4. RESULTS

4.1. Results of treatments performed on rabbits

4.1.1. Pharmacokinetics of Carboplatin in the rabbit

Determination of concentrations via AAS in the retina, choroid, vitreous and optic nerve following subconjunctival injection or iontophoretic carboplatin delivery revealed significantly higher levels than those achieved with systemic administration.

Table 8.

Pharmacokinetic distribution of carboplatin in target tissues post subconjunctival injection, Coulomb-controlled iontophoresis (CCI), and systemic administration.

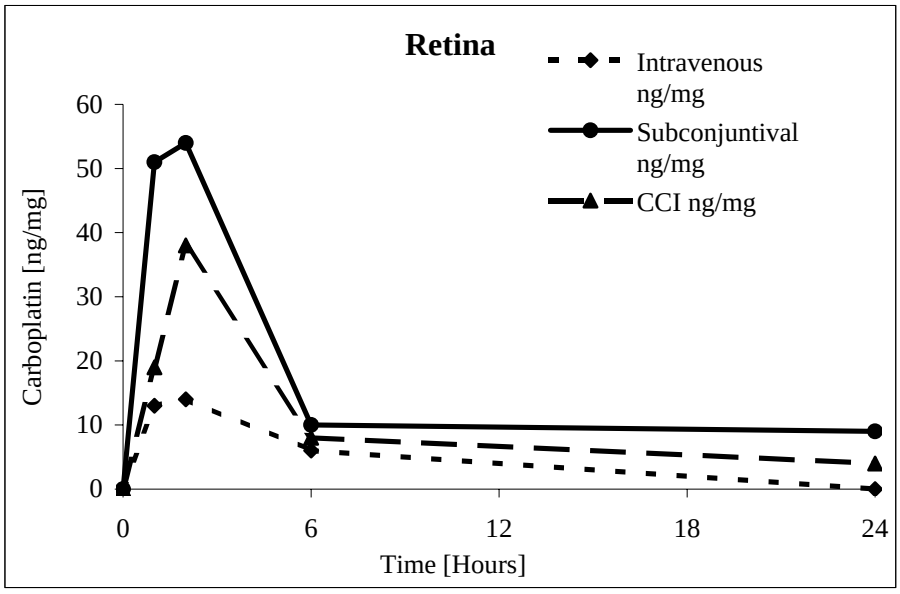
Treatment Modality	Time (hours)	Choroid (ng/mg)	Retina (ng/mg)	Optic nerve (ng/mg)	Vitreous (ng/ml)	Blood Plasma (ng/ml)
Subconjunctival	1	612.36±211.51	51.58±22.12	43.52±16.57	4560±1053.53	182±452.11
Subconjunctival	2	205.65±86.22	53.68±34.72	30±14.11	3305±813.56	327±21.21
Subconjunctival	6	26.94±7.04	10.16±6.72	13.87±4.79	860±56.12	75±56.57
Subconjunctival	24	18.54±3.67	8.93±8.27	7.3±1.08	1124±176.52	14±14.14
CCI	1	483±448.08	19±36.04	19±13.08	1575±850.37	261±20.81
CCI	2	155±131.25	38±28.29	37±48.14	1655±1645.61	178±43.27
CCI	6	23±23.78	8±3.08	8±7.25	1955±946.08	121±36.02
CCI	24	8±36.03	4±0.98	4±2.32	680±205.42	103±5.57
Systemic	1	48±16.55	13±9.36	13±3.12	332±126.87	6222±2554.89
Systemic	2	40±30.37	14±15.61	24±18.11	685±276.82	3452±1928.39
Systemic	6	15±2.51	6±0.78	6±2.06	1220±1029.93	397±66.58
Systemic	24	0.001±0.001	0.001±0	0.001±0	804±1	8±5

Mean values ±standard deviation

Carboplatin levels in the retina peaked at 2hours with 53.68ng/mg post subconjunctival injection and following iontophoretic and intravenous delivery with concentrations of 38ng/mg and 14ng/mg, respectively. **(Graph 1A)**

Graph 1A.

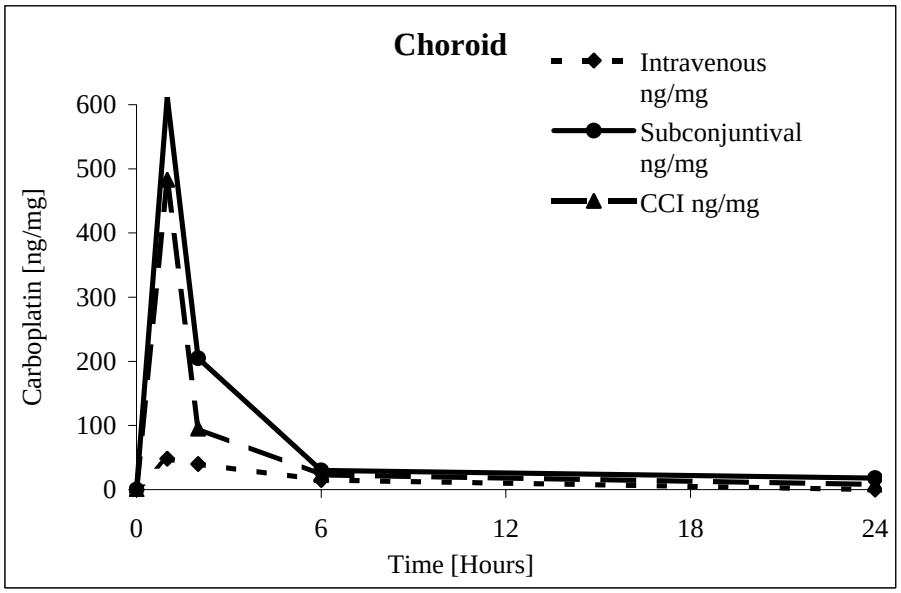
Pharmacokinetics of carboplatin in the retina comparing concentrations following subconjunctival injection, CCI, and intravenous (iv.) administration. Time course curves indicate carboplatin concentrations in the retina following subconjunctival injection and CCI delivery are significantly higher than after iv. injection (p=0.005).



The values achieved by local administration were significantly higher than those obtained in the choroid by intravenous administration (p<0.001). Concentration versus time curves revealed higher levels of carboplatin in the choroid following focal drug delivery compared to intravenous injection. **(Graph 1B**) Peak levels of 612.36ng/mg carboplatin in the choroid were measured following subconjunctival injection at 1hour post administration. With iontophoretic delivery peak levels reached 483ng/mg and 48ng/mg intravenous administration in the choroid at 1hour post delivery.

Graph 1B.

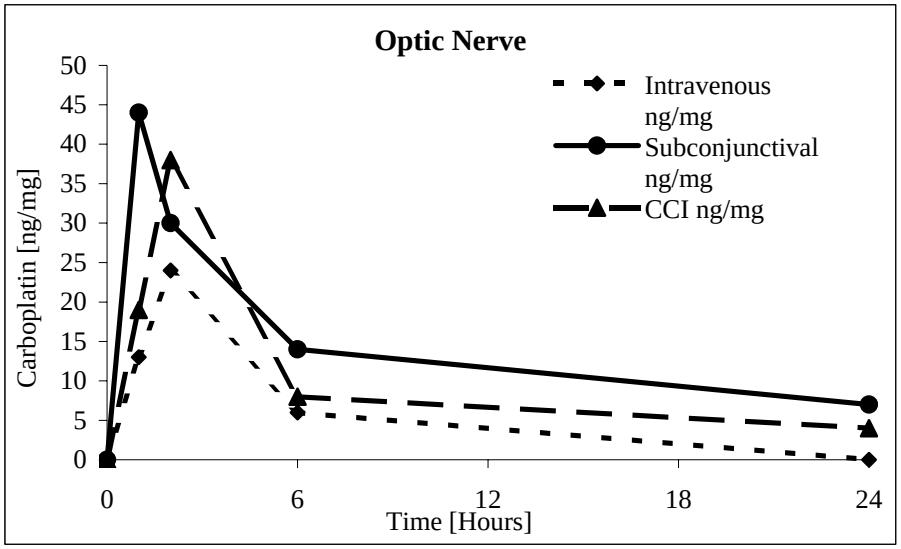
Pharmacokinetics of carboplatin in the choroid comparing concentrations following subconjunctival injection, CCI, and intravenous (iv.) administration. Time course curves indicate carboplatin concentrations in the choroid following subconjunctival injection and CCI delivery are significantly higher than after iv. injection ($p<0.001$).



