Ocular tolerance to cyanoacrylate monomer tissue adhesive analogues

Antonio R. Gasset, C. Ian Hood, Emily D. Ellison, and Herbert E. Kaufman

Ocular tolerance to cyanoacrylate tissue adhesives was evaluated in rabbits. In the experimental studies, tissue adhesives were implanted intralamellarly, subconjunctivally, and in the anterior chamber. The eyes were examined clinically and histologically at different time intervals. In the cornea and conjunctiva, the adhesive reacted as any inert material. The reaction was considerably less than that to silk or catgut. In the anterior chamber, the reaction was moderate in most cases.

The first plastic tissue adhesive alkyl-2-cyanoacrylate was discovered by Coover and associates in 1959. What makes this adhesive most useful in the field of surgery is the fact that unlike most conventional adhesives that function by the application of heat and pressure, addition of a catalyst, or evaporation of a solvent, the cyanoacrylate types of tissue adhesive are converted from liquid to the solid state by polymerization when simply pressed into a thin film between two adherents. Moreover, this polymerization occurs at room temperature, and does not require the use of a solvent or added catalysts.

Plastic tissue adhesives first attracted the interest of ophthalmologists soon after Eastman 910 (methyl cyanoacrylate) was made available. Ellis and Levine found methyl cyanoacrylate to have excellent adhesive qualities and to show promise of being suitable for use in many ocular surgical procedures. Bloomfield and associates also found the rapid bonding action of Eastman 910 especially useful in ocular surgery, and concluded after a careful evaluation, that it could be safely employed in ocular surgery, particularly subconjunctivally. However, Straatsma and associates found Eastman 910 to produce a severe toxic reaction subconjunctivally.

While the data concerning the ocular tolerance of this original material have remained both confusing and contradictory, new less toxic materials such as isobutyl, hexyl, heptyl, octyl, and decyl cyanoacrylate were developed. Their clinical use in ophthalmic surgery was first reported with the epikeratoprosthesis. Other applications of these analogues have also been reported and confirm their utility.

The purpose of this investigation was to systematically evaluate the ocular tolerance of the higher analogues of cyanoacrylates, and also to compare these reactions to those produced by other materials commonly used in ophthalmic surgery.
Material and methods

Sterile tissue adhesive was supplied by Ethicon for experimental use in sterile disposable 1 ml. tubes with a polyethylene dispenser nozzle and needle plunger. The adhesive itself is a clear, colorless liquid of low viscosity. The following cyanoacrylate monomers were evaluated: isobuty1, hexyl, octyl, and decyl-2-cyanoacrylate.

Experimental studies. Albino rabbits, weighing 1.5 to 2.0 kilograms, were used. The animals were anesthetized by intravenous injections of sodium pentobarbital. In addition, 0.5 per cent proparacaine hydrochloride was topically applied in all cases. A total of 56 applications of either the adhesive or one of the control materials were made and examined both clinically and histologically.

Corneal tolerance. In order to evaluate the tolerance of these adhesives, two different experiments were carried out.

An intracorneal tract was carefully made approximately in the middle of the corneal stroma, from the limbus toward the center, with a 27 gauge needle attached to a tuberculin syringe, and a small amount of tissue adhesive was deposited as the needle was being withdrawn.

In order to best compare the reaction of the cornea to the adhesive, 3 different analogues were tested in each cornea, each being injected in a different quadrant, and the reaction to each compared with that provoked by either silk, catgut, or simple needle tract. The quadrant in which a particular adhesive was applied was randomized in each animal.

Subconjunctival tolerance. A 27 gauge needle was introduced under the conjunctiva at either the 12, 3, 6, or 9 o’clock position, and small amounts of adhesive were injected as the needle was being withdrawn. For comparison, silk and catgut material were also placed subconjunctivally.

Intracocular tolerance. A 0.1 c.c. amount of the tissue adhesive was injected through a 27 gauge needle introduced into the anterior chamber through the limbus. Care was taken to avoid mechanical trauma to the iris, lens, or corneal endothelium. For comparison, catgut or silk was placed in the anterior chamber. This was accomplished by placing a through and through suture, cutting the ends as close as possible to the cornea and pushing the ends into the anterior chamber with a 27 gauge needle.

Evaluation. Double-blind examination was carried out daily and signs of edema, infiltrate, vascularization, scarring, perilimbal flush, cells, and flare in the anterior chamber as well as dilatation of iris vessels were graded from no reaction to severe reaction. All eyes were photographed at frequent intervals, and the photographs were also compared and evaluated.

