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Evaluation of the Release Behavior of the Dexamethasone Embedded in Polycarbonate Polyurethane Membranes: An In Vitro Study[1]

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Purpose: To evaluate the release behavior of dexamethasone embedded in a polycarbonate polyurethane membrane.

Materials and Methods: Both water-soluble and water-insoluble dexamethasone were tested, and the release behavior of five water-insoluble dexamethasone films of different thickness (78 to 211 μm) was also evaluated. The amount of Dexamethasone used was 10% of the total weight of the polyurethane film mass. Each film was placed in a centrifuge tube containing 25 ml of 0.1-M neutral phosphate buffer, and the tubes were placed in a shaking incubator to quantify the amount of drug released into the buffer, absorption spectroscopy ($\lambda max = 242$ nm) was employed.

Results: In the test involving water-soluble dexamethasone, 60% of the drug was released during the first two hours of the study. Films containing water-insoluble Dexamethasone, on the other hand, released 40%, 60% and 75% of the dexamethasone in one, three and seven days, respectively. Both types of film maintained low-dose drug release for 28 days. When release behavior was compared between water-insoluble films of different thickness, thicker film showed less initial burst and more sustained release.

Conclusion: Dexamethasone release behavior varies according to drug solubility and membrane thickness, and may thus be conrolled.

Index words : Drugs, side effects
Stents and prostheses
Experimental study

Prostheses such as metallic stents show poor long-term patency due to smooth muscle proliferation in the intima around them (1). Inhibitory drugs such as the potent anti-inflammatory and antiproliferative agent Dexamethasone have been administered systemically in animal models and clinical trials, and are now in clinical use (2 - 5). The systemic use of powerful medications may, however, give rise to adverse side effects, and to limit these while achieving and sustaining high levels in tissue, site-specific drug delivery systems are being used.

Research into local drug delivery rather than systemic drug administration currently underway includes the use of polymeric or coated stents, perfusion or hydrogen-coated balloon catheters and a number of other ap-

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proaches. Techniques to provide sustained local drug delivery have focused on polymers as matrices for drug incorporation and elusion. The purpose of our in-vitro study was to evaluate the release behavior of dexamethasone embedded in polycarbonate polyurethane membranes.

Materials and Methods

Dexamethasone/Polyurethane Film Design and Manufacture

The film solution was made using phosphate-based water-soluble and acetate-based water-insoluble dexamethasone (Sigma, St Louis, Minn., U.S.A.), and polycarbonate polyurethane (Cardiotech, Woburn, Mass., U.S.A.). 0.132 g of dexamethasone was added to 5 ml of dimethylacetamide (DMAc), and when the Dexamethasone had completely dissolved, 6 ml of 22% polyurethane was added to the mixture. To ensure complete admixture, a magnetic stirrer was used for 24 hours until the solution became transparent. Dexamethasone accounted for approximately 10% of the polyurethane mass.

The film was made using a specially designed, four-way thickness gauge roller known as a doctor's blade (patent pending). This device ensured that the liquid solution conformed to the thickness required for the study. The film was then dried for three days in an oven, and then for three more days in a vacuum oven. Once dried, a round punch 1cm in diameter was employed to make the samples. Each of five water-soluble and five water-insoluble films were used in this study. The thickness of two types was, respectively, 78 ± 9 μm, and 89 ± 9 μm; the difference was not statistically significant ($p = 0.257$). To evaluate Dexamethasone release behaviour, water-insoluble films of five different thicknesses (78 to 211 μm) were made. For surface analysis, scanning electron microscope (SEM) was used to compare the morphology of the two types of film.

Release Test

Four round films were inserted into separate centrifuge tubes (Falcon Labware) containing 25 ml of 0.1-M neutral phosphate buffer, and the tubes were placed in a shaking incubator. Absorption spectroscopy ($\lambda max = 242$ nm) was employed to quantify the amount of dexamethasone released into the buffer, which was changed after each measurement. The procedure was repeated at two, four, and eight hours, and then daily for 28 days.

Results

The study showed that for the two types of film, the results were significantly different. The water-soluble Dexamethasone/DMAc/polyurethane solution became transparent after 24 hours of magnetic stirring, and the water-soluble film released 60% of the drug within the first two hours, with low-dosage drug release continuing for 28 days (Fig. 1). SEM surface analysis of the film demonstrated a fibrous pattern (Fig. 2).

