

## Update on Botulinum Toxin

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### ABSTRACT

*Botulinum toxin type-A (BTX-A) is a neurotoxin which blocks presynaptic release of acetylcholine. It interferes with neuromuscular transmission<sup>1</sup>, temporarily paralyzing the affected muscle<sup>6</sup>. Of special interest for dermatologists is the unlabelled cosmetic applications, for conditions such as wrinkles and hyperhidrosis. Labelled indications in Europe are for cervical dystonia and cerebral palsy. In the US, it is approved for treatment of strabismus, blepharospasm and hemifacial spasm in adults<sup>2</sup>. After repeated use of high doses, antibodies can develop in some individuals, making further treatment ineffective indefinitely. Even when used in high doses for neurological conditions, the development of antibodies occurs in < 5% of patients. In 1997, the US FDA approved a new bulk toxin source for use in the manufacture of BTX-A. It has a higher specific potency than original BTX-A formulations, reducing the amount of utilized neurotoxin protein, and thereby reducing antibody production<sup>9</sup>. Another form of this neurotoxin (type B) also appears to be effective in patients who have developed antibodies to BTX-A. It is awaiting US FDA approval for treatment of cervical dystonia.*

### PHARMACOLOGY

Botulinum toxin type-A (BTX-A) is a neurotoxin produced by *C. botulinum* which blocks presynaptic release of acetylcholine. When a minute amount is injected into a muscle, it prevents neuromuscular transmission<sup>1</sup> temporarily paralyzing the affected muscle, and can provide symptomatic relief for up to three months or more after a single injection<sup>6</sup>. This can be useful for a wide variety of conditions.

### Cosmetic Uses

BTX-A has had a lot of publicity recently for its off-label cosmetic use in facial wrinkles<sup>11</sup>. It is currently in widespread use for the treatment of glabellar frown lines, crow's feet, and horizontal forehead lines<sup>1</sup>. Other more recent uses include more extended management of cosmetic problems, including platysmal bands and horizontal neck lines as well as lines in the lower part of the face. The nasolabial fold, mental crease, and upper lip wrinkling have

all been successfully treated using BTX-A although these indications are not without controversy<sup>3</sup>.

### Hyperhidrosis

Hyperhidrosis is another condition that has been managed successfully using BTX-A intracutaneously<sup>4,5</sup>, though some researchers report some associated muscle weakness<sup>5</sup>.

### Refractory Pain Associated with Spasticity

BTX-A offers an alternative for patients with refractory pain associated with spasticity. This includes dystonia due to abnormal posture, sustained muscle spasm and tremor. Investigators are looking at a wide range of disorders characterized by chronic soft tissue pain. These include fibromyalgia, chronic fatigue syndrome and temporal mandibular joint pain. Headache that is secondary to pericranial muscle tension may also respond to injection of BTX-A<sup>7,10</sup>.

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## LABELLED INDICATIONS

In Europe, BTX-A is approved for cervical dystonia and cerebral palsy, but in the US, the only approved indication is treatment of blepharospasm and strabismus associated with dystonia, although a supplemental NDA for cervical dystonia is pending. It is in late stage development in Europe and the US for upper limb spasticity, and in early phase development for headache/migraine and lower back spasm/pain<sup>11</sup>.

## A NEW GENERATION OF BOTULINUM TOXIN

While this drug is gaining popularity, its effect is temporary and most patients require repeat treatments. In some, BTX-A given in doses greater than 100u can induce the development of antibodies that make further treatment ineffective for an indefinite period<sup>8</sup>. However, even when used in high doses for neurological conditions, the development of antibodies occurs in < 5% of patients.

In 1997, the US Food & Drug Administration approved a new bulk toxin source for use in the manufacture of BTX-A. The new product, called *current* BOTOX<sup>®</sup>, is comparable in clinical efficacy to the *original* BOTOX<sup>®</sup>, but the higher specific potency reduces the amount of neurotoxin protein utilized, which in turn, leads to a reduction in the production of antibodies<sup>9</sup>.

NeuroBloc<sup>®</sup>, produced by Elan in Dublin, Ireland, is new and contains one of the other subtypes of botulinum toxin, type B. In clinical trials, this product has also been shown to be effective in patients who have developed antibodies and have stopped responding to BTX-A. It is currently awaiting US approval for use in the treatment of cervical dystonia<sup>11</sup>.