A similar pharmacokinetic distribution pattern was found in the optic nerve. **(Graph 1C)** Peak concentrations in the optic nerve reached 43.52ng/mg with subconjunctival injection, 37ng/mg with iontophoretic delivery and 24ng/mg with intravenous administration at 2hours post treatment. Time course curves indicate carboplatin concentrations in the optic nerve following subconjunctival injection are significantly higher than those after intravenous injection ($p=0.006$).

Graph 1C.

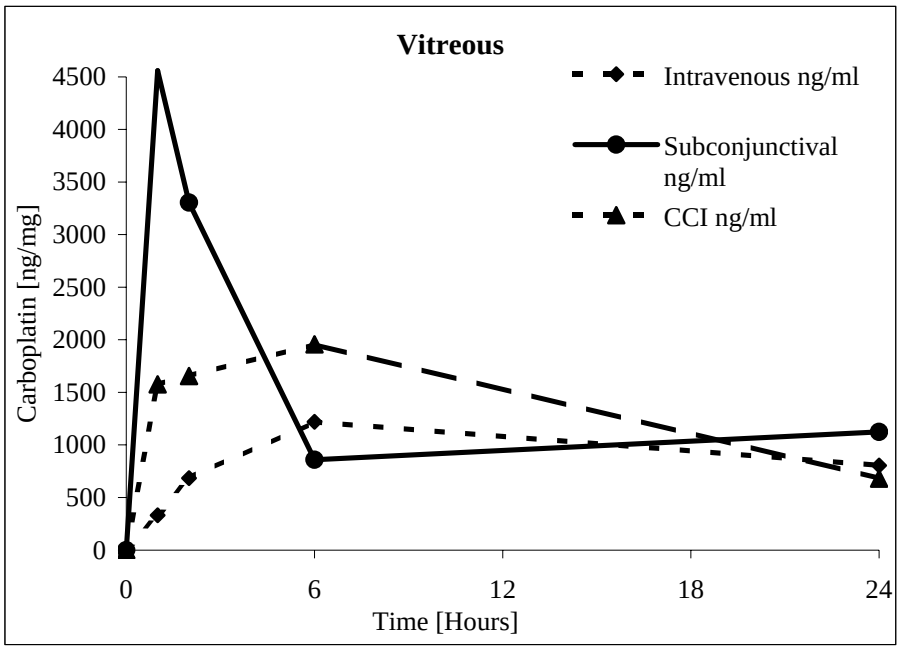
Pharmacokinetics of carboplatin in the optic nerve comparing concentrations following subconjunctival injection, CCI, and intravenous (iv.) administration. Time course curves indicate carboplatin concentrations in the optic nerve following subconjunctival injection and CCI delivery are significantly higher than after iv. injection (p=0.006).



The concentration of carboplatin in the vitreous humor over time demonstrated differential pharmacokinetic distribution dependent on the treatment administration. **(Graph 2A)** Concentrations in the vitreous following subconjunctival injection peaked at 1hour (4560ng/ml) and decreased thereafter. The drug concentration in the vitreous post iontophoretic administration was 1565µg/ml at 1hour and slowly increased to peak at 1955ng/ml at 6hours post treatment. Intravenous delivery of carboplatin resulted in a peak of 1220ng/ml 6hours after administration (p<0.001).

Graph 2A.

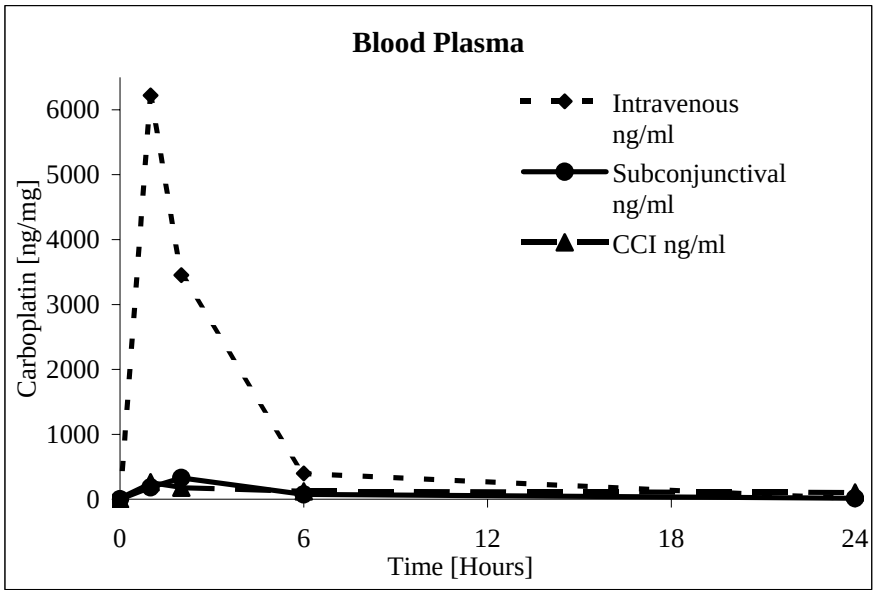
Pharmacokinetics of carboplatin in the vitreous comparing concentrations following subconjunctival injection, CCI, and intravenous (iv.) administration. Time course curves indicate carboplatin concentrations in the vitreous following subconjunctival injection and CCI delivery are significantly higher than after iv. injection ($p<0.001$).



Carboplatin concentrations in the plasma were found to be significantly higher following intravenous delivery (6222ng/ml at 1hour) compared to subconjunctival (182ng/ml at 1hour) and iontophoretic (261ng/ml at 1hour) delivery ($p<0.001$). Blood plasma levels remained high (3452ng/ml) throughout the two-hour time point after intravenous delivery. **(Graph 2B)**

Graph 2B.

Pharmacokinetics of carboplatin in the blood plasmacomparing concentrations following subconjunctival injection, CCI, and intravenous (iv.) administration. Time course curves indicate carboplatin concentrations in the blood plasma following subconjunctival injection and CCI delivery are significantly higher than after iv. injection ($p<0.001$).

