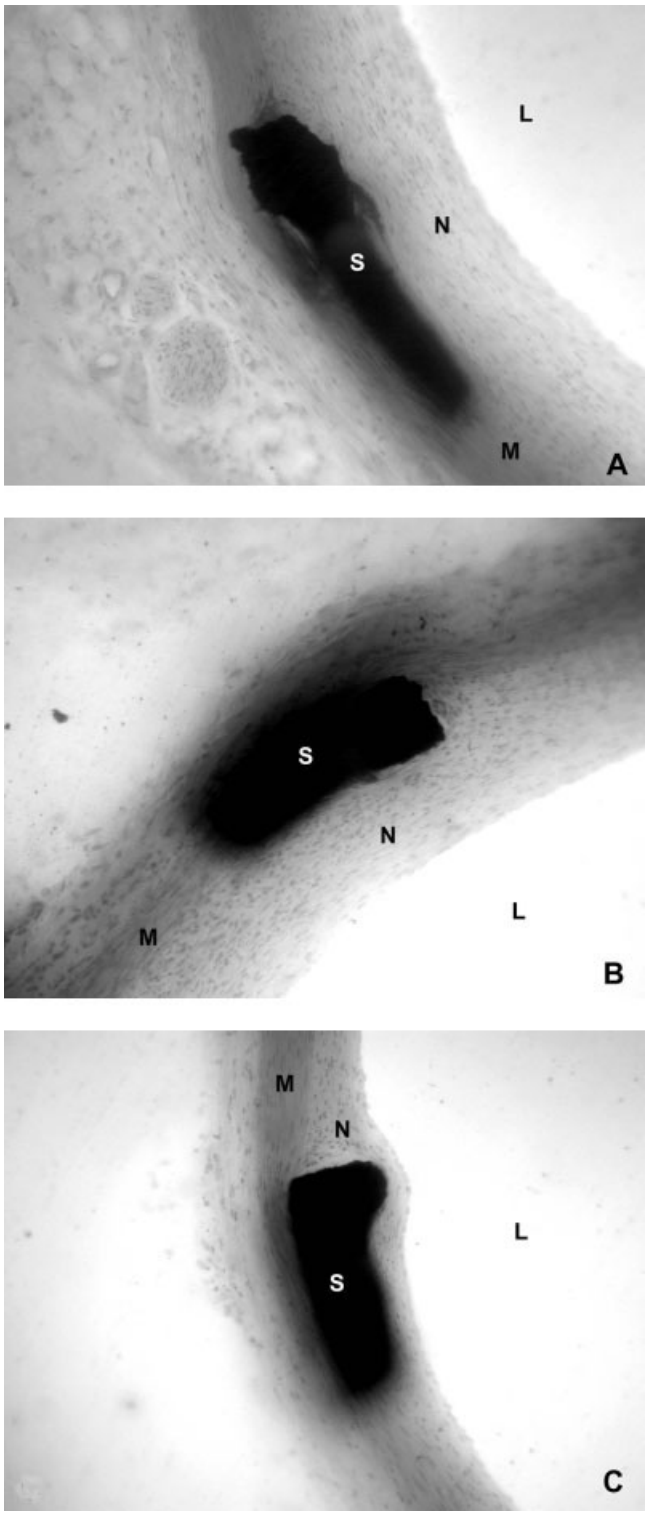

Fig. 3. Microphotographs of representative histological sections at original magnification of ×40. (a) Stented control section: there is abundant neointima (N) and media (M) has been partially disrupted. (b) Stented low-dose irinotecan section: reduced neointimal formation and media is intact. (c) Stented high-dose irinotecan section: minimal neointimal proliferation and media is intact. (S), stent struts; (L), lumen.

