

ADCON[®]-L HYDROGEL AS A VITREOUS SUBSTITUTE: PRELIMINARY RESULTS

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ABSTRACT

The ideal vitreous substitute has still to be found. This report concerns the preliminary results of a translucent hydrogel, ADCON[®]-L, used successfully in neurosurgery. We have used this hydrogel as a vitreous substitute in the right eye of New-Zealand albino rabbits following vitrectomy. The follow-up period was four weeks and the evaluation was followed by biomicroscopy, indirect ophthalmoscopy, and electroretinography. The results obtained suggest a potential retinotoxicity of this hydrogel as shown by the statistically significant reduction of the mean B-wave amplitude at day 14 ($p < 0.05$) and day 28 ($p < 0.005$), as well as an important postoperative inflammatory reaction. Another transparent formulation of the same molecule is currently under investigation.

RÉSUMÉ

Le substitut vitréen idéal n'a pas encore été découvert. Le présent rapport concerne les résultats préliminaires d'un hydrogel translucide, ADCON[®]-L, utilisé avec succès en neurochirurgie. Cet hydrogel a été utilisé comme substitut vitréen après vitrectomie dans l'oeil droit de lapins albinos pendant quatre semaines. Le suivi comprenait un examen biomicroscopique, une ophtalmoscopie indirecte, et l'électrorétinographie. Les résultats obtenus suggèrent une rétinotoxicité potentielle de l'hydrogel au vu de la diminution statistiquement significative de l'amplitude moyenne de l'onde B au jour 14 ($p < 0.05$) et au jour 28 ($p < 0.005$), ainsi qu'une réaction in-

flammatoire post-opératoire importante. Une préparation transparente de la même molécule est actuellement investiguée.

KEY WORDS:

ADCON-L, vitreous substitute, hydrogel.

MOTS CLÉS:

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INTRODUCTION

Advances in retinal surgery have been very promising in the last few years, especially concerning the treatment of retinal detachment. Still, results are limited by the lack of a long-term vitreous substitute which has no toxicity and has physical properties that allow its use as a tamponade agent. Many chemicals have been tested, some resembling the vitreous (collagen, hyaluronic acid), others not (silicone oil, poly(1-vinyl-2-pyrrolidinone),...) (2,5,6,8). None of these chemicals responded to all the criteria of an ideal vitreous substitute.

ADCON[®]-L is a hydrogel currently used in neurosurgery (3). It is used during laminectomies to prevent excessive scarring at the operating site. It is a polymer of proteoglycan esters in porcine gelatine, saturated with water. In vitro and in vivo it has been shown to have no cytotoxic effect on surrounding structures and it does not prevent the normal healing process (9,10).

The good results in neurosurgery lead us to hope this hydrogel could potentially be a good vitreous substitute. There are many similarities between the central nervous system and the retina, the visco-elastic properties of the hydrogel are adapted to the eye, this hydrogel is preservative free, and could possibly inhibit the development of proliferative vitreo-retinopathy (PVR) as it is capable to inhibit fibroblastic proliferation and migration. Furthermore, in a recent review, hydrogels clearly seemed to be the ideal candidates for vitreous substitute (2). Just one characteristic of ADCON[®]-L is not appropriate, the hydrogel being nontransparent, but another transparent formulation of the same molecule exists and will be tested in the future.

This paper reports the preliminary results of the evaluation of ADCON[®]-L as a vitreous substitute in the rabbit eye.

MATERIAL AND METHODS:

Five New-Zealand female albino rabbits (mean weight 3Kg) were used for the in vivo evaluation of the hydrogel. All experiments were conducted in accordance to the ARVO recommen-

dations on the right eye of each rabbit, the left eye being used as a control. All surgery was performed in clean but non-sterile conditions.

The pupils of the right eye were dilated with topical phenylephrine hydrochloride 10% and tropicamide 0.5%. After general anaesthesia with ketamine (25mg/kg-body weight) and xylazine hydrochloride (5mg/kg) and local anaesthesia with oxybuprocaine hydrochloride topical drops, a pars plana vitrectomy was performed. Under constant pressure infusion of Balanced Salt Solution (BSS) the cortical vitreous was totally removed. Following the vitrectomy, the BSS was substituted by approximately 1,5 g of ADCON[®]-L (Gliatech) hydrogel injected through a 30-gauge needle. The sclerotomies were closed with 7-0 vicryl sutures. After surgery all the rabbits received one dose of hydrocortisone-oxytetracycline-polymyxine B topical ointment.