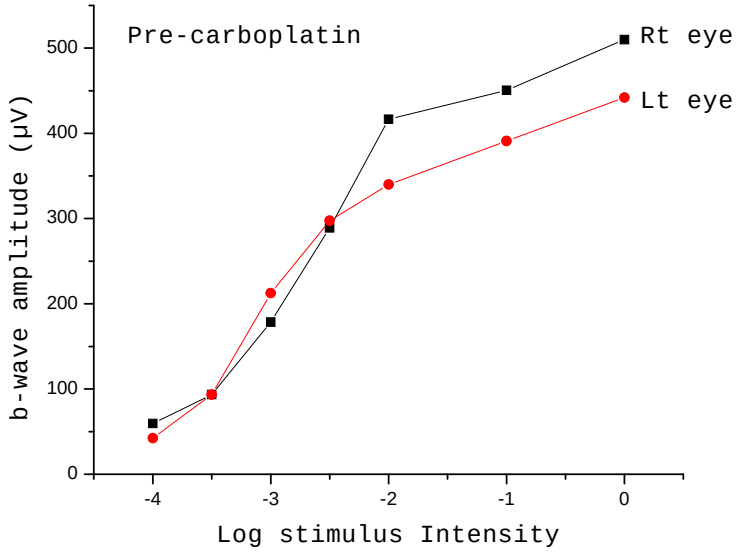


4.1.2. ERG results on rabbit eyes after repetitive CCI application

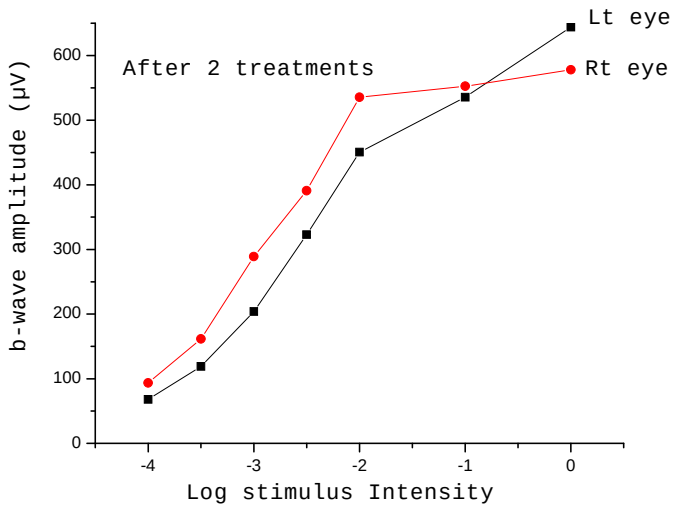
The amplitude of the b-waves of the right (treated) and left (untreated) eyes is plotted. These results demonstrate that the b-waves were not reduced by the CCI treatment. The implicit times of the b-wave were also not altered. Thus, even after applying the highest soluble concentration of carboplatin of 14 mg/ml, no electrophysiological evidence of retinal toxicity was observed in this eye after receiving six transscleral CCI applications. Similar results were obtained with repetitive treatment of transscleral CCI with BSS. **(Graphs 3A, B, C)**

Intensity response curves for the b-wave amplitude of the right (iontophoresis) and left (no treatment) eyes of a rabbit. ERGs were recorded pre-carboplatin, after 2 Carboplatin treatments, and 4 weeks after 6 BSS treatments. The b-wave amplitudes are plotted on the ordinate and the log of the stimulus intensity on the abscissa. Stimulus intensity at 0 = 2.53 log cds/m^2.

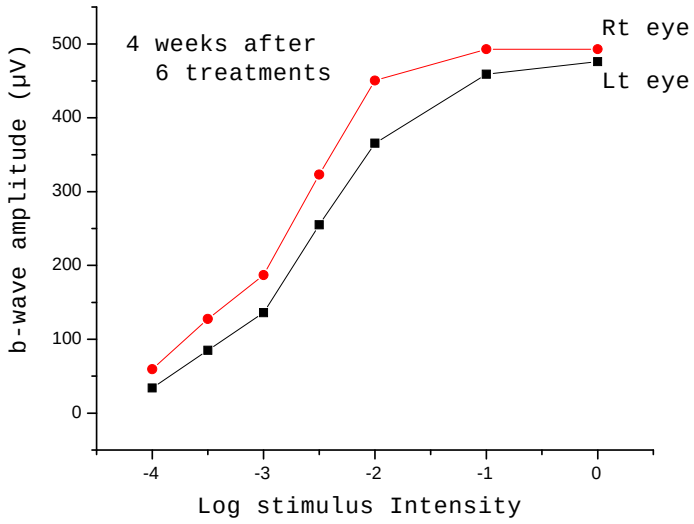
Graph 3A.



Graph 3B.



Graph 3C.



4.1.3. Histopathology of repetitively CCI treated rabbit eyes

A slight conjunctival injection was noticed on a few eyes after removal of the applicator, which disappeared before the following treatment session. Gross examination of the eyes revealed no evidence of ocular toxicity or signs of inflammation in the anterior and posterior segments of the all eyes. Photomicrographic documentation of the globe, and the histological preparation of the different tissues appeared to be free of any abnormal characteristics. **(Fig. 8)** Eyes of the control treatment with BSS were free of signs of inflammation or ocular toxicity.

Figure 8.

Photomicrograph of histopathologic section adult New Zealand White rabbit eye enucleated four weeks post completion of six transscleral carboplatin CCI given at 72-hrs intervals (14.0mg/ml,20 min at 2.5mA)

A) Central cornea- note intact epithelium, endothelium and absence of stromal abnormality (H&E x70).

B) Ciliary body/iris root- note ciliary body epithelium and iris (H&E x70).

C) Retina- note intact sclera, choroid and retina (H&E x70).

D) Longitudinal section of optic nerve and peripapillary retina demonstrating normal architecture (H&E x40).

Figure 8A)

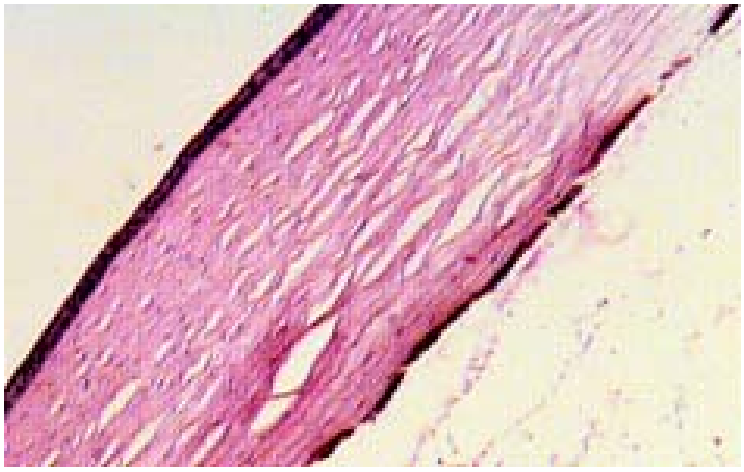


Figure 8B)

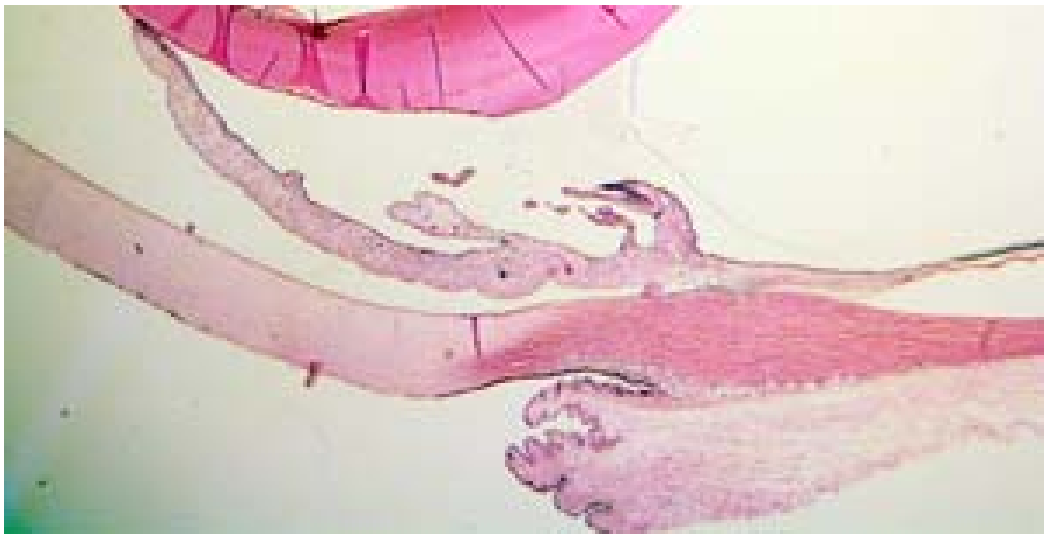


Figure 8C)