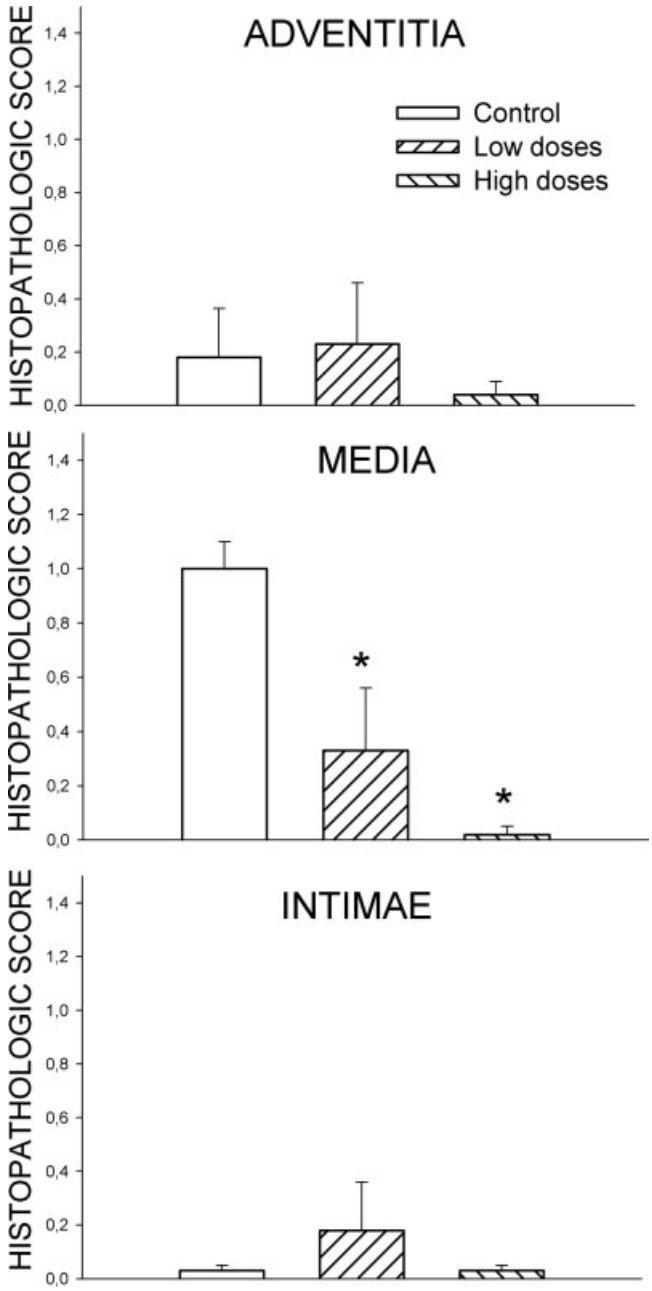

Fig. 4. This bar graph shows the presence of necrosis at the adventitia, media, and intimae. As shown, necrosis values at the adventitia and the intimae are minimal. Interestingly, irinotecan decreased the necrosis values in the media layer.

dothelial growth factor (VGEF) in a dose and time dependent manner under normoxic and hypoxic condition.

Different studies showed that the pharmacological characteristics of the drugs used in drug eluting stents contribute to the efficacy of the release at the location of the implant. Thus, Hwang et al. [20] showed that hydrophobic drugs, such as paclitaxel, reach a much higher average concentration and remain closer to the

