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**BOTULINUM TOXIN A FOR THE TREATMENT OF REFRACTORY
CHRONIC ANAL FISSURES AND INTERNAL ANAL SPHINCTER
ACHALASIA IN PEDIATRIC PATIENTS**

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Invitation.

This document was developed to assist decision-making in the McGill University Health Centre. All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.

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GLOSSARY

Anal fissure – split in the skin of the distal anal canal.

Hirschsprung's disease – condition characterized by an extremely dilated colon.

Internal anal sphincter achalasia – failure of the internal anal sphincter to relax.

Myectomy – excision of a portion of muscle.

Off-label drug use – use of a drug outside the terms indicated in the product license.

Sphincterotomy - Surgical cutting or weakening of a sphincter (internal sphincterotomy - Incision of the internal anal sphincter).

Unlicensed drug – drug that has never been approved.

EXECUTIVE SUMMARY

This report is prepared in response to a request from the pharmacy of the Montréal Children's Hospital to review the use of botulinum toxin A for the treatment of pediatric patients with chronic anal fissure refractory to other treatments, and for persistent obstructive symptoms (internal anal sphincter achalasia) in children who underwent treatment for Hirschsprung's disease.

Chronic anal fissure. No data on pediatric patients treated with botulinum toxin A for chronic anal fissure are available in the peer-reviewed literature. In adults, healing occurs in approximately 70% of patients with chronic anal fissure treated with botulinum toxin A. While relapses occur in approximately one third of these patients. Studies have shown that repeated injections of botulinum toxin A may improve the healing rate.

Comparative studies, also in adults, show a better response rate with lateral internal sphincterotomy compared to botulinum toxin A. However, sphincterotomy may be associated with permanent complications such as incontinence. In contrast, permanent complications do not occur with botulinum toxin A treatment as its effect wears off after a few months.

Achalasia of the internal anal sphincter. Five non-comparative pediatric studies using botulinum toxin A for the treatment of internal anal sphincter achalasia were identified in the peer-reviewed literature. A total of 60 patients were included in the five publications. In general, the studies have shown a good initial response to the treatment, although the treatment had to be repeated in most cases as the effect of botulinum toxin A wears off after a few months. Surgical treatment (myectomy) is often successful, but it may be associated with incontinence and it does not exhibit the same efficacy in patients with obstructive symptoms due to causes other than internal anal sphincter achalasia such as mechanical obstruction, aganglionosis, intestinal motility disorder, and functional megacolon. Botulinum toxin A may be used in order to identify the patients who would potentially have a good response to surgery, avoiding the surgical risks in those unlikely to respond to it.

Reported complications in these studies were infrequent and not serious. However, serious and systemic complications have been reported in patients treated with botulinum toxin A for other indications. Resistance to the drug especially after repeated injections has also been reported in patients with neurological conditions treated with botulinum toxin.

The estimated cost to the MUHC for each treatment with botulinum toxin A for either chronic anal fissures or internal anal sphincter achalasia is approximately \$500. It is estimated that approximately four pediatric patients (one with chronic anal fissure and three with internal anal sphincter achalasia) will require treatment with botulinum toxin A annually at the MUHC. Therefore, the total budget impact to the MUHC is expected to be between \$2,000 and \$4,000, in the case of repeated injections.

TAU RECOMMENDATIONS

Given the sparse evidence of the efficacy and safety of botulinum toxin A in chronic anal fissures and internal sphincter achalasia in pediatric patients, recognition of these two applications of botulinum toxin A as routine or “accepted” technologies at the MUHC is not recommended at this time. However, recognizing that definitive studies

of these relatively rare conditions are unlikely to be available soon, the small anticipated budgetary impact, and the possibility that their use may avoid some unnecessary surgery, the TAU recommends that:

1 - Botulinum toxin A could be used in the following exceptional circumstances (approximately 4 patients per year), and only after consultations with at least two specialists:

- In pediatric patients with ***chronic anal fissures*** refractory to conservative treatment and who are not eligible for surgery.

- In pediatric patients with ***internal anal sphincter achalasia*** refractory to conservative treatment, botulinum toxin A could be used as a means of identifying those patients who would benefit from surgical treatment, thus avoiding operating on patients who would likely not benefit from surgery and who might nonetheless be at risk of developing permanent complications.