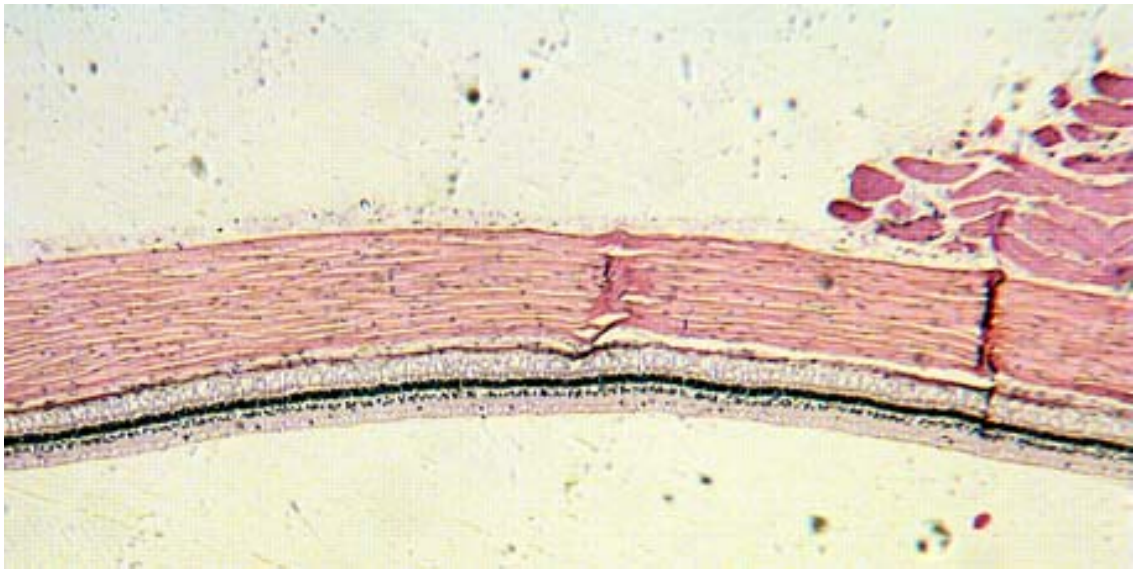
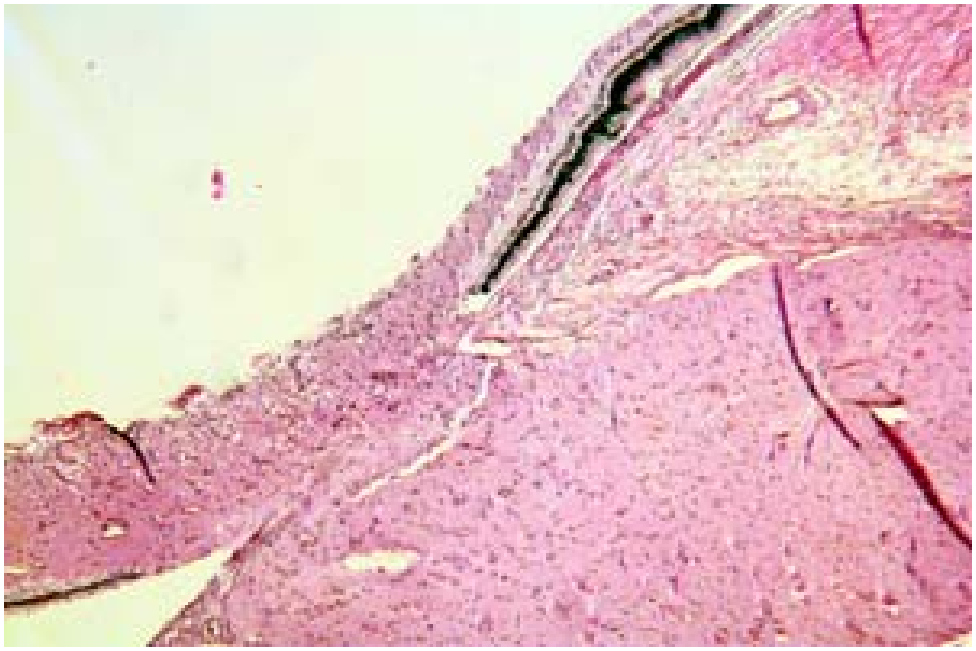


Figure 8D)



4.2. Results from the treatments performed on transgenic mice

4.2.1. Histopathology of repetitively CCI treated mice eyes

The investigation of CCI parameters for the treatment of retinoblastoma in this mouse model revealed an optimal transmittance of drug and absence of conjunctival, corneal and scleral damage at a current density of 2.57mA/cm^2. No damage to the ocular tissues was observed in treatment times varying from 2 to 5 minutes in duration utilizing this current density. A current density greater than 5.14mA/cm^2 was associated with corneal/limbal toxicity at all treatment times evaluated.

4.2.2. Iontophoretic treatment of transgenic mice

All untreated left eyes and placebo-treated eyes revealed large intraocular tumors (54 of 54 untreated eyes, 10 of 10 placebo treated eyes). **(Fig. 9A)** Experimental eyes treated at carboplatin concentrations of 1.4mg/ml demonstrated a reduction in tumor volume when compared to untreated control eyes; however, none of the eyes at this dose exhibited complete tumor control. **(Fig. 9B)** At carboplatin concentrations of 14mg/ml (maximum solubility of carboplatin in BSS) all eyes (9 of 9,100%) exhibited complete tumor control. Toxicity is evident in all animals treated at this concentration with some eyes developing phthisis.

Figure 9.

Histopathologic examination of enucleated globes of 4 month-old transgenic retinoblastoma mice after 6 serial CCI carboplatin treatments. **A**) A control eye receiving balanced salt solution. Large retinal tumor is present. **B**) Eye treated with 1.4 mg/ml of carboplatin. Note a moderately sized tumor is present demonstrating reductions in tumor volume yet lack of complete tumor control. **C**) Eye treated with 14mg/ml of carboplatin. Tumor is absent. Note extreme carboplatin toxicity evident at this concentration resulting in phtisical eye

Figure 9A)