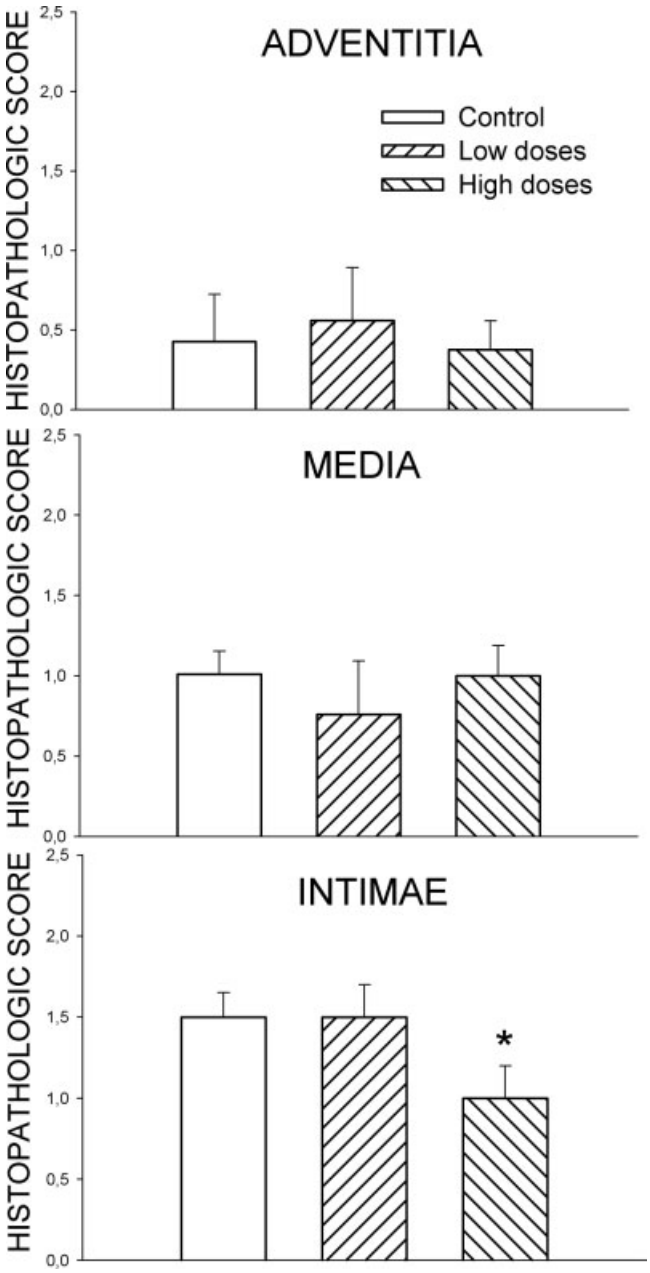

Fig. 5. The inflammatory infiltrate was observed in the three arterial layers, but even thus, irinotecan high-dose stent significantly decreased the infiltrate at the intimae.

intima than the hydrophilic drugs such as heparin. On the other hand, Levin et al. [21] has also shown that the tissue loading profile for paclitaxel and rapamycin are indistinguishable. However, the transmural drug distribution was markedly different, reflecting different modes of binding to specific tissue elements. Rapamycin distributes evenly throughout the artery, whereas paclitaxel, which binds specifically to microtubules, remains primarily in the subintimal space. For this reason, the kinetics of drug release at the level of the arterial wall should not be the most important matter to be considered, but the binding of the drug on each component of the arterial wall. Another important matter to be addressed in drug eluting stents is the polymers to which the drug is attached and, particularly, the kinetics of its release in the arterial wall. A biphasic elution curve is characteristic of drugs from many polymer-coated stents, including phosphorylcholine-coated stent [15,22]. We have also shown that the elution of irinotecan from coated stents respond to an exponential decay pattern as has been already shown by Swanson et al. [15] in coated stent with paclitaxel. These authors evaluated the absorption and kinetics of paclitaxel release in phosphoryilcholine-coated stents (ByodivYsio drug delivery stent) showing that paclitaxel, a hydrophobic drug like rapamycin, in a similar fashion than other combinations such as antithrombotics and abciximab, has a biphasic release pattern. This is probably because of the very rapid wash-out of very lightly adherent drug molecules on or near the surface of the polymer, followed by the slower release of drug from the polymer surface. After 24 hr, 13% of paclitaxel remained on the stent; by 48 hr almost all (96%) of the original amount had eluted from the stent [15]. In our study, the duration of the exponential decay for irinotecan was also similar to that observed for paclitaxel.

We have not performed a study on irinotecan release in phosphorylcholine-coated stents on the arterial wall, because that was not the objective of the present study, but we are reporting the in vitro irinotecan elution curve in phosphorilcholine-coated stents. Since irinotecan, paclitaxel, and rapamycin are hydrophobic drugs, we could assume that the irinotecan tissue loading profile in the arterial wall should be, at least similar to that of paclitaxel or rapamycin, as the already mentioned kinetics curve was also performed in phosphorylcholine-coated stents such as our stents, where irinotecan was attached to phosphorylcholine. On the other hand, although the drug concentration and the release kinetics of irinotecan at the vascular wall were not measured, our study showed that in adequate doses and when locally released, this drug can successfully control or reduce neointimal hyperplasia and inflammation. The fact that we observed a decrease in the neointimal growth after 2 months and that the SN-38, the active metabolite of irinotecan, is hydrophobic as well as paclitaxel, would allow thinking that the kinetics and irinotecan release in coated stents could be similar to paclitaxel's.

Although inflammatory cell infiltration was found in all three groups, the magnitude of the cellular infiltration was small as shown by the semi quantitative analysis, and in addition it was inhibited by irinotecan elu-

tion. This beneficial anti-inflammatory effect could have favorably affected the obtained inhibition effect on neointimal hyperplasia. As shown by Rogers et al. [23], the more present inflammatory elements are, the thicker neointimal becomes, and vice versa. However, it was impossible to determine in our model the direct relationship between inflammation and neointimal growth. Perhaps this lack of correlation in our study may be due to the low degree of inflammation present in our specimens.

