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Ocular Tissue Concentrations of Mitomycin C With Variable Dose and Duration of Application Time in Rabbits

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Abstract: We measured mitomycin C (MMC) concentrations in ocular tissues in rabbits with variable dose (0.1, 0.2, or 0.4 mg) and duration of application time (1, 3, or 5 minutes) of MMC using high-performance liquid chromatography. Mitomycin C concentrations at the administered site after single subconjunctival application of MMC and after irrigation showed significant correlation with dose and duration of time of application. By multiple regression analysis, MMC concentrations (μg/g) at the conjunctiva were described as $-6.73 + 67.4 \times$ Dose (mg) $+ 1.66 \times$ Time (minutes) (R^2 0.65); at the sclera, $-1.85 + 38.2 \times$ Dose $+ 0.927 \times$ Time (R^2 0.63); at the cornea, $-0.727 + 8.44 \times$ Dose (R^2 0.46). With a 0.2-mg MMC dose, in all three application times (1, 3, or 5 minutes), MMC concentrations in the conjunctiva at the administered quadrant were three times higher than in the neighboring quadrants and 6 to 7 times higher than in the opposite quadrant. In the sclera, MMC concentrations were 3.5 times higher than in the neighboring sites and over 8 to 9 times higher than in the opposite site. In the cornea, MMC concentrations were 2 to 3 times higher than in the neighboring sites and opposite site. In the iris-ciliary body, MMC concentrations were 0.61 μg/g at the administered site with 0.2 mg for 3-minute application, 2 times higher than in neighboring sites, and 2 times higher than in opposite sites. **Jpn J Ophthalmol 1998;42:193–198** © 1998 Japanese Ophthalmological Society

Key Words: Ciliary body, concentration, conjunctiva, cornea, high-performance liquid chromato-graphy, iris, mitomycin C, rabbits, sclera.

Introduction

Mitomycin C (MMC) is used intraoperatively to inhibit subconjunctival proliferation after trabeculectomy.[1–8] In cultured human Tenon capsule fibroblasts, 0.4 mg/mL of MMC has been shown to inhibit 77% of the cell proliferation in 1-minute application and 90% in 5-minute application.[9] In filtration surgery in rabbits, the survival of the filtering bleb was reported to be longer with use of 0.4 mg/mL of MMC for 5-minute application than in 0.2 mg/mL of MMC for 5-minute application.[10] In human eyes, Kitazawa et al reported successful intraocular pressure control in 100% of uncomplicated primary open-angle glaucoma cases using 0.2 mg/0.5 mL of MMC for 5 minutes and in 63.6% of cases using 0.02 mg/0.5 mL of MMC for 5 minutes.[1] Thus, it is evident that dose and duration of application time of MMC are related to the success of trabeculectomy. On the other hand, it was reported that, in rabbit experiments, complications after filtration surgery, including endophthalmitis, transient corneal opacification, corneal neovascularization, and a presumed bleb leak, were found in eyes treated with 0.4 mg/mL of MMC, but complications were not found in eyes with 0.2 mg/mL. Kitazawa et al reported that maculopathy and cataract progression were noted in the use of 0.2 mg/0.5 mL of MMC for 5-minute eye applications exclusively and did not occur in the use of 0.02 mg/0.5 mL of MMC for 5-minute eye applications.[1] There have been no reports, however, on the tissue concentrations with variable dose and duration of application time of MMC. We studied the relationships between MMC concentrations in ocular tissues (conjunctiva, sclera, cornea, iris) and variable

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dose and duration of application time of MMC in the rabbit.

Materials and Methods

We used 50 dutch rabbits (body weight between 2500 and 3000 g) in all experiments and followed the Association for Research in Vision and Ophthalmology Statement on the Use of Animals in Ophthalmic and Vision Research.