2 - The patients' families should be informed that these are off-label treatment indications for botulinum toxin A that have not been approved by Health Canada.

3 - The efficacy and safety outcomes of these patients should be recorded and reviewed in a systematic fashion.

BOTULINUM TOXIN A FOR THE TREATMENT OF REFRACTORY CHRONIC ANAL FISSURES AND INTERNAL ANAL SPHINCTER ACHALASIA IN PEDIATRIC PATIENTS

FOREWORD

In July 2005, Mr. Jean-François Guévin, associate director of pharmacy of the Montreal Children's Hospital (MUHC), requested that the Technology Assessment Unit (TAU) review the use of botulinum toxin A for the treatment of pediatric patients with chronic anal fissures refractory to other treatments, and for the treatment of and for persistent obstructive symptoms (internal anal sphincter achalasia) in children who underwent treatment for Hirschsprung's disease.

INTRODUCTION

Anal fissure is characterized by a split in the skin of the distal anal canal that occurs more often in the posterior midline¹. Although it is more often diagnosed in the third decade of life, it occurs in patients of all ages², including children^{3 4 5}.

Chronic anal fissure. Anal fissures can be caused by constipation or straining, but it has also been suggested that local ischemia and internal anal sphincter spasm/hypertonia may play a role in the pathogenesis of the condition^{1 6}. Its symptoms include bleeding and pain that can be severe and of short duration in acute fissures or it can last for hours after defecation in patients with chronic fissures⁷.

Most acute fissures heal spontaneously, but a small proportion becomes chronic and requires treatment². Conservative treatment (dietary advice, stool softeners, and sitz baths) is expected to heal anal fissures in many of the affected children. However, it is not curative in all cases³. Persistent (chronic) fissures in pediatric patients may be treated with manual anal dilation or lateral internal sphincterotomy³. These procedures, although effective, may result in complications such as incontinence, seen in adults with a rate of up to 35%³. Incontinence can become permanent in some cases³. Incontinence can negatively affect the patient's quality of life⁸, and in order to

avoid permanent complications, chemical treatments that decrease the internal anal sphincter tonus have been developed⁹, such as topical nitrates, topical calcium channel blockers, and botulinum toxin A injections⁷. It is believed that permanent complications associated with surgical treatment may not occur with botulinum toxin A as its effect lasts for only 3-6 months¹⁰.

Internal anal sphincter achalasia. This is an uncommon condition¹¹ caused by failure of the internal anal sphincter to relax in response to rectal distension¹². It is mostly seen in patients with Hirschsprung's disease¹¹. Approximately 10% of the patients who undergo surgery for Hirschsprung's disease still present with obstructive symptoms^{10 13}, sometimes caused by internal anal sphincter achalasia¹⁴.

One of the treatment options available for pediatric patients with internal anal sphincter achalasia is myectomy¹². Although efficacious, this surgical procedure may be associated with different degrees of incontinence (gas, mucus or stool)¹². Other treatment alternatives include anal dilation and topical nitrates¹⁵.

Botulinum toxin A injected into the internal anal sphincter may in theory have the same effect as an internal anal myectomy¹⁴. However because the effect of botulinum toxin A is temporary, i.e., lasts for 3-6 months¹⁰, the permanent potential complications associated with the surgery may be avoided¹⁴.

There are seven known types of toxin produced by *Clostridium botulinum*, i.e., botulinum toxin A-G¹⁶. Only botulinum toxins A and B have been approved for clinical use, and botulinum toxin A has mainly been used to treat gastrointestinal disorders¹⁶. Therefore, our report focuses on botulinum toxin A.

BOTULINUM TOXIN A

Botulinum toxin A is produced by the bacteria *Clostridium botulinum*¹⁷. It is sterilized and purified to be used in the injectable form¹⁷. Botulinum toxin A inhibits the release of acetylcholine from the presynaptic nerve terminals at neuromuscular junctions

leading to the relaxation of the internal anal sphincter^{18 19}. The effect of botulinum toxin normally starts to appear within a few days of the injection²⁰ and may last for three or more months^{1 21}.

Botulinum toxin A has been used since the 80s in an increasing number of conditions^{22 23}. It was first used for the treatment of chronic anal fissures in 1993²⁴. It is approved by Health Canada for the indications listed in table 1, which do not include chronic anal fissures or internal anal sphincter achalasia²⁵.