The water-insoluble Dexamethasone/DMAc/polyurethane solution, on the other hand, became transparent within five minutes of magnetic stirring, and the water-insoluble film released 40, 60 and 75% of the drug in one, three and seven days respectively (Fig. 1). Low dosage drug release also continued for 28 days. SEM surface analysis of the water-insoluble film indicated a smooth surface (Fig. 3). Comparison of dexamethasone release behavior between the water-insoluble films of different thickness showed that thicker film showed less initial burst and more sustained release (Fig. 4).

Discussion

In the field of vascular intervention, metallic stents show poor long-term patency due to smooth muscle cell proliferation or neointimal hyperplasia around the stent, resulting in restenosis (1). To prevent this, systemic administration of numerous drugs has been tried (2 - 4),

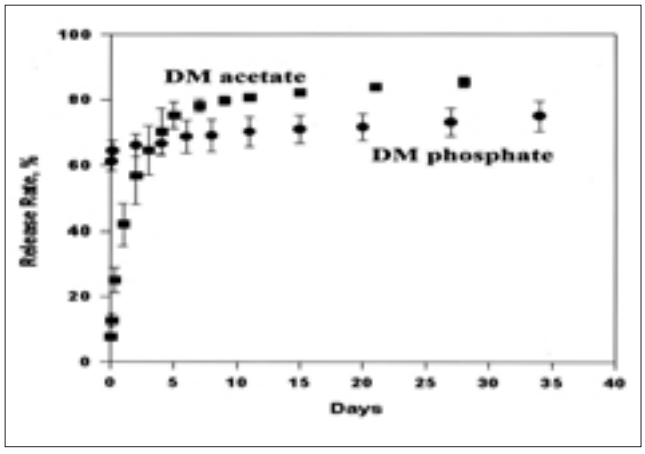

Fig. 1. The change of water-soluble Dexamethasone (DM phosphate) and water-insoluble Dexamethasone (DM acetate) release rate over time. 60% of the drug is released from water-soluble Dexamethasone film during the first 2 hours. 40% of the drug is released from water-insoluble Dexamethasone film during the first 24 hours.

but adverse side effects have sometimes arisen. In an attempt to achieve and sustain high tissue levels of the drug, and decrease or avoid these potential side effects, new approaches to more effective site-specific drug delivery are being directed toward local delivery system rather than systemic drug administration. Glucocorticoids have a potent anti-proliferative effect and have been shown to inhibit smooth cell proliferation in-vitro (6 - 8, 12).

Several studies have indicated that dexamethasone reduces restenosis in the field of vascular intervention. Stone et al. (13) randomly administered 125 mg methylprednisolone intramuscularly to 52 patients the night before and in the morning of the day of repeat percutaneous transluminal coronary angioplasty (PTCA). The restenosis rate was 36% in the steroid group and 40% in the control group, and while this difference was not statistically significant, it was interpreted as suggesting a trend in favor of steroid treatment to reduce restenosis. In a study using sustained release from biodegradable nanoparticles, Voisard (9) found that a significant amount of dexamethasone was present in the treated segment for up to 14 days after a single infusion, through none of the drug was detected in plasma after the first three hours. There was a 31% reduction in the intima-media ratio in animals treated with local dexamethasone nanoparticles compared with the control group. Strecker et al. (5) percutaneously implanted Strecker stents coated with a biodegradable membrane containing into the femoral artery of 14 dogs, finding that in comparison with non-coated stents, they reduced neointimal hyperplasia (5).

In local drug delivery studies by Lincoff et al. (10) and Muller et al. (11), poly-L-lactic acid (PLLA) and silicone were used, respectively, showing respective rate of 0.8 mg/day over 6 days, and 5 mg/day for the first 3 days and 0.3 mg/day thereafter. Lincoff et al., using stents coated with Dexamethasone in high-molecular-weight PLLA, found no decrease in neointimal hyperplasia, concluding that the stent used for elution appeared to be a well-tolerated and effective means of providing sustained, site-specific drug delivery to porcine coronary artery wall for at least 28 days. Muller et al. used dexamethasone-impregnated silicone polymers (20% by weight), and the intimal hyperplasic response was not reduced (11). According to previously published literature, drug concentration and duration within tissue were the most important criteria when evaluating a drug's anti-inflammatory and anti-proliferative effects.