Another process that requires particular attention is repair or scarring. Ideally, this kind of therapy with cytostatics should avoid neointimal proliferation to allow adequate stent re-endothelization. In studies carried out with radioactive stents [23], an inadequate re-endothelization was observed, with persistence of fibrin deposits beyond those observed in conventional stents. Inadequate re-endothelization includes the risk of thrombosis, whereas the presence of fibrin indicates that the reparation process is not finalized. Given that the reparation phenomenon is directly linked to neointimal hyperplasia, an incomplete reparation would imply that the proliferation continues and the risk of restenosis as well. Consequently, it is necessary to know whether we are definitively inhibiting the neointimal hyperplasia process. At the same time we need to know whether the reparation process continues its normal course. The fact that in our study we found very small quantities of fibrin deposits allows us to suggest that under our experimental conditions, an adequate scarring process should accompany the inhibition process of neointimal hyperplasia. However, the presence of fibrin deposits in our experiments, although in very small amounts, also forces us to be cautious with this conclusion. The presence of fibrin deposits after completion of the 8 weeks follow-up could suggest that the obtained differences in intimal hyperplasia could be modified, if we prolong the follow-up period. This was observed by Virmani et al. [24] in a group of animals after three months following paclitaxel-coated stents implant. Since fibrin contents in our specimens were very small, it would reduce the possibility of late restenosis.

It remains unclear whether or not prolonging the follow-up period for more than 8 weeks could modify the presence of fibrin deposits. This was observed by Farb et al. and Virmani et al. [24,25] when they followed up animals up to 3 months after paclitaxel stents implantation. However, the small amount of fibrin found in our specimens probably reduces this possibility.

Limitations of the Study

We used an animal model of hypercholesterolemic rabbits, where stents were implanted in the aorta artery followed by a 2-month follow-up period. The aorta is an elastic artery, whereas coronary arteries are muscular. As the inflammatory response to stent implant could vary from one type of artery to another, direct extrapolation of the results, in the present study, to the use of these stents in the coronary arteries should be carried out with caution. Also, despite the fact that we found a significant reduction in neointimal hyperplasia with high doses of irinotecan, we cannot ensure that long term follow-up would modify the study results. Therefore, this could limit the interpretation of results and its clinical projection. We did not measure systemic collateral effects to rule out drug effects on other body parts. However laboratory data were normal, suggesting that at least the already known deletereal effect of the cytostatics on blood cells was not present.

CONCLUSION

Therefore, we conclude that tubular stainless steel 316L stents, phosphorylcholine-coated, and loaded with irinotecan 1.29 mg attenuated neointimal proliferation in hypercholesterolemic rabbits, without evidence of cellular toxicity at the doses used 2 months after implantation. The very small amount of fibrin deposits and the decrease of the inflammatory infiltrate found in the specimens that received high doses suggest that at least in our experimental conditions, the healing or scarring process was almost complete at the time.

ACKNOWLEDGMENTS

The technical assistance of Ana Chiaro (University of Buenos Aires) and Eduardo Bertolotti (Hospital Italiano of Buenos Aires) is gratefully acknowledged.

REFERENCES

1. Betriu A, Masotti M, Serra A, Alonso J, Fernandez-Aviles F, Gimeno F, Colman T, Zueco J, Delcan JL, Garcia E, Calabuig J. Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): A four-year follow-up. J Am Coll Cardiol 1999;34:1498–1506.
2. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331:496–501.
3. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331:489–495.
4. De Scheerder I, Wang K, Wilczek K, Van Dorpe J, Verbeken E, Desmet W, Schacht E, Piessens J. Local methylprednisolone inhibition of foreign body response to coated intracoronary stents. Coron Artery Dis 1996;7:161–166.