## CONCLUSION

BTX-A has had a lot of publicity recently for its off-label cosmetic use in facial wrinkles<sup>11</sup>. These unlabelled cosmetic applications are of special interest for dermatologists. However, repeated use of this product can induce the development of antibodies in some individuals, making further treatment ineffective for an indefinite period. Treating patients with a preparation of botulinum toxin (type A or B) that minimizes exposure to neurotoxin complex proteins may be preferable for reducing the risk of antibody formation<sup>9,11</sup>.

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## FORMS OF BOTULINUM TOXIN — TYPES A & B

Form + Company	Description	Comments
<b>Original Botox<sup>®</sup></b> (Allergan)	Botulinum toxin type A	Cost: \$462.50US (from Redbook 1999)
<b>Current Botox<sup>®</sup></b> (Allergan)	Same formulation but with higher specific potency of the improved bulk toxin reducing the neurotoxin protein utilized to deliver the same 100 units to 20% of original. Replaces Original Botox <sup>®</sup>	Development of antibodies is reduced. Cost: \$370.00 US \$335.00 – 350.00 CDN (from Allergan)
<b>Dysport<sup>®</sup></b> (Speywood)	Lower potency in humans per mouse unit. Produced using column-based purification.	2½ to 5 times the dose of Botox is necessary.
<b>NeuroBloc<sup>®</sup></b> (Elan)	Botulinum toxin — type B	Awaiting US FDA approval.

# N-2-butylcyanoacrylate (GluStitch™)

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## ABSTRACT

Cyanoacrylates are surgical adhesives that provide another option for wound closure. When compared to sutures, cyanoacrylates were found to be as effective as sutures in low tension lacerations and for the attachment of some full-thickness skin grafts. In addition, clinical practitioners have found cyanoacrylates easier to apply, time saving, and more economical. There are a number of surgical adhesives either currently available or under development. The presently available butylcyanoacrylates and octylcyanoacrylates are reviewed.

## PHARMACOLOGY

N-2-butylcyanoacrylate is a liquid compound that polymerizes rapidly in the presence of hydroxyl ions and is used for the closure of uncomplicated skin lacerations. It is useful in emergency rooms, for pediatric physicians, and in first-aid situations where wound closure is necessary and sutures are not warranted<sup>1</sup>. Since its discovery in 1949, several different forms of cyanoacrylates have been developed. Tissue adhesives constitute one part of an ever-expanding range of surgical adhesives. These products have been used successfully for hair transplantation<sup>4</sup>, split-thickness skin grafting<sup>5</sup>, punctal occlusion<sup>6</sup>, cerebrospinal fluid leak closure<sup>7</sup>, facial plastic surgery<sup>8</sup>, and corneal perforations<sup>9</sup>.

## CLINICAL TRIALS

### *N-2-butylcyanoacrylate vs Sutures*

When dealing with low-tension lacerations, physicians have compared skin closure using cyanoacrylates to skin closure using sutures, and found the tissue adhesive to offer some advantages with few of the disadvantages of conventional suture techniques<sup>8,13,14,15</sup>, especially in the pediatric setting<sup>2,11,12,13,14</sup>. It is less traumatic, eliminating the pain associated with the injection of local anesthetic, which may frighten an already traumatized child<sup>1</sup>.

Overall, the application of cyanoacrylate is a painless alternative to suturing for wound repair<sup>3,11,12</sup>, and has comparable cosmetic results<sup>14</sup>. It can be applied rapidly

and is cost effective<sup>1,14</sup>. Further, n-2-butylcyanoacrylate has been shown to reduce the risk of wound infection when compared to sutures<sup>15,16</sup>.

Wound strength on the day after closure using cyanoacrylates is only 10–15% of sutured wounds. However, careful technique may improve the outcome<sup>3</sup>, and routine tapestrip reinforcement of the wound is recommended by the manufacturer. Ointments must be avoided, because they will weaken the glue/skin bond.

### *Octylcyanoacrylate vs Sutures*

Another form of cyanoacrylate (i.e., octylcyanoacrylate) has also been compared with sutures. In a randomized, controlled study, physicians at the University of Michigan concluded that octylcyanoacrylate effectively closes selected lacerations, and is a relatively painless and fast method of wound repair. They estimate that this product can replace the need for suturing several million lacerations each year<sup>3</sup>.