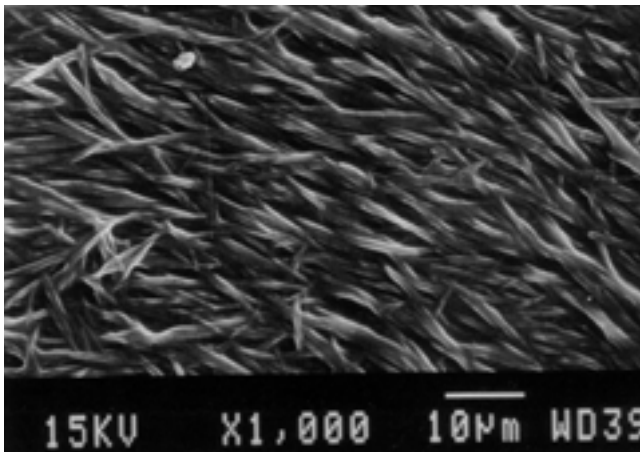

Fig. 2. SEM Photograph of water-soluble Dexamethasone film(×1,000). The surface of the matrix shows fiber pattern.

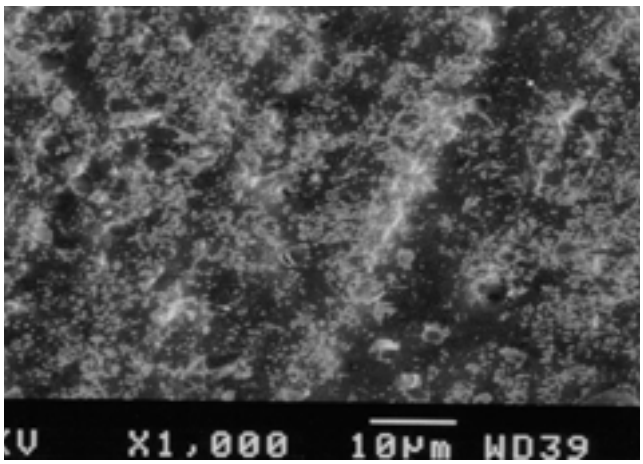

Fig. 3. SEM Photograph of water-insoluble Dexamethasone film(×1,000). The surface of the matrix is smooth compare to that of water-soluble Dexamethasone film.

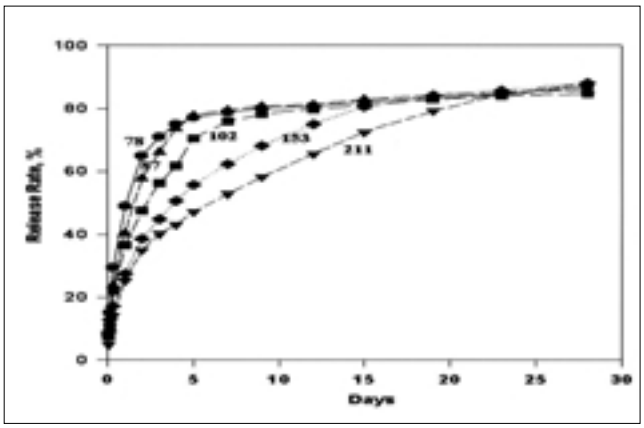

Fig. 4. Comparison of the Dexamethasone release behavior among the water-insoluble films of different thickness. The figures of the graphs represent the thickness of the films (㎛). Thicker film showed less initial burst and more sustained release.

DMAc is an ideal solvent for polyurethane because it contains an amide group, which dissolves solutes that have a urethane linkage. It is also a good solvent for the water-insoluble dexamethasone, but a poor one for the water-soluble dexamethasone, as evidenced by the time required for the solute to dissolve. In our study, the water-soluble dexamethasone-dimethyacetamide solution, we believe, affected the shape of the polyurethane surface. During the drying procedure, the polyurethane chains formed tighter bonds, separated from the water-soluble dexamethasone which, unprotected by the polymer chains, was rapidly released from the film, as the large initial burst indicated. DMAc is a good solvent for both water-insoluble dexamethasone and polyurethane. There was little separation of the drug from the polymer chains during the drying procedure, as the homogeneous polymer surface indicated, and for this film, drug release was therefore much slower.

We also found that the initial drug release was slower in thick film than in thin, and believe this is because the drug on the surface can be released easily from the polymer matrix and that the thicker film has a lower surface/volume ratio, and thus less surface effect. Film thickness, however, cannot be infinitely increased, as this would increases the diameter of the stent delivery catheter.