Experiment 1

The purpose of this experiment was to determine the relationships between the dose and the duration of application time of MMC and MMC concentrations in ocular tissues. After administering intravenous anesthesia (1.0 g/kg of Urethane), a limbal-based conjunctival flap was made, and the sclera was exposed at the superior temporal quadrant by incising the conjunctiva 5 mm posterior to the limbus and extending the incision circumferentially for approximately 60 degrees. Then a sliced surgical sponge (MQA, Inami, Tokyo, Japan), which had absorbed 0.5 mL of MMC solution (0.02%, 0.04%, or 0.08%) was placed between the conjunctiva and the sclera for 1 to 5 minutes. After removal of the sponge, exposed tissues were rinsed with 200 mL of saline. Dose and duration of application time of MMC were set at a dosage of 0.1 mg (0.02%, 0.5 mL) for 3 or 5 minutes; 0.2 mg (0.04%, 0.5 mL) for 1, 3, or 5 minutes; and 0.4 mg (0.08%, 0.5 mL) for 1 or 3 minutes. Each experiment was done in one eye of five rabbits. We sacrificed rabbits with intravenous injections of 10 mL of 5% pentobarbital sodium immediately after the rinsing. Then, we enucleated eyes and immediately froze the eyeballs at −80°C. Each eyeball was cut into anterior and posterior halves at the equator, and we excised a quadrant of the anterior half, including the cornea, conjunctiva, and anterior sclera at the site where the MMC had been administered. The MMC concentration in each tissue was measured by high-performance liquid chromatography technique according to the method reported by Kawase et al.[11]

Using multiple regression analysis, statistical analyses were conducted to investigate the relationships between MMC concentrations in each ocular tissue and the dose and duration of application time of MMC. In the analyses, the tissue concentration was analyzed as a function of dose and duration of application time of MMC.

Experiment 2

The purpose of this experiment was to determine the tissue concentrations of MMC in each quadrant of the anterior segment of the eye. In rabbits other than those used in Experiment 1, after application of 0.2 mg of MMC (0.04%, 0.5 mL) for 1, 3, or 5 minutes in the same manner as in Experiment 1, the anterior segment (including the cornea, conjunctiva, anterior sclera, and iris-ciliary body) was sectioned into four quadrants—administered site, neighboring sites (temporal and nasal), and the opposite site. After excision of the conjunctiva, sclera, cornea, and iris-ciliary body from each quadrant, the MMC concentration of each specimen was measured using the high-performance liquid chromatography technique as mentioned above. Five eyes were used at each application time of MMC. The MMC concentrations in each tissue at the different quadrants were compared for each application time. We used the nonpaired *t*-test for analysis and set $P < 0.05$ as the significance level.

Results

Experiment 1: MMC Concentration at the Administered Site

Conjunctiva. Minimum MMC concentration was 6.2 ± 3.3 μg/g (mean ± SD) with a 0.1-mg dose for the 3-minute application; maximum concentration was 31.7 ± 10.6 μg/g with a 0.4-mg dose for the 3-minute application (Table 1). The MMC concentration in the conjunctiva increased with greater application time for all three doses of MMC; with a 0.2-mg dose, MMC concentration was 9.7 ± 2.7 μg/g for 1-minute application, 12.6 ± 1.3 μg/g for 3-minute application, and 14.9 ± 5.0 μg/g for 5-minute application (Figure 1). In the 3-minute application, tissue concentration increased as MMC dose was increased: 6.2 ± 3.3 μg/g with a 0.1-mg dose, 12.6 ± 1.3 μg/g with a 0.2-mg dose, and 31.7 ± 10.6 μg/g with a 0.4-mg dose (Figure 2). The MMC concentration in the conjunctiva was significantly related to both dose ($P < 0.01$) and

Table 1. Tissue Concentrations of Mytomycin C (μg/g) with Variable Dose and Duration of Application Time

	Conjunctiva	Sclera	Cornea
0.1 mg, 3 minutes	6.2 ± 3.3	3.3 ± 2.2	0.4 ± 0.3
0.1 mg, 5 minutes	8.2 ± 2.4	4.9 ± 1.1	0.6 ± 0.3
0.2 mg, 1 minute	9.7 ± 2.3	8.7 ± 2.0	1.3 ± 1.0
0.2 mg, 3 minutes	12.6 ± 1.3	10.3 ± 1.3	1.3 ± 0.9
0.2 mg, 5 minutes	14.9 ± 5.0	11.3 ± 1.1	1.7 ± 1.1
0.4 mg, 1 minute	23.0 ± 9.5	12.6 ± 4.3	2.4 ± 1.8
0.4 mg, 3 minutes	31.7 ± 10.6	17.4 ± 3.4	3.3 ± 1.1

Data are expressed as mean ± standard deviation.