The rabbits were examined postoperatively at day 1, day 7, day 14, day 21 and day 28. Evaluation consisted of biomicroscopic examination of the cornea, the anterior chamber, the iris, the lens and the vitreous. Indirect ophthalmoscopy was used to examine the eye fundus. The ocular tension was estimated subjectively by finger pressure.

Electroretinography (ERG) was performed before the vitrectomy, and controlled at day 14 and day 28 postoperatively. The rabbits were dark adapted for 20 minutes before ERG recordings. During the recordings the rabbits were anaesthetised as during vitrectomy and the pupils were dilated with tropicamide and phenylephrine topically. The ESPRIT system of NICOLET (Deckers, Belgium) was used. Animals were stimulated by a supramaximal intensity light flash located at right angles and at 15 cm of the eye. The right eye was always tested first, and compared to the left eye. Corneal electrodes recorded the electrical responses. The reference and ground electrodes were respectively placed subcutaneously at the forehead and in the right ear. Five stimuli of 1 msec at 70 sec interval were averaged for each eye. The amplitude of the b-wave was calculated for each measure.

The animals were sacrificed by an intracardiac injection of barbiturates (natrii aethyl(1-methylbutyl)barbituras) after general anaesthesia, 4 weeks after surgery.

Statistical analysis on the B-wave results of the ERG was performed with the Student t-test.

RESULTS

Clinical findings:

After one day all rabbits presented signs of ocular inflammation such as hyperaemia of the conjunctiva and the iris, and posterior synechia. The cornea and the lens presented no defects. The ocular tension was normal. With indirect ophthalmoscopy the retina was not visible because of the hydrogel located in the vitreous, and only an orange reflection could be seen.

At day 7, ocular inflammation receded and only the posterior synechiae remained. The cornea and the lens were normal. The ocular tension seemed somewhat low. The hydrogel still totally filled the vitreous.

After 2 weeks, the anterior segment remained normal except of the posterior synechiae and a small superficial corneal opacity in one rabbit. The anterior and posterior capsules of the lens were apparently thickened in all five rabbits. In three rabbits, the hydrogel was still visible but in the other two rabbits, fibrous membranes developed on the posterior lens capsule masking the eye fundus. Three eyes still seemed hypotonic.

After three weeks, small superficial corneal opacities were visible in two rabbits. The posterior synechiae were stable. The posterior and anterior capsules of the lens remained thickened. The hydrogel was no more visible in any of the five rabbits. The retina seemed normal but was hidden partially in four rabbits by fibrous deposits on the posterior surface of the lens. In one rabbit fibrous membranes were also observed in the vitreous cavity. Ocular tension seemed normal in all rabbits.

After four weeks, the same two rabbits still had superficial corneal opacities that spread slowly. Posterior synechia were unchanged, as were the anterior and posterior capsules of the lens. There was a posterior luxation of the lens in one rabbit. The retina was visible in only two rabbits and seemed normal. In the other three rabbits, fibrous membranes resembling PVR in the anterior vitreous and on the posterior lens capsule prevented the retina to be seen. The ocular tension was normal. Global clinical results after four weeks are described in table 1.

Electroretinography:

The preoperative ERG had a normal morphology in all the eyes tested. B-wave values varied from 331 μ V to 429 μ V (29.6% variation). The maximal variation between the right and the left eye in a given rabbit was 13% and the mean variation between both eyes was 9.2%. At the first control (day 14), the mean variation between both eyes was 38.4 %. After 4 weeks, this value was 52.2%. These results correspond to a statistically significant decrease of the mean B-wave values at day 14 ($p < 0.05$) and at day 28 ($p < 0.005$).