In this study, we showed that the delivery rate of dexamethasone could be affected greatly by different chemical structures of the drug, as well as the film thickness of the drug-carrying matrix. In addition, polyurethane film was found to be a good matrix for sustained local delivery of dexamethasone. We believe that water-insoluble dexamethasone can more effectively present hyperplasia, as drug delivery is more sustainable. An animal study in which water-insoluble Dexamethasone is used is currently underway.

References

1. Villa AE, Guzman LA, Chen W, Goromb G, Levy RJ, Topol EJ. Local delivery of dexamethasone for prevention of neointimal proliferation in a rat model of balloon angioplasty. *J Clin Invest* 1994;93(3):1243-1249
2. Pepine CJ, Hirshfeld JW, Macdonald RG, et al. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. *Circulation* 1990;81:1753-1761
3. Van Put DJ, Van Hove CE, De Meyer GR, Wuyts F, Herman AG, Bult H. Dexamethasone influences intimal thickening and vascular reactivity in the rabbit collared carotid artery. *Eur J Pharmacol* 1995;294(2-3):753-61
4. Dangas G, Fuster V. Management of restenosis after coronary intervention. *Am Heart J* 1996;132:428-436
5. Streker EP, Gabelmann A, Boos I, et al. Effect on intimal hyperplasia of dexamethasone released from coated metal stents compared with non-coated stents in canine femoral arteries. *Cardiovasc Intervent Radiol* 1998;21:487-496
6. Longenecker JP, Kilty LA, Johnson LK. Glucocorticoid influence on growth of vascular wall cells in culture. *J Cell Physiol* 1982;113:197-202
7. Jarvelainen H, Halme T, Ronnemaa T. Effect of cortisol on the proliferation and protein synthesis of human aortic smooth muscle cells in culture. *Acta Med Scand Suppl* 1982;660:114-122
8. Nichols NR, Olsson CA, Funder. JW. Steroid effects on protein synthesis in cultured smooth muscle cells from rat aorta. *Endocrinology* 1983;113:1096-1101
9. Voisard R, Seitzer U, Baur R, et al. Corticosteroid agents inhibit proliferation of smooth muscle cells from human atherosclerotic arteries in vitro. *Int J Cardiol* 1994;43:257-267
10. Stone GW, Rutherford BD, Mcconahay DR, et al. A randomized trial of corticosteroids for the prevention of restenosis in 102 patients undergoing repeat coronary angioplasty. *Cathet Cardiovasc Diagn* 1989;18:227-231
11. Guzman LA, Labhasetwar V, Song C, et al. Local intraluminal infusion of biodegradable polymeric nanoparticles. A novel approach for prolonged drug delivery after balloon angioplasty. *Circulation* 1996;94(6):1441-1448
12. 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 Cadiol* 1997;29(4):808-816
13. 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(5):435-442

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덱사메타손을 함유한 폴리카보네이트 폴리유레탄 피막의 약물 방출 형태에 대한 연구[1]

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목적: 덱사메타손을 포함한 폴리우레탄 피막으로부터 방출되는 약물의 양과 속도를 알아보고자 하였다.
대상과 방법: 수용성 및 지용성 덱사메타손을 사용 하였으며, 지용성 덱사메타손을 포함하는 필름은 여러 가지 두께(78 - 211 ㎛)로 제작하여 두께에 따른 방출 속도를 측정하였다. 덱사메타손의 양은 폴리우레탄 피막 무게의 10% 를 사용하였다. 각각의 필름은 25 mL의 0.1 M 포스페이트 버퍼가 들어 있는 튜브에 넣고 세이킹 인규베이터에서 방출시킨 후 스펙트로스코피(λmax=242 nm)를 이용하여 방출된 약물의 양을 측정하였다.
결과: 수용성 덱사메타손을 포함한 필름에서는 2시간 만에 60%의 덱사메타손이 방출되었으나 지용성 덱사메타손을 포함한 필름에서는 1일, 3일, 7일에 각각 40%, 60%, 75%의 덱사메타손이 방출되었다. 수용성과 지용성 필름 모두에서 28일까지 소량의 약물이 지속적으로 방출되었다. 지용성 덱사메타손을 포함하는 서로 다른 두께의 필름에서는 두께가 두꺼운 필름에서 초기 방출량이 두께가 얇은 필름과 비교하여 적었으며 방출량이 서서히 증가하였다.
결론: 덱사메타손을 포함하는 폴리우레탄 피막으로부터 방출되는 약물의 양은 약제의 성상(수용성/지용성)과 피막의 두께에 의하여 조절될 수 있을 것으로 생각된다.