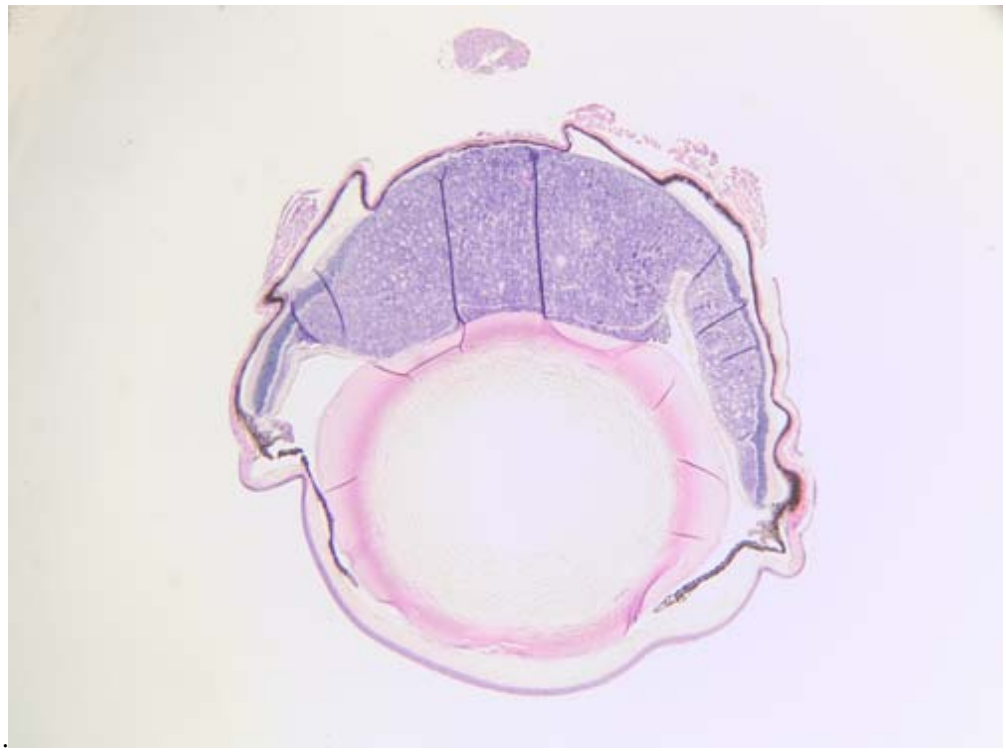


Figure 9B)

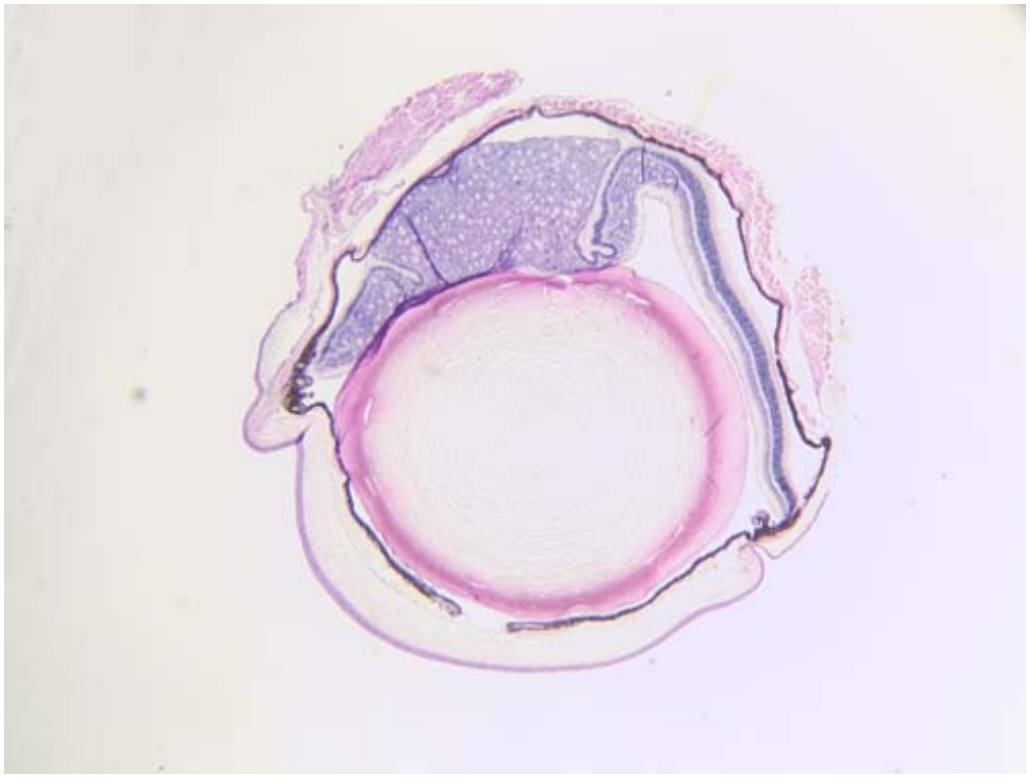
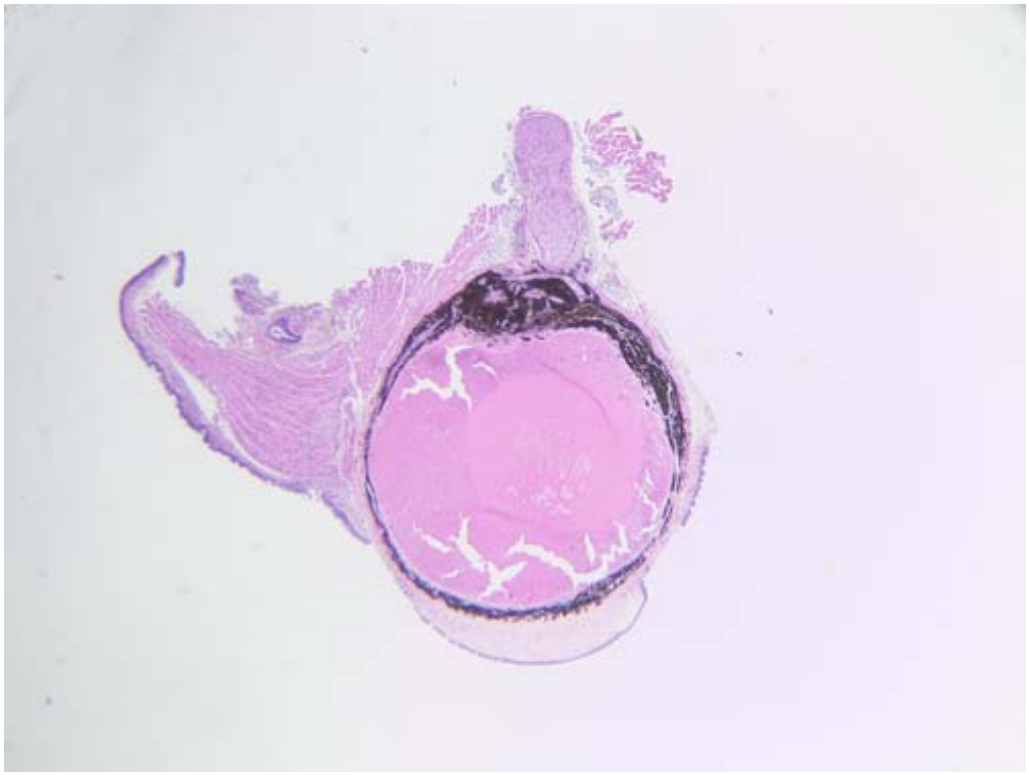


Figure 9C)



Histopathologic examination of enucleated globes of transgenic mice treated with six serial iontophoretic carboplatin applications at a concentration of 7.0mg/ml, documented complete tumor control in 50 % of the treated eyes (4 of 8). **(Fig. 10B)** There was no evidence of cataract, scleral thinning, corneal decomposition, or retinal abnormality in any of the eyes treated at this dose.

Figure 10.

Histopathologic examination of enucleated globes of transgenic retinoblastoma mice after 6 serial CCI carboplatin treatments. **A**) Eye treated with 7mg/ml of carboplatin without applied current. Note large retinal tumor. **B**) Eye treated with 7mg/ml of carboplatin with applied current of 2.57mA/cm^2. No evidence of cataract, scleral thinning, corneal decomposition, or retinal abnormality is present. Note complete tumor control.