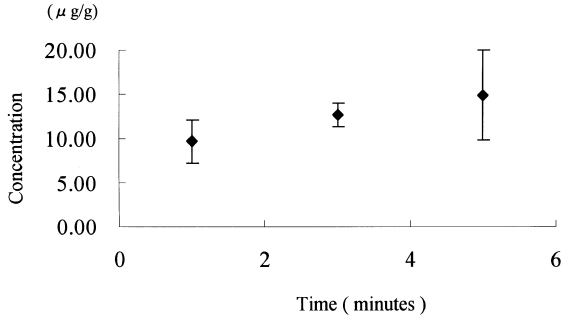

Figure 1. Mytomycin C (MMC) concentrations in the conjunctiva with 0.2 mg of MMC. The *y* axis shows MMC concentrations of the conjunctiva (μg/g), and the *x* axis shows application time (minutes) of MMC. Bar = SD.

duration of application time ($P < 0.05$). This relationship was described by the following equation:

MMC Concentration =
−6.73 + 67.4 × Dose (mg) + 1.66 × Time (minutes)

R^2 of the regression line was 0.652 (Table 2).

Sclera. Minimum MMC concentration was 3.3 ± 2.2 μg/g (mean ± SD) with a 0.1-mg dose for the 3-minute application; maximum concentration was 17.4 ± 3.4 μg/g with a 0.4-mg dose for the 3-minute application (Table 1). The MMC concentration in the sclera increased with greater application time for all three doses of MMC, as in the conjunctiva. With a 0.2-mg dose, the concentration was 8.7 ± 2.0 μg/g for the 1-minute application, 10.3 ± 1.3 μg/g for the 3-minute application, and 11.3 ± 1.1 μg/g for the 5-minute application (Figure 3). In the 3-minute application, tissue concentration increased as MMC dose was increased: 3.3 ± 2.2 μg/g with a 0.1-mg dose, 10.3 ± 1.3 μg/g with a 0.2-mg dose, and 17.4 ± 3.4 μg/g with a 0.4-mg dose (Figure 4). The MMC concentration in the sclera was significantly related to both dose ($P < 0.01$) and duration of application time ($P < 0.05$). The relationship was described by the following equation:

MMC Concentration =
−1.85 + 38.2 × Dose (mg) + 0.927 × Time (minutes)

R^2 of the regression line was 0.630 (Table 2).

Table 2. Correlation Between the Mytomycin C Concentration and Dose or Duration of Application Time

	Dose		Time		
	α	*P* Value[a]	β	*P* Value	R^2
Conjunctiva	67.4	<0.001[a]	1.66	0.013[b]	0.65
Sclera	38.2	<0.001[a]	0.927	0.030[b]	0.63
Cornea	8.44	<0.001[a]	0.139	0.291	0.46

[a]Shows $P < 0.01$ between dose and concentration.
[b]Shows $P < 0.05$ between time and concentration.

Cornea. Minimum MMC concentration was 0.4 ± 0.3 μg/g (mean ± SD) with a 0.1-mg dose for the 3-minute application; maximum concentration was 3.3 ± 1.1 μg/g with a 0.4-mg dose for the 3-minute application (Table 1). The MMC concentrations in the cornea increased with greater dose of MMC ($P < 0.01$), but the concentrations did not relate to the change in application time ($P = 0.29$). With the 0.2-mg dose, MMC concentration as 1.3 ± 1.0 μg/g for the 1-minute application, 1.3 ± 0.9 μg/g for the 3-minute application (Figure 5), and 1.7 ± 1.1 μg/g for the 5-minute application. In the 3-minute application (Figure 6), tissue concentration increased with greater dose of MMC: 0.4 ± 0.3 μg/g with a 0.1-mg

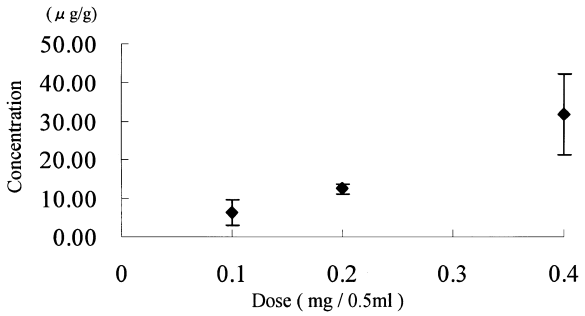

Figure 2. Mytomycin C (MMC) concentrations in the conjunctiva after 3-minute application of MMC. The *y* axis shows MMC concentrations of the conjunctiva (μg/g), and the *x* axis shows dose of MMC (mg). Bar = SD.