5. Lincoff AM, Furst JG, Ellis SG, Tuch RJ, Topol EJ. Sustained local delivery of dexamethasone by a novel intravascular eluting stent to prevent restenosis in the porcine coronary injury model. J Am Coll Cardiol 1997;29:808–816.
6. Muller DW, Golomb G, Gordon D, Levy RJ. Site-specific dexamethasone delivery for the prevention of neointimal thickening after vascular stent implantation. Coron Artery Dis 1994;5:435–442.
7. Drachman DE, Edelman ER, Seifert P, Groothuis AR, Bornstein DA, Kamath KR, Palasis M, Yang D, Nott SH, Rogers C. Neointimal thickening after stent delivery of paclitaxel: Change in composition and arrest of growth over six months. J Am Coll Cardiol 2000;36:2325–2332.
8. Farb A, Heller PF, Shroff S, Cheng L, Kolodgie FD, Carter AJ, Scott DS, Froehlich J, Virmani R. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. Circulation 2001;104:473–479.
9. Heldman AW, Cheng L, Jenkins GM, Heller PF, Kim DW, Ware M Jr, Nater C, Hruban RH, Rezai B, Abella BS, Bunge KE, Kinsella JL, Sollott SJ, Lakatta EG, Brinker JA, Hunter WL, Froehlich JP. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation 2001;103:2289–2295.
10. Hong MK, Kornowski R, Bramwell O, Ragheb AO, Leon MB. Paclitaxel-coated Gianturco-Roubin II (GR II) stents reduce neointimal hyperplasia in a porcine coronary in-stent restenosis model. Coron Artery Dis 2001;12:513–515.
11. Gallo R, Padurean A, Jayaraman T, Marx S, Roque M, Adelman S, Chesebro J, Fallon J, Fuster V, Marks A, Badimon JJ. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. Circulation 1999;99:2164–2170.
12. Marx SO, Jayaraman T, Go LO, Marks AR. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. Circ Res 1995;76:412–417.
13. Covey JM, Jaxel C, Kohn KW, Pommier Y. Protein-linked DNA strand breaks induced in mammalian cells by camptothecin, an inhibitor of topoisomerase I. Cancer Res 1989;49:5016–5022.
14. Hertzberg RP, Caranfa MJ, Hecht SM. On the mechanism of topoisomerase I inhibition by camptothecin: Evidence for binding to an enzyme-DNA complex. Biochemistry 1989;28:4629–4638.
15. Swanson N, Javed Q, Hogrefe K, Gershlick A. Human internal mammary artery organ culture model of coronary stenting: A novel investigation of smooth muscle cell response to drug-eluting stents. Clin Sci (Lond) 2002;103:347–353.
16. Guo J, Verma UN, Gaynor RB, Frenkel EP, Becerra CR. Enhanced chemosensitivity to irinotecan by RNA interference-mediated down-regulation of the nuclear factor-κB p65 subunit. Clin Cancer Res 2004;10:3333–3341.
17. Diaz-Rubio E. New chemotherapeutic advances in pancreatic, colorectal, and gastric cancers. Oncologist 2004;9:282–294.
18. Makkar R, Whiting J, Li A, Honda H, Fishbein MC, Knapp FF, Hausleiter J, Litvack F, Eigler NL. Effects of β(−)-emitting (188)Re balloon in stented porcine coronary arteries: An angiographic, intravascular ultrasound, and histomorphometric study. Circulation 2000;102:3117–3123.
19. Kamiyama H, Takano S, Tsuboi K, Matsumura A. Anti-angiogenic effects of SN38 (active metabolite of irinotecan): Inhibition of hypoxia-inducible factor 1 alpha (HIF-1α)/vascular endothelial growth factor (VEGF) expression of glioma and growth of endothelial cells. J Cancer Res Clin Oncol 2005;131:205–213.
20. Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. Circulation 2001;104:600–605.
21. Levin AD, Vukmirovic N, Hwang CW, Edelman ER. Specific binding to intracellular proteins determines arterial transport properties for rapamycin and paclitaxel. Proc Natl Acad Sci USA 2004;101:9463–9467.
22. Foo RS, Gershlick AH, Hogrefe K, Baron JH, Johnston TW, Hussey AJ, Garner I, de Bono DP. Inhibition of platelet thrombosis using an activated protein C-loaded stent: In vitro and in vivo results. Thromb Haemost 2000;83:496–502.
23. Rogers C, Welt FG, Karnovsky MJ, Edelman ER. Monocyte recruitment and neointimal hyperplasia in rabbits. Coupled inhibitory effects of heparin. Arterioscler Thromb Vasc Biol 1996;16:1312–1318.
24. Virmani R, Farb A, Kolodgie FD. Histopathologic alterations after endovascular radiation and antiproliferative stents: Similarities and differences. Herz 2002;27:1–6.
25. Farb A, Tang AL, Shroff S, Sweet W, Virmani R. Neointimal responses 3 months after (32)P β-emitting stent placement. Int J Radiat Oncol Biol Phys 2000;48:889–898.