Figure 10A)

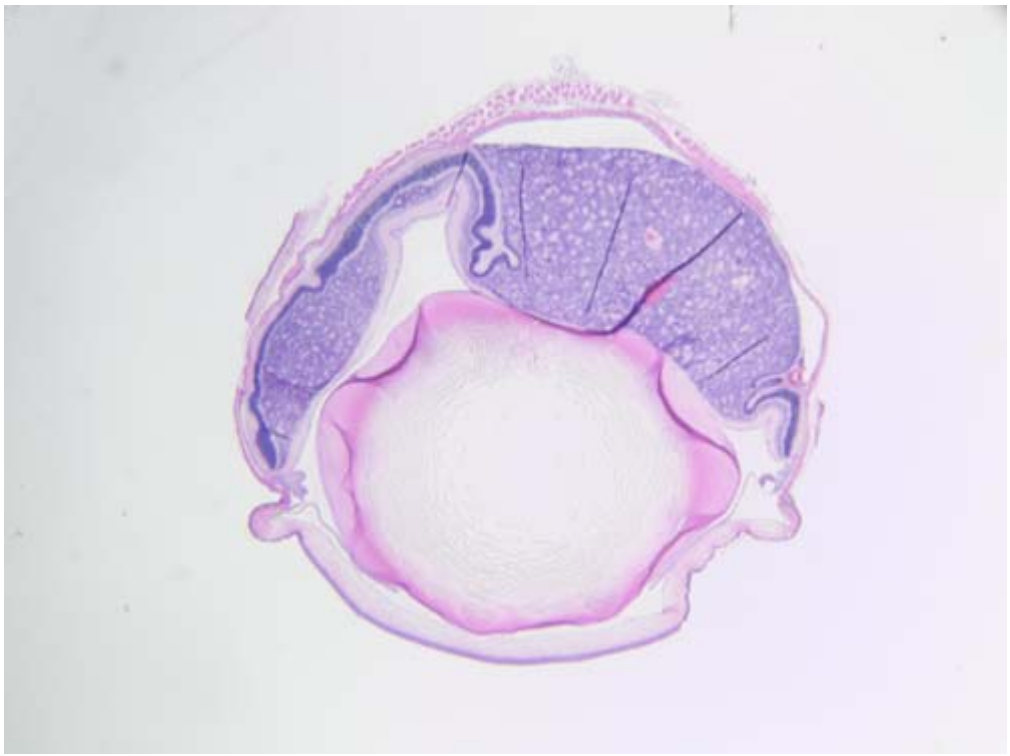
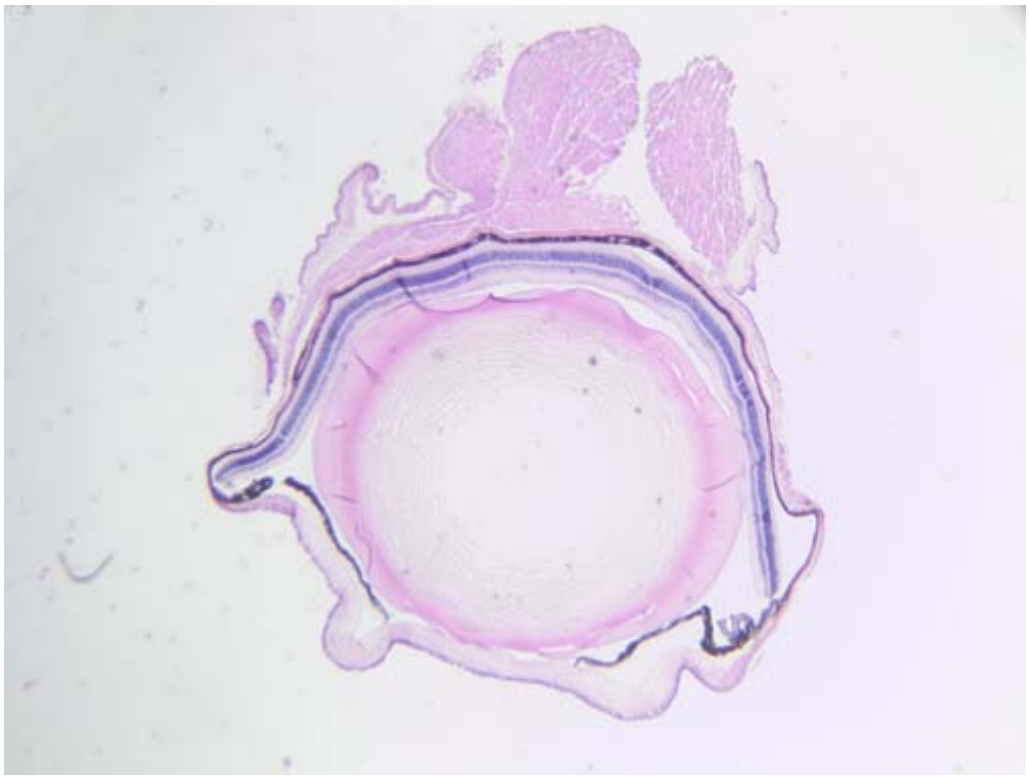


Figure 10B)



A dose-dependent inhibition of intraocular tumor was observed following repetitive iontophoretic treatment. **(Graph 4, Table 9)** The tumor control dose for 50% of eyes treated (TCD_{50}) with iontophoretic carboplatin was determined by regression analysis to occur at a carboplatin concentration of 7.0mg/ml. At carboplatin concentrations of 10,g/ml most of the treated eyes revealed moderate corneal toxicity upon histopathological examination. Eyes treated with carboplatin concentrations of 14mg/ml all revealed complete corneal destruction as well as cataract and severe retinal and choroidal toxicity. No corneal toxicity was observed in eyes treated at carboplatin concentrations under 10mg/ml. LogXact logistical regression analysis was used to calculate a dose-response curve to estimate the relationship between carboplatin concentration and tumor control. The logistic regression analysis demonstrated the increased tumor control is directly correlated with increased carboplatin concentration ($p<0.001$).

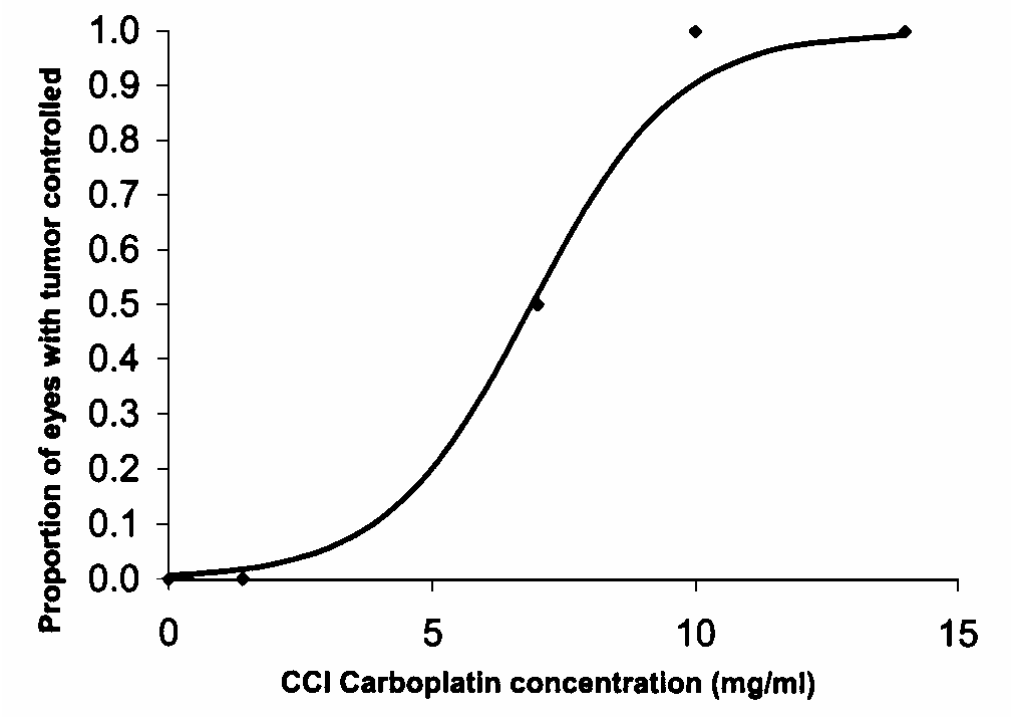
Table 9.