Table I. Clinical evaluation of rabbit corneas injected intralamellarly with cyanoacrylate tissue adhesives as compared to control materials

<table>
<thead>
<tr>
<th>Material</th>
<th>No. of eyes</th>
<th>No reaction</th>
<th>Minimal</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silk</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Catgut</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isobutyl</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hexyl</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Octyl</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decyl</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control trauma</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Results

Intracorneal tolerance. A total of 30 intralamellar implantations of the tissue adhesive and the control materials were evaluated. Results are summarized in Table I and indicate that all of the cyanoacrylate monomers were similarly well tolerated.

Clinical evaluation. A moderate iritis resulted from the intracorneal implantation of either silk or surgical gut; this usually subsided by the third postoperative day. In 4 of the 6 eyes where silk was used, blood vessels were seen invading the cornea to the site of the suture after the suture had been in place one month. One developed hypopyon, neovascularization, and marked corneal edema around the suture material. In another case, a large corneal ulcer was seen; all these occurred after one month.

On the other hand, of the 23 implantations of the adhesives, none showed any signs of irritation from 4 hours after injection of the adhesive until the eyes were removed for histology (Fig. 1). However, in 3 eyes, a superficial blood vessel invaded the cornea to the site of the adhesive after one month when the tract was in the 12 o’clock position. No further vascularization was seen during the second month.

Histological evaluation. Fifteen corneas with intralamellar implantation of adhesive were satisfactory for histologic study (5 from one month, and 10 from 2 months...
after implantation). Adhesives represented were octyl, decyl, and hexyl cyanoacrylate (6, 5, and 4 samples, respectively).

In all of the histologic preparations (hematoxylin and eosin, Masson’s trichrome, and PAS), the various adhesives and the associated tissue reactions were indistinguishable (Fig. 2).

In all tracts sectioned lengthwise, in which the surface orifice of the tract was present, there was epithelial downgrowth (Fig. 3). Squamous epithelium, in one or
Fig. 3. Intracorneal needle tract filled with decyl cyanoacrylate adhesive, 2 months’ duration. Note epithelial downgrowth into mouth of tract, adhesive plug in contact with displaced but otherwise intact stromal lamellae, scattered multinucleate giant cells at periphery of adhesive, and between its threads. Fibrous scar at mouth of tract probably traumatic in origin. (Hematoxylin and eosin; x275.)

Table II. Clinical evaluation of rabbit eyes injected subconjunctivally with cyanoacrylate adhesives as compared to control materials

<table>
<thead>
<tr>
<th>Material</th>
<th>No. of eyes</th>
<th>Clinical evaluation up to 2 months’ duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No reaction</td>
</tr>
<tr>
<td>Silk</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Catgut</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Isobutyl</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hesyl</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Octyl</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Decyl</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

more layers, continuous with the surface corneal epithelium, separated the adhesive from the corneal stroma in the superficial parts of the tracts. More deeply, adhesive lay in contact with the lamellae which were frequently scalloped about the congeries of adhesive threads, but which generally showed no evidence of necrosis or other damage to collagen fibers or keratocytes. Multinucleated giant cells, sometimes apparently epithelial in origin, and sometimes more definitely or foreign-body type, were present in varying numbers, mostly small, adjacent to the adhesive, and also in its interstices. Superficially, particularly adjacent to its exposed surface, there were often polymorphs and amorphous debris in the interstices of the adhesive.

Those tracts of 2 months’ duration tended to show more epithelial downgrowth. In 2 tracts, there were acute polymorphonuclear infiltrates between the adhesive and epithelial lining and also external to the epithelium in the surrounding stroma. The depths of these tracts were free from acute inflammation.

Subconjunctival application. A total of 13 subconjunctival applications of either the adhesive or the control material were evaluated up to 2 months. The results are summarized in Table II.

Clinical evaluation. Subconjunctival
placement of the adhesive resulted in moderate injection of the conjunctiva only at the site of the adhesive. This lasted less than one week and resulted in mild congestion of blood vessels in the area immediately over the adhesive. All of the adhesives caused the same extent of reaction (Fig. 4).

Histological evaluation. Seven conjunctival specimens with submucosal implantation of adhesive were satisfactory for histologic study (3 from one month, and 4 from two months after implantation). Adhesives represented were octyl, decyl, and hexyl cyanoacrylate (3, 2, and 2, respectively).

In histologic preparations, the various adhesives and the associated tissue reactions were indistinguishable.

In all, there was a thin, often delicate, fibrous capsule surrounding the adhesive. Foreign-body type giant cells in varying numbers, sometimes numerous, were present between the adhesive and its capsule and also in the interstices between the adhesive threads. Polymorphonuclear leukocytes and amorphous debris were also present locally in the interstices in some samples. This reaction was generally limited to the superficial parts of the adhesive mass anteriorly where it most elevated the conjunctiva and/or protruded through it. In one sample, an epithelial downgrowth separated a small area of the adhesive from its capsule. Samples of one and 2 months could not be identified or separated histologically (Figs. 5 and 6).