Table 1 – List of botulinum toxin A indications currently approved by Health Canada²⁵.

Patient population	Indication
Not specified	- Hyperhidrosis of the axila
Adults	- Cervical dystonia - Focal spasticity including upper limb spasticity associated with stroke
12 years and older	- Blepharospasm - Strabismus
2 years and older	- Dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy

Expected side effects

According to the manufacturer, expected side effects with botulinum toxin A treatment include localized pain, tenderness, and/or bruising at the injection site, and local weakness²⁵. Other events such as skin rash, pruritus, allergic reaction, and facial paralysis have been reported to occur more rarely (<0.1%)²⁵.

The current product label does not mention the expected side effects of the use of botulinum toxin A in the internal anal sphincter. The side effects, especially local ones, may differ between indications since they are a consequence of the diffusion of the toxin to adjacent muscles²². One expected side effect of injections of botulinum toxin A into the internal anal sphincter is incontinence to flatus, liquids or feces. However, this effect is expected to be temporary²⁹.

Although authors believe that treatment with botulinum toxin A is relatively safe with mostly local side effects^{16 23 30 31}, there have been reports of systemic side-effects in patients treated for different conditions^{16 23 30 31}. These include generalized weakness^{23 30 31}, ranging in incidence from 0.06% with doses of 25-50U to 20% with doses of 100-280U²³, gall bladder dysfunction^{16 30}, nausea (0.1-5.9%), pruritis (0.3%), and flu-like syndrome^{16 23 30}. There have been rare reports of cardiovascular side-effects^{16 25 26 27}, including myocardial infarction, one case of heart block^{16 27}, heart rate variability and death^{27 25}. Death may also be associated with dysphagia, pneumonia, or significant debility²⁵. However, the association between the treatment and these events cannot be determined with certainty. Although these events were considered uncommon, their precise incidence has not been reliably determined³¹.

The long-term safety of repeated botulinum toxin A administration has not been determined³⁰.

Resistance to botulinum toxin A

Resistance to botulinum toxin A has been reported in patients with neurologic disorders as a consequence of formation of antibodies against the toxin¹⁶, leading to diminished efficacy³⁰. It has been reported more frequently in patients given higher doses and more frequent administration¹⁶. Some of these patients later showed a good response when switched to botulinum toxin B¹⁶.

TREATMENT AVAILABILITY IN CANADA

Botulinum toxin A is available in Canada (Botox®) although it is not approved by Health Canada for chronic anal fissures or internal anal sphincter achalasia²⁵.

A topical 2% nitroglycerin ointment (Nitrol®) is available in Canada, however, like Botox®, its indications do not include anal fissures or internal anal sphincter achalasia²⁵. No topical calcium channel blocker preparations are currently available in Canada²⁵.

Reimbursement

Botulinum toxin A (Botox®) is covered by the RAMQ for use for specific indications that do not include chronic anal fissures (medicament d'exception)³³. The MUHC covers the costs of the drug treatments received in the hospital, even if the patients are not hospitalised.

METHODS

Literature Search

The literature search was performed by using the Pubmed, EMBASE and INAHTA databases, and the Cochrane Database of Systematic Reviews.

Chronic anal fissure

The search terms used were: “botulinum toxin” **and** “anal fissure”. Included studies had to report clinical outcomes including rates of healing, relapses, repeated treatment, and treatment complications in pediatric patients.

Internal anal sphincter achalasia

The search terms used were: “botulinum toxin” and “achalasia” and “anal”, and “children or pediatric”. Included studies had to report clinical outcomes such as spontaneous bowel movement^{12 11} or improvement of obstructive symptoms^{10,13,14}.

More details of the literature search are found in Appendix 1.

Cost Analysis

The cost of treatment with botulinum toxin A for both chronic anal fissures and internal anal sphincter achalasia was calculated from the perspective of the McGill University Health Centre (MUHC) and therefore included equipment, materials, medications, and nursing fees incurred in the treatment. Physicians are paid directly by the RAMQ and were therefore not included in the cost calculations. Overhead costs were also

excluded as we expect that the small number of patients who will receive these treatments will not impact the MUHC overhead costs.