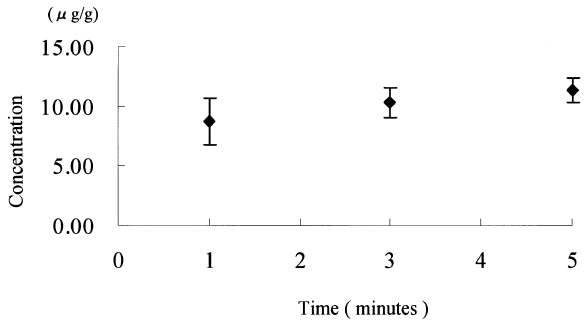

Figure 3. Mytomycin C (MMC) concentrations in the sclera with 0.2 mg of MMC. The *y* axis shows MMC concentrations of the sclera (μg/g), and the *x* axis shows application time (minutes) of MMC. Bar = SD.

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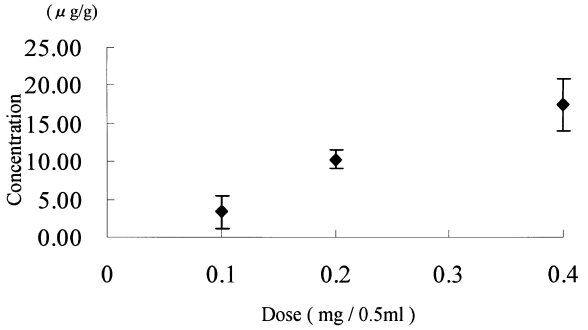

Figure 4. Mytomycin C (MMC) concentrations in the sclera after 3-minute application of MMC. The *y* axis shows MMC concentrations of the sclera (μg/g), and the *x* axis shows dose of MMC (mg). Bar = SD.

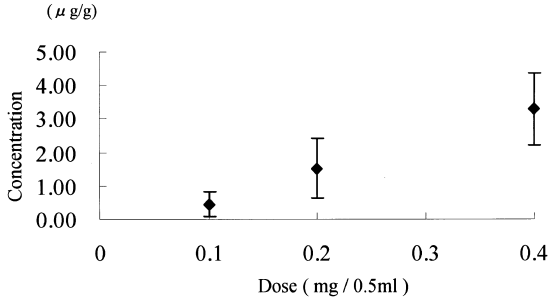

Figure 6. Mytomycin C (MMC) concentrations in the cornea after 3-minute application of MMC. The *y* axis shows MMC concentrations of the cornea (μg/g), and the *x* axis shows dose of MMC (mg). Bar = SD.

dose, 1.3 ± 0.9 μg/g with a 0.2-mg dose, and 3.3 ± 1.1 μg/g with a 0.4-mg dose. The tissue concentrations of 0.5 mL of MMC were described by the following equation:

$$\text{MMC Concentration} = -0.727 + 8.44 \times \text{Dose (mg)}$$

R^2 of the regression line was 0.461 (Table 2).

Experiment 2: MMC Concentration at Each Quadrant

Tissue concentrations of MMC in the conjunctiva, cornea, and sclera at the administered quadrant with a 0.2-mg dose of MMC for the 1-, 3-, and 5-minute applications were not statistically different from the results obtained in Experiment 1. In each tissue sample, concentration of MMC at the administered site was significantly higher than in the temporal ($P < 0.01$) or nasal ($P < 0.01$) neighboring sites and opposite site ($P < 0.01$). There was no significant difference in tissue concentration between temporal and nasal neighboring sites. In the conjunctiva, with all three application times (1, 3, and 5 minutes), MMC concentration at the administered site was 3 times higher than in the neighboring sites and 6 to 7 times higher than in the opposite site. In the sclera, tissue concentration at the administered site was 3.5 times higher than in neighboring sites and over 8 to 9 times higher than in the opposite site. In the cornea, tissue concentration at the administered site was 2 to 3 times higher than in the neighboring sites and opposite site. In the iris-ciliary body, tissue concentration at the application site was 2 to 2.5 times higher than in the neighboring sites and 5 times higher than in the opposite site (Table 3).