Coulomb Controlled Iontophoretic (CCI) delivery of carboplatin to transgenic retinoblastoma mice.

Carboplatin Concentration (eye cup)	No. (%) of Eyes With Corneal Toxicity	No. (%) of Eyes With Complete Tumor Control
14mg/ml	9/9 (100)	9/9 (100)
10mg/ml	5/6 (83)	6/6 (100)
7.0mg/ml	0/8 (0)	4/8 (50)
1.4mg/ml	0/7 (0)	0/7 (0)
BSS	0/7(0)	0/7 (0)

Graph 4.

Carboplatin dose-response curve demonstrating the proportion of tumor containing eyes controlled by repetitive carboplatin CCI. TCD_{50}=7mg/ml. Increased tumor control is directly correlated with increased carboplatin concentration ($p<0.001$).



5. DISCUSSION

The application of chemotherapy in the management of retinoblastoma has become a mainstay in the initial treatment of the tumor (Reese-Ellsworth stage III – V). Several investigators have reported on the effectiveness of initial systemic chemotherapy, termed chemoreduction [208-210]. In a short-term study, Shields et al. reported a mean decrease of 35% in base and 49% in thickness in children initially treated with intravenous chemotherapy [175]. Though effective in tumor reduction, this treatment modality alone is unable to achieve complete tumor control and thus requires adjuvant, focal treatment. Chemoreduction combined with local therapies including laser hyperthermia and cryoablative therapy have been utilized with much success [178-179, 182, 211]. However, seeding of cancer cells into the vitreous remains a problem in patients treated with these combined therapies. It appears that insufficient concentrations of the chemotherapeutic drug are achieved in the retina and vitreous via systemic administration. Dose limitations and renal clearance of the drug may also be contributing factors.

Previous studies performed at the Bascom Palmer Oncology laboratory were successfully demonstrating the efficacy of carboplatin intravitreal and subconjunctival administration in the treatment of murine retinoblastoma [192-194, 212]. Although efficacious, direct injection into the vitreous cavity creates possibility of tumor dissemination from the injection tract and may increase the risk of extraocular metastasis and, therefore is not utilized in clinical practice. Subconjunctival and iontophoretic focal delivery of carboplatin may deliver high dose chemotherapy to the vitreous and posterior segment of the eye without the risks associated with globe penetration.

As already mentioned iontophoresis utilizes a low potential, continuous electrical field incorporating two conductive electrodes to transfers ions across a tissue barrier. In the last decade, numerous studies have documented the delivery of various drugs into ocular tissues in both the anterior and posterior with varying degrees of success [29, 31-57].

However, as demonstrated by several toxicity and safety studies, this treatment modality is not without risk of complications. [29, 108, 110] Transscleral iontophoresis may lead to retinal and choroidal cell damage, resulting in thinning and disorganization of retinal layers. When tissues are being damaged by heat, changes in hydration level, and/or mechanical disorganization during treatment, their impedance changes with time, resulting in variable electrical fields (V/cm^2), which affects the iontophoretic drug transfer characteristics. This can easily occur at the epithelial surface (conjunctiva) when high current densities are applied. To avoid these problems a Coulomb Controlled Iontophoresis system was developed. [213]

The Coulomb controlled iontophoresis (CCI) device used in this study is specifically designed for ophthalmological application. The utilized system maintains a constant current density (mA/cm^2), a constant concentration of carboplatin (mg/ml), and a constant suction throughout the treatment period of either 25mmHg for transscleral CCI on rabbits or 5mmHg for transcorneoscleral CCI on mice. Which results in effective transmission of drug into the ocular tissues without high charge density and fluctuation, thus reducing complications such as tissue burning. The electrode that contains the drug (active electrode) is placed over the treatment site and the second (passive) electrode, is placed elsewhere on the body, and closes the electric circuit. The electrical field (E) and the potential (V) are selected to produce a small direct electrical current (DC) across the treatment tissue.

When iontophoresis is used for drug delivery, the best candidate drug is a low molecular weight charged molecule. The chemical properties of carboplatin are uniquely attractive for the application of Coulomb controlled iontophoresis in the local ocular treatment of retinoblastoma. Carboplatin, an analog of cisplatinum, is a crystalline powder with the molecular formula of $C_6H_{12}O_2PtO_4$ and a low molecular weight of 371,25. The polar molecule is neutral, but takes on a positive charge when dissolved in balanced salt solution. Carboplatin is soluble in balanced salt solution to a maximal concentration of 14mg/ml at a pH of 5.5. In vivo, carboplatin is metabolized to diamminoplatinum and a non-platinum ‘carboxyl’ moiety. Both carboplatin and its metabolite, maintain the cytotoxic mechanism of action associated with the creation of inter- and intra-strand DNA linkages that impair cell replication.

In the first part of this study we were able to demonstrated that focal delivery of carboplatin utilizing subconjunctival injection or transscleral iontophoretic delivery transmit drug more effectively than intravenous delivery into the target tissues of the vitreous, choroid, retina, and optic nerve in the rabbit eye. Both focal applications resulted in significantly higher peak concentrations of carboplatin in the choroid, retina, optic nerve, and vitreous than those obtained following intravenous delivery. Focal chemotherapeutic administration resulted in dramatically decreased carboplatin levels in the blood plasma compared to intravenous delivery.

Locally administered carboplatin resulted in high concentrations of the drug in the vitreous humor, which may be of clinical importance in the treatment of human retinoblastoma. Peak levels of 4560ng/ml after subconjunctival carboplatin injection (5.0mg) and 1965ng/ml after iontophoretic delivery (14mg/ml). These carboplatin levels in the vitreous reported in the current study compare well with those reported by Mendelsohn et al. in a recent primate study of ocular pharmacokinetics [190]. In this latter study, similar carboplatin levels in the vitreous humor were measured following peribulbar or episcleral local delivery of carboplatin; peak

vitreous levels were 2380ng/ml (10mg carboplatin) and 2950ng/ml (10mg carboplatin) peribulbar administration and episcleral balloon delivery respectively.

The pharmacokinetics of carboplatin obtained in the vitreous following CCI resulted in a distinctly different pattern of drug distribution than observed following subconjunctival injection. Carboplatin levels peaked at one-hour post subconjunctival delivery and slowly diminished thereafter. The distribution in the vitreous following iontophoretic delivery demonstrated heightened levels of carboplatin from one to six hours with the lowest measured levels at 24hours post treatment. This observation in the ocular drug distribution obtained by Coulomb controlled iontophoresis appeared similar to ocular tissue drug concentrations measured after CCI application of aspirin [53], ganciclovir [46] and methylprednisolone [52], which were performed in our laboratories of at the Biophysics Center of the Bascom Palmer eye institute and at the Laboratoires du développement, vieillissement et pathologie de la rétine unité INSERM U450; Laboratoire de Recherches ophtalmologiques Hôpital Hôtel Dieu unité INSERM U 86, Paris, France.