DISCUSSION

Many potential vitreous substitutes have been tested in the animal or in the human eye. Most of them have been reviewed by Chirila and al. in 1994 (2). They can be divided into two main classes: semisynthetic polymers (hyaluronan products, chondroitine sulfate, collagen, hydroxypropyl methylcellulose (HMPC),...) and synthetic polymers (polyvinylpyrrolidone (PVP), polyacrylamide, polyglyceryl methacrylate (PGMA), polyvinylalcohol (PVA), poly(2-hydroxyethyl acrylate) (PHEA), silicone oil,...). Still, despite the amount of different substan-

Table 1:

Rabbit	Corneal opacity	Iris synechia	Lens capsule thickening	Lens luxation	Vitreous fibrous membranes
1	+	+	+	-	-
2	+	+	+	+	+
3	-	+	+	-	±
4	-	+	+	-	+
5	-	+	+	-	+

Table 1. Global clinical results after four weeks of intravitreal hydrogel.

ces tested, none has been found to fulfil all the conditions of an ideal substitute: most of them are toxic for the eye at short or long term, or resorbed too quickly. More recently, chemical manipulations of existing molecules have been experimented (methylated collagen (7), poly(N-vinylpyrrolidinone) (1)) but the results still remain doubtful. An ideal vitreous substitute that fulfils all the conditions listed in table 2 thus remains to be found.

Adcon®-L (Anti-Adhesion Barrier Gel) is a hydrogel principally composed of a polymer of semi-synthetic proteoglycans. These proteoglycans have been shown to act as a barrier to fibroblasts by inhibiting fibroblastic proliferation and migration in vivo and in vitro (4,9,10). Adcon®-L has been used as a barrier gel to reduce post-operative scar formation and adhesions in vivo after laminectomies with no inhibition on the healing process and no cytotoxicity. These promising results on neurologic tissues, and the fact that Adcon®-L is a hydrogel, gave us the hope that it could be a well tolerated vitreous substitute. Furthermore, its antifibrotic properties could be an effective way in inhibiting PVR after vitreo-retinal surgery. Finally, it is heavier than water, which makes it easy to inject after vitrectomy.

Our first results unfortunately do not seem promising. Two weeks after the hydrogel had been injected, signs of ocular toxicity already clearly appeared, and worsened after 4 weeks. In two out of five rabbits superficial corneal opacities appeared. All rabbits developed to some degree an anterior and posterior cataract.

Even more worrying are the results of the ERG which show signs of retinal toxicity increasing even after the hydrogel had macroscopically disappeared from the eye.

Severe fibrous proliferation occurred in the vitreous of 3 out of 5 rabbits, closely resembling PVR. This will be evaluated by histology.

As the hydrogel is not transparent, eye fundus examination is impossible as long as the hydrogel is in the eye.

Finally, the rapidity of biodegradation of the hydrogel is faster than expected (four weeks when used after laminectomies) and the hydrogel had already totally disappeared macroscopically after 3 weeks.

The good neurological tolerance of this hydrogel compared with the poor eye results may be

Table 2:

1/	Clarity and transparency
2/	Biologically and chemically inert
3/	Refractive index and density similar to the natural vitreous
4/	Sufficient rigidity to act as a tamponade agent
5/	Allow transfer of metabolites
6/	Nonabsorbable and nonbiodegradable
7/	Hydrophilic
8/	Injectable through a small-gauge needle

Table 2. Characteristics of an ideal vitreous substitute (according to Chirila et al. 1994)

due to the different immune responses of these organs. Furthermore, the mechanisms of fibroblastic inhibition of the hydrogel are not totally understood. It could be that it interferes with cell to cell interactions via proteoglycan similarities not only with fibroblasts, but also with other cell types (especially with keratocytes and hyalocytes that resemble fibroblasts). It could also alter the inflammatory response of the eye induced by a surgical intervention by blocking or enhancing the action of inflammatory regulators. In addition there seems to be a direct toxicity of the hydrogel on the sensory retina as shown by the ERG.

In conclusion, this hydrogel does not appear to be an acceptable vitreous substitute. Still, another more liquid and transparent formulation of the same polymer has been developed and will be tested as well, before definitive conclusions can be made about the effectiveness of this molecule.

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