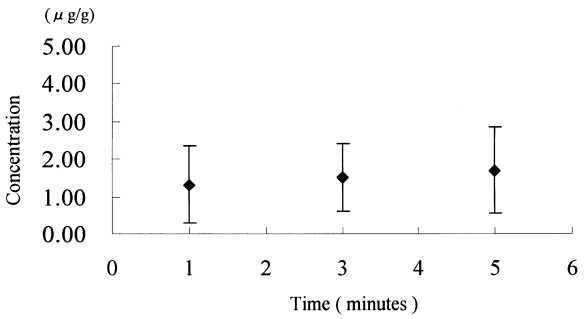

Figure 5. Mytomycin C (MMC) concentrations in the cornea with 0.2 mg of MMC. The *y* axis shows MMC concentrations of the cornea (μg/g), and the *x* axis shows application time (minutes) of MMC. Bar = SD.

Discussion

The MMC concentration in the conjunctiva, sclera, cornea, and iris-ciliary body of the anterior segment was determined by high-performance liquid chromatography after subconjunctival MMC application with variable dose and application time.

Throughout the present study, we used the same surgical microsponge (MQA, Inami, Tokyo), which has been used in our clinic in routine trabeculectomy with adjunctive MMC since William et al reported that different sponges showed different absorption and release of MMC.[12] To estimate the reproducibility of the experiments, we determined the tissue concentrations in Experiments 1 and 2 independently using different rabbits at the same dose (0.2 mg) and the same duration of application times (1, 3, or 5 minutes). The tissue concentrations determined in the conjunctiva, cornea, and sclera in both experiments indicated good reproducibility.

In this study, we determined the tissue concentration of MMC immediately after application. Kawase et al reported that tissue concentration of MMC after

Table 3. MMC Concentration (μg/g) at Each Quadrant of 0.2-mg Application

Tissue	Site	1 Minute	3 Minute	5 Minutes
Conjunctiva	Application	9.6 ± 6.9	11.8 ± 3.7	14.4 ± 7.2
	Neighbor (NS)	3.3 ± 3.6	3.5 ± 1.8	3.8 ± 1.6
	Neighbor (TI)	3.6 ± 2.2	4.1 ± 2.6	4.4 ± 2.9
	Opposite	1.4 ± 0.9	1.9 ± 1.4	2.1 ± 1.6
Sclera	Application	7.3 ± 4.2	9.1 ± 3.7	10.8 ± 2.9
	Neighbor (NS)	2.0 ± 2.6	2.5 ± 1.0	3.3 ± 1.1
	Neighbor (TI)	2.1 ± 1.2	2.7 ± 1.3	3.4 ± 1.4
	Opposite	0.8 ± 0.3	1.1 ± 0.8	1.3 ± 0.6
Cornea	Application	1.1 ± 0.5	1.3 ± 1.0	1.8 ± 1.3
	Neighbor (NS)	0.3 ± 0.1	0.4 ± 0.2	0.6 ± 0.3
	Neighbor (TI)	0.4 ± 0.2	0.5 ± 0.2	0.7 ± 0.4
	Opposite	0.4 ± 0.2	0.5 ± 0.3	0.6 ± 0.1
Iris-ciliary body	Application	0.53 ± 0.11	0.61 ± 0.3	0.93 ± 0.1
	Neighbor (NS)	0.26 ± 0.17	0.34 ± 0.2	0.35 ± 0.1
	Neighbor (TI)	0.24 ± 0.16	0.31 ± 0.18	0.38 ± 0.1
	Opposite	0.10 ± 0.04	0.10 ± 0.05	0.14 ± 0.10

Data are expressed as mean ± standard deviation. NS: nasal superior. TI: temporal inferior.

subconjunctival application through surgical sponges in rabbit eyes decreased rapidly with a halflife of 0.30 hour in the conjunctiva and 0.32 hour in the sclera.[11] Our results, therefore, indicated the maximum concentrations of MMC in each ocular tissue. The MMC concentrations in the conjunctiva after application for 5 minutes with 0.2 mg of MMC in this study (14.9 ± 5.0 μg/g in Experiment 1; 14.4 ± 7.2 μg/g in Experiment 2) were comparable to the values of 12.3 ± 6.4 μg/g immediately after application of 0.2 mg of MMC for 5 minutes administered in the same manner as reported in Kawase et al's experiment. The MMC concentrations in the sclera after 5-minute application of 0.2 mg of MMC (11.3 ± 1.1 μg/g in Experiment 1; 10.9 ± 2.3 μg/g in Experiment 2), however, were higher than that obtained in Kawase et al's study (4.3 ± 2.4 μg/g). This difference may result from the difference in the size of tissue section excised for the measurements or the difference in the sponges used. In our study, a quadrant of the segment anterior to the equator was excised, where the conjunctiva was about 15 × 15 mm and the sclera was about 10 × 7 mm. Kawase et al's conjunctiva was 15 × 15 mm, and the sclera was 15 × 17 mm. We used microsurgical sponges (MQA), and they used another surgical sponge (Spongel, Yamanouchi Pharmaceutical Co., Tokyo).