In the ocular aspirin CCI administration study transscleral CCI resulted in a high initial drug concentration in the anterior segment tissues, producing a depot effect, and prolonged diffusion through the choroid and retina. It appears as if the migration of drug molecules from the anterior chamber to the posterior segment is not using the direct pathway from the iris/ ciliary body through the vitreous to the posterior pole. A direct distribution by the vitreous diffusion route would probably result in higher immediate or early post treatment vitreous drug levels than those measured in the mentioned experiment. It seems much more likely that the transscleral CCI induced drug molecule migration may go from the anterior to the posterior pole using the directly affected tissues such as the sclera, retina and choroid. Finally the delayed high peaks of the vitreous drug levels may be the result of drug molecules being distributed from the posterior segment tissues into the liquid of the vitreous by simple passive diffusion out of the saturated tissues. Elsewhere, such as the retina and choroid, the drug distribution pattern appears to be more affected by factors like the blood flow for systemic distribution or in the case of transscleral CCI on the area of the electrode placement. Simple topical application of the studied drugs, like aspirin resulted in the lowest ocular tissue concentrations demonstrating that indeed the electrical field induced the drug penetration into the eye.

The ability to deliver carboplatin in a controlled, sustained manner to the vitreous may have significant clinical value. Current clinical treatment failures of children receiving primary systemic chemotherapy of retinoblastoma often fail due to proliferation of cancerous cells seeded in to the vitreous. [214]. We hypothesize that this may be secondary to insufficient carboplatin

penetration. Sustained delivery of chemotherapy at high concentrations may be necessary due to the high mutagenic nature of these cells. Iontophoretic delivery of the drug may be the preferential treatment for children displaying vitreous seeding at treatment onset. Subconjunctival therapy may be most useful in large tumor where it is necessary to rapidly reduce tumor size with frequent chemotherapy treatment cycles.

Systemic administration of carboplatin has also been evaluated in children undergoing enucleation management of intraocular retinoblastoma [178]. In this study, Murphree et al. noted intratumoral concentrations of carboplatin to be 2.17pg/µg DNA. These levels are lower than those reported in the current study.

Complications due to increased carboplatin levels in the blood plasma obtained after systemic intravenous administration have profound implications clinically. As already mentioned systemic therapy is an effective treatment option in the treatment of children with retinoblastoma resulting in reduction in tumor size, enhanced efficacy of other treatment modalities, and the possible prevention of micrometastasis. However, still serious complications should be taken in consideration while applying chemotherapy [161, 215]. Systemic chemotherapy has been associated with retinal detachment, myolosuppression, nephrotoxicity, ototoxicity, sepsis, and may increase the risk of acute nonlymphatic leukemia and other secondary malignancies later in life [160-161, 187, 189, 215-216].

Previous experiments performed at the Oncology Laboratory at the Bascom Palmer Eye institute indicate that focal carboplatin delivery (subconjunctival injection) minimize concerns associated with the morbidity in the treatment of murine retinoblastoma [192-194, 212].
In the pharmacokinetic study of the this experimental trial we demonstrated that subconjunctival and transscleral CCI administration of carboplatin on rabbits revealed their ability to deliver therapeutic drug doses into the eye. Further investigations on the subject of repetitive clinical chemotherapy assured safety and the reproducibility of local treatments.

The second part of the study focused on the safety of multiple applications of carboplatin by means of transscleral CCI on rabbit eyes. Repetitive control treatments with BSS revealed the safety of the procedure, and thereby the ability to apply transscleral CCI without risk of ocular damage due to the passage of electrical current through the eye. Furthermore, we successfully demonstrated under simulated clinical conditions of 6 chemotherapy sessions, that this focal noninvasive method of carboplatin administration did not induce any ocular histopathologically or functionally evident retinal damage.

The threshold for avoiding ocular toxicity due to transscleral iontophoresis has been determined to be a current density of 25mA/cm^2 for a duration of 5 min [107]. In our experiment

we administered a current density of 5mA/cm^2, which is 5 times less than this recommended safety parameter. Though applying CCI for 20min instead of 5min, by keeping the applied current density at such a low level we were able to avoid retinal toxicity. Furthermore, the electrode lies over the less visually critical pars plana. Since the electrode covers an annular area between the limbus and pars plana with a clear corneal window, corneal exposure is also avoided.

We demonstrated that transscleral CCI, a short-term local non-invasive application, significantly exceeded ocular tissue levels of carboplatin obtained by systemic administration. Carboplatin concentrations obtained by subconjunctival administration, which in contrast to transscleral CCI implies an injection of a defined volume and longer contact between the drug and the orbital space, were comparable for posterior segment tissues including the vitreous. The risk of a higher and longer, depending on the speed of passive tissue absorption, exposure of carboplatin to orbital tissues such as the conjunctiva, muscle and cornea with subconjunctival injection than with transscleral CCI should be taken in consideration. High drug concentrations achieved by subconjunctival administration could lead to orbital or extraorbital complications due to the potential toxicity of local chemotherapy.

Repetitive CCI carboplatin administration for the treatment of retinoblastoma is not only focal and completely non-invasive but also capable of obtaining therapeutic drug levels in the eye while avoiding ocular, extraorbital, or systemic toxicity. The results of the pharmacokinetic and safety study, demonstrating increased intraocular concentrations of carboplatin following local delivery compared to systemic delivery indicate that local chemotherapy combined with other local treatments may be more successful and less toxic than current combined regimens.
The third part of this trial was concentrated on the efficacy of Coulomb controlled iontophoresis of carboplatin on the transgenic retinoblastoma model of the mice. Dose-response curves demonstrate tumor control can be achieved safely and effectively in this tumor model.

One limitation to the current study is that direct extrapolation from the murine model of retinoblastoma to the human is not possible. The intraocular volumes, vascular supply, and tissue sizes differ between the species. Unlike the human cornea, the mouse cornea encompasses nearly half of the eye, almost to the equator. Therefore, it was difficult to completely avoid contact of the electrode with the cornea. This may have resulted in corneal epithelial damage not indicative of treatment on human eye.

Transcorneoscleral iontophoretic delivery of carboplatin is an effective and relatively non-invasive application of focal therapy for the treatment of murine retinoblastoma. Dose dependent inhibition of intraocular retinoblastoma was documented with an excellent therapeutic

window and a tumor control dose for 50% of treated eyes occurring at 7mg/ml for a treatment application of 5 minutes. This study establishes a framework for further investigation of the clinical application of Coulomb controlled iontophoretic carboplatin delivery in children with intraocular retinoblastoma.

In conclusion, the use of transscleral CCI was shown in animal studies to be painless, easy to apply and the treatment time was relatively short. The application of the CCI electrode does not require any surgical skills. In pilot human trials a similar ocular electrode was used and the return electrode, a 3M patch, was placed on the skin of the forehead. The participating patients did not demonstrate or report any subjective signs of discomfort or pain [217]. Additional studies on the safety and efficiency of human ocular CCI administration need to be performed.

The integration of Coulomb-controlled iontophoresis of carboplatin in the complex care system of retinoblastoma offers the opportunity of a more selective treatment for the most common ocular cancer of childhood.