### *Butylcyanoacrylate vs Octylcyanoacrylate*

One recent study compared two forms of cyanoacrylate: butylcyanoacrylate and octylcyanoacrylate. Pediatric patients with facial lacerations were treated, and the investigators examined issues of cosmesis, time of application, pain perceived by the patient, and wound healing. They concluded that there was little or no difference between these two forms of cyanoacrylate<sup>2</sup>. Cost difference may dictate choice.

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## Full-Thickness Skin Grafts

N-2-butylcyanoacrylate has been investigated as an alternative to the meticulous and time-consuming suturing required to position full-thickness skin grafts. It has been found to be useful particularly for relatively immobile areas such as the temple, forehead, and distal nose<sup>10</sup>.

## CONCLUSION

Cyanoacrylates are becoming increasingly popular for use in wound closure in low tension lacerations and for the attachment of some full-thickness skin grafts. Of the many minor procedures carried out in ambulatory offices (e.g., excisions and biopsies in low tension areas), a method of wound closure such as this is easier, more time saving, and more economical than traditional methods.

### SOME SURGICAL ADHESIVES CURRENTLY AVAILABLE<sup>17</sup>

Product	Manufacturer	Packaging format	Cost
<b>GluStitch™</b> (n-2-butylcyanoacrylate)	GluStitch Inc.	Single use plastic applicator, violet or clear. Multiuse, 1.0 ml, 5.0 ml, violet or clear.	\$12.00 US \$25.00 US/ml
<b>Dermabond™</b> (2-octylcyanoacrylate)	Ethicon Johnson & Johnson	Single use glass ampule	\$22.00 US
<b>HistoAcryl™</b> (n-2-butylcyanoacrylate)	B. Braun Melsungen A.G.	Single use plastic ampule containing 0.5ml, violet	\$80.00 US/ml
<b>Indermil™</b> (n-2-butylcyanoacrylate)	Loctite Corp.	Single use plastic ampule containing 0.5ml, clear	\$80.00 US/ml
<b>LiquiBand™</b> (n-2-butylcyanoacrylate)	MedlogicGlobal Available in Europe only	Single use plastic, clear	£7 UK

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# Soft Tissue Augmentation with Silicone

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## ABSTRACT

*Adatosil<sup>®</sup> is a viscous silicone oil which was granted FDA approval in 1994. This designation removes the legal obstacles to usage for soft tissue augmentation. However, physicians are advised to exercise discretion when using this product. There are several caveats which govern its use, including several contraindications, as well as difficult technical application.*

## PHARMACOLOGY

This product, an extremely viscous silicone oil, is labeled for ophthalmologic usage. After many years of controversy, the FDA granted approval in 1994, to Adatosil<sup>®</sup> (Escalon Medical Corporation, Chicago). This designation removes the legal obstacles to usage for soft tissue augmentation. Caveats to the legal status include the fact that this product cannot be advertised, and the decision to use it must be based upon the unique needs of the patient<sup>1</sup>.

At 5,000 centistokes viscosity, Adatosil<sup>®</sup> is roughly 14 times as viscous as the 350 centistoke variety that was used for years without FDA approval. It is too viscous to be injected with a needle under 26 gauge in size. A large diameter 1 cc Luer-lock syringe (B-D-W12811) is usually employed, containing only 0.2cc attached to a zyplast assist done to maximize leverage. Pretreatment with EMLA<sup>®</sup> Cream will minimize discomfort. Lip treatment should be preceded by a local anesthetic in the circumoral area.

## CONTRAINDICATIONS

Because of the force needed to inject this viscous material, great care should be taken when injecting the glabella to avoid intravascular injection. In addition, all forms of permanent implants may interact with bacterial or viral infection or allergic phenomena. Lip augmentation should be avoided in patients with histories of dental carries or other oral problems, or those with multiple allergies. A less viscous product is under development, which will make this easier to use. Aspirin or NSAIDs must be avoided for two weeks before injections. Patients who participate in contact

sports, those with histories of repeated infections, and those taking anti-coagulants may be inappropriate candidates for silicone injections.