The present study showed that the tissue concentrations depended on both dose and duration of application time of MMC. The dose of MMC applied, however, affected the tissue concentrations more than the duration of application time for not only the conjunctiva and the sclera but also the cornea. For example, according to the conjunctiva equation, additional application of 0.1 mg of MMC increases the MMC concentration by 6.7 μg/g, and 1-minute prolongation of application time increases the concentration by 1.7 μg/g. (If dose is increased from 0.2 mg to 0.4 mg, MMC concentration in the conjunctiva would increase by 13 μg/g. If application time is prolonged from 3 minutes to 5 minutes, the concentration would increase to 3.3 μg/g). Even though the data obtained in rabbits in our experiments cannot be directly applied to clinical trabeculectomy, Kawase et al reported that MMC concentrations in a human corneo-scleral block obtained during trabeculectomy after the application of 0.5 mL of 0.04% MMC (0.2 mg) for 5 minutes and after irrigation were identical to that in the rabbit sclera.[11] Our data in these experiments, therefore, can be useful as a reference for clinical use. In a recent study on human primary trabeculectomy, Cohen et al reported that there was no difference in intraocular pressure control with three different application times (0.5, 0.75, and 1 minute) of 0.5 mg/mL of MMC. They also stated that the duration of MMC exposure (1 to 3 minutes) did not affect the intraocular pressure control in glaucoma eyes with a history of previous intraocular surgery. These results suggest that the tissue concentrations of MMC were affected by dose more than exposure time, as shown in the present study. Cheung et al also could not find a relationship among the concentration of MMC (0.2–0.5 mg/mL), exposure time (0.5–5 minutes), and surgical failure in a series of 157 trabeculectomies. In their series, however, the concentration and exposure time of MMC

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varied based on the risk failure for each patient, and all cases received 0.5 or 0.4 mg/mL of MMC except for one eye that received 0.2 mg/mL of MMC. Kitazawa et al stated that the most appropriate dose of MMC in 5-minute exposure would be between 0.2 mg/mL and 0.02 mg/mL according to their results of 100% success with the former dose compared with 63.6% success using the latter dose.[1] Therefore, in Cheung et al's study, the concentration of MMC in ocular tissue may be beyond the dose level for discussing the relationship between the success rate of trabeculectomy and the dose of MMC.

Regarding the complications after MMC trabeculectomy, Twer et al reported that there was a higher incidence of hypotony and choroidal effusion with 0.5 mg/mL for 5-minute application than with 0.25 mg/mL for 3-minute application.[5] Neelakantan et al found that serious choroidal detachment was more frequent with 0.5 mg/mL for 5-minute application than with 0.4 mg/mL for 3-minute application.[4] These data suggest that dose and/or duration of application time of MMC relates not only to intraocular pressure control but also to complications.

Nuits et al found that toxic changes, such as myeline figures, increased melanolipofuscin granule, vacuolated cytoplasm, and disrupted mitochondria in the ciliary body epithelium at the administered site of 0.5 mg MMC/mL for 5 minutes in human eyes.[13] Mietz et al reported that, in the rabbit eye, application of 0.2 mg MMC/mL for 5 minutes induced cytotoxic changes, such as large intracellular vacuoles and swollen mitochondria on the ciliary epithelium.[14] In the present study, after application of 0.2 mg of MMC for 1 to 5 minutes, MMC was detected in the iris-ciliary body not only at the administered site (0.53–0.93 μg/g) but also at the opposite site (0.10–0.14 μg/g). Even though these concentrations were less than one tenth of the concentrations at the conjunctiva and sclera, further investigation is needed to determine possible adverse effects of MMC on the ciliary body.

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