Intraocular tolerance. A total of 10 eyes were used in this group, and the reaction was evaluated daily for up to 2 months. Results are summarized in Table III.

Clinical evaluation. Some reaction followed the application of the adhesive in the anterior chamber. It did not follow any particular pattern; all eyes had an initial iritis which lasted one week. All but the reaction to the hexyl cyanoacrylate spontaneously subsided. In the latter case, the application of the adhesive resulted in...
Fig. 5. Subconjunctival implantation of hexyl cyanoacrylate adhesive, one month’s duration. Note development of a distinct but generally thin fibrous capsule, multinucleate giant cells in and about the adhesive, and absence of other acute or chronic inflammatory cells. (Masson trichrome; x275.)

Fig. 6. Subconjunctival and episcleral implantation of octyl cyanoacrylate, 2 months’ duration. Note development of a distinct fibrous capsule, somewhat thicker than at one month, scattered multinucleate giant cells but absence of other acute or chronic inflammatory cells. (Masson trichrome; x275.)
iris glued to corneal endothelium and in permanent clouding and vascularization of the cornea (Fig. 7). The adhesive polymerized in the aqueous in various sized particles from microscopic to several millimeters in diameter. The smaller could be seen on the endothelium or on the iris, and caused no gross irritation; the larger particles on the endothelium caused local areas of edema (Fig. 8).

**Histological evaluation.** Seven eyes with adhesive implanted in the anterior chamber were satisfactory for histologic study (5 from one month and 2 from 2 months after implantation). Adhesives represented were octyl, decyl, hexyl, and isobutyl cyanoacrylate (4, 1, 1, and 1 samples, respectively).

In histologic preparation, the adhesive and the associated tissue reactions were indistinguishable. In all except one case,
there were foreign-body type giant cells associated with the adhesive. There were frequently fibrous or fibrovascular plaques on the cornea or iris adjacent to the adhesive and often one or more breaks in Descemet’s membrane (Fig. 9). In several locations, endothelium contiguous with the glue was absent or distorted while that in the rest of the chamber appeared normal.

Discussion

The reaction obtained when any foreign material is applied to the ocular tissues may be a function of trauma and mechanical irritation, as well as reaction to the material. In our early attempts to standardize the technique of testing the cyanoacrylate monomers, many severe reactions due to mechanical irritation were encountered. We soon found that if these adhesives are instilled onto the eye, internal polymerization occurs within seconds which results in the transformation of the adhesive from the liquid into a solid state. These flaky particles freely moving and rubbing against cornea and conjunctiva, unquestionably result in epithelial damage, mechanical keratoconjunctivitis, and infections in the majority of cases. However, this reaction is indistinguishable from that caused by other inert substances placed in the conjunctival sac.

Also, it was found that when placing large amounts of these materials intra-laminarily, the cornea may melt centrally due to interruption of fluid flow from the anterior chamber with dessication and necrosis anterior to the impermeable layer. Careful examination of the studies by Girard’s Group at Baylor suggests that these irritative mechanical and dessication artifacts caused many of the difficulties of their study and should be disregarded in assessing true tolerance to these substances. In this study we attempted to minimize all reactions not due to toxicity so that tolerance of the adhesive could be best evaluated.

The conclusions drawn from this investi-
tion are that under the conditions of these experiments, cyanoacrylate monomers were as well tolerated as the controls when applied in small amounts intralamellarly or subconjunctivally. There was considerable reaction when these materials were placed in the anterior chamber. From this study, it can be seen that the application of the adhesive has to be evaluated for each site. The use of adhesive for the bonding of a methyl methacrylate lens to the denuded stroma is very well tolerated in animals and man; in this case, no mechanical irritation is caused since the adhesive is applied at the cornea-contact lens interface. It must be emphasized that in these experiments, relatively small "physiological" amounts of adhesive were used and the observation period was limited. It is always possible that excessive adhesive could cause problems and that later complications could occur in these animals. The fact that little or no wound healing or fibroblast migration through the material occurred when small amounts of these materials were placed in the cornea or under the conjunctiva during the two months that they were studied, means that further studies should be continued if these materials are to be used in any type of surgical wound in which wound healing is expected.

No difference was found between the tolerance of isobutyl, hexyl, octyl, or decyl cyanoacrylates. Therefore, it seems that selection of one of these materials over the others should be made on the basis of such factors as polymerization time, viscosity, and availability, rather than on tolerance of the material. A major problem with tissue adhesives as manufactured at present time is the variability and lack of stability of the manufactured material. The release of the sulfur dioxide used as stabilizer results in loss of the bonding power of these adhesives. Every time an ampule is opened the constitution of the material changes as the sulfur dioxide volatilizes. In addition, the commercial adhesive varies appreciably from batch to batch. This variability and lack of stability is a major cause of the spontaneous early detachment of the epikeratoprosthesis.

REFERENCES