Physicians are advised to use discretion when using this product. This includes careful pre- and post-treatment counselling as well as explanations to the patients about risks and benefits and the need for repeated treatments to achieve maximum results. Physicians would be well advised to discuss their plans with their malpractice carriers, and they should be familiar with the indications and drawbacks for liquid silicone as outlined in a recent publication<sup>2</sup>. Patients who have had prior nonFDA approved silicone implants should not receive this product since subsequent problems with the existing silicone may then be attributed to the Adatosil<sup>®</sup>. Practitioners also need to use careful technique because fluid viscosity makes postinjection dispersion more difficult. Any practitioner wishing to use this filler should undergo proper training.

## COSTS

In the United States, the cost of Adatosil<sup>®</sup> to clinical practitioners is approximately \$450 per 10 ml vial. Patients in the United States can expect to pay between \$350 and \$550 for each treatment, depending on the type of treatment they are receiving and volume utilized.

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## Update on Drugs

Class	Name/Company	Approval Dates and Comments
<b>Antibacterial</b>	<b>Mupirocin</b> Bactroban® SmithKline Beecham	The United States FDA approved the addition of pediatric indications, including topical treatment of impetigo.
<b>Anti-acne</b>	<b>Roxithromycin</b> Rulid® Hoechst Marion Roussel	Approved by Japanese drug regulatory authority for treatment of severe acne. Rulid was first launched in 1991, and has numerous other indications.
<b>Anticancer</b>	<b>Temoporfin</b> Foscan® Scotia	The United States FDA designated priority review in March, 1999, to this photodynamic therapy for the palliative treatment of recurrent, refractory or second primary squamous cell carcinomas of the head and neck in patients considered to be incurable with surgery or radiotherapy. Scotia hopes to file an NDA for this product by the end of September, 1999.
<b>Anti-inflammatory</b>	<b>Fluticasone propionate</b> Cutivate® Cream Glaxo Wellcome	HPB Ottawa approved for the treatment of atopic dermatitis in infants three months of age or older.
<b>Vaginal preparation</b>	<b>17-Beta-Estradiol</b> Vagifem® Novo Nordisk	The United States FDA has approved this vaginal tablet insert for treatment of atrophic vaginitis. There are a number of contraindications, including known/suspected breast carcinoma, estrogen-dependent neoplasia, pregnancy, abnormal genital bleeding, porphyria, thrombophlebitis or thromboembolic disorders, and hypersensitivity to VAGIFEM constituents.
<b>Antifungal</b>	<b>Itraconazole injection</b> Sporanox® IV injection Janssen	The United States FDA approved this antifungal agent in March, 1999, for treatment of histoplasmosis, blastomycosis, and refractory aspergillosis, including use in immunocompromised patients. Contraindications include use with specific other drugs, such as Propulsid (cisapride), Halcion (triazolam), Versed (midazolam), Mevacor (lovastatin) or Zocor (simvastatin).
<b>Wound care</b>	<b>Becaplermin</b> Regranex® Gel 0.1% Johnson & Johnson/McNeil	The European Commission approved this wound healing agent in April, 1999, for the treatment of full thickness neuropathic, chronic diabetic ulcers.
<b>Topical Anesthetic</b>	<b>Lidocaine/prilocaine</b> EMLA® cream Astra	The United States FDA approved the additional indication of use in pediatric patients.
<b>Drug Warning</b>		
<b>Herbs and Anesthesia</b>	The American Society of Anesthesiologists ( <i>JAMA</i> 1999; 281:1882) is advising that the use of herbal products be discontinued for $\geq 2$ weeks before surgery. Anesthesiologists have reported substantial changes in heart rate or blood pressure in some patients who were taking herbals such as St. John's wort, ginkgo biloba and ginseng.	
<b>Deaths Related to Liposuction</b>	A study in the <i>New Engl J Med</i> (1999;340:1471-75) suggests that tumescent liposuction can be fatal, possibly due to lidocaine toxicity or lidocaine related drug interactions. A total of 48,527 deaths were investigated, and of those, 5 occurred during or after liposuction. In this procedure, lidocaine doses can range from 10-88 mg/kg, much higher than the maximum recommended dose of 4.5mg/kg typically used for SC infiltration.	

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