RESULTS

Studies in Patients with Chronic Anal Fissures

No studies in pediatric patients with chronic anal fissures treated with botulinum toxin were identified in the peer-reviewed literature. Studies in adult patients were identified in the literature, the list of these studies with a brief description their design is given in Appendix 2.

Other publications on the use of botulinum toxin A in chronic anal fissures consisted of a Technology Assessment report based on previously published systematic reviews relating to patients of all ages³⁴, a medical position statement from the American Gastroenterological Association³⁵ and recommendations from The American Society of Colon and Rectal Surgeons²⁹. These publications and the results of the studies in adult patients are summarized below.

Technology Assessment Reports and Treatment Recommendations for Chronic Anal Fissures

A report from the Alberta Heritage Foundation for Medical Research (AHFMR) published in February 2004 concluded that it was too early at that point to define the importance of botulinum toxin A in the treatment of anal fissures, and although it seemed promising in patients refractory to conservative care, long-term efficacy, safety and cost-effectiveness compared to other alternatives needed to be studied further³⁴. Other issues raised were lack of regulatory approval for the indication and lack of information on its chronic use in pediatric patients³⁴. Nevertheless, the authors believe that botulinum toxin A may be an option for patients with few or no other alternatives and for those who prefer to avoid more invasive procedures³⁴.

The American Gastroenterological Association believes that despite the possibility of relapses, and the fact that there are still discussions regarding the optimal site of

injection, high cure rates have been observed in the treatment of chronic anal fissures with botulinum toxin A and therefore, together with topical treatments, it should be regarded as a treatment options due to its safety profiles³⁵.

The American Society of Colon and Rectal Surgeons recommendations issued in 2004 stated that although uncertainties still exist regarding the use of botulinum toxin to treat chronic anal fissures, it can be used in cases that are refractory to conservative treatment²⁹.

Studies in adult patients treated with botulinum toxin A for chronic anal fissures

The comparative studies in adult patients with chronic anal fissures identified included a total of 279 patients treated with botulinum toxin A and 252 with other treatments (placebo, topical nitrates, sphincterotomy)^{36 37 38 39 40 41 42 43 44}. Their results have shown that approximately 70% of the patients with chronic anal fissures are healed with one injection of botulinum toxin A and up to one third of the healed fissures may relapse within the first year. Some studies showed that repeating the botulinum toxin A injection in patients with unhealed or relapsed fissures may improve the healing rate^{1 21 9 45}. The total dose of botulinum toxin A per treatment used in the studies varied from 5U to 50U, and different injection sites were used in different studies (appendix 3).

Although the results in adults with chronic anal fissures show that botulinum toxin was superior to placebo and topical therapy, compared to sphincterotomy, healing rates were lower. The literature shows a good response with sphincterotomy⁴⁶ but one concern with this treatment is that it may cause permanent complications such as anal incontinence^{6 9 19}. It is believed that this permanent complication could be avoided with treatment with botulinum toxin A injections^{9 19 40} as its effect lasts for 3-4 months^{9 40}, or with topical treatments¹⁷. Reported rates of anal incontinence after sphincterotomy vary widely in the literature, 5% to 35%⁴⁰, and it is also dependent on the type of incontinence i.e., flatus, liquid or solid⁴⁷. In contrast, some authors classify anal incontinence after sphincterotomy as minor⁷ or acceptable²⁹. One episode of

permanent incontinence with botulinum toxin A was reported⁴⁸ and two such episodes were identified in the peer-reviewed literature in patients undergoing sphincterotomy⁴⁹. Pooling the results of these studies together yielded a statistically higher risk of transient incontinence with sphincterotomy compared to botulinum toxin A. Nevertheless, firm conclusions should not be drawn considering that the overall number of patients evaluated is relatively small.

The longest follow-up reported in the chronic anal fissures studies identified was 2-3 years. Appendix 3 provides additional information on these studies.

Safety (Chronic Anal Fissures)

Complications reported in the comparative studies in adult patients treated with botulinum toxin A were perianal thrombosis (18% vs. 9% with placebo)³⁸ subcutaneous abscess (4.5% vs. 13.6% with placebo)³⁸, hematoma (2.5% vs. 2.5% with sphincterotomy)⁴⁹.

Complications reported in non-comparative adult studies were anal spasm (5%)⁵⁰, flu-like syndrome (1.7%), hemorrhoid thrombosis (1.1%) or protrusion (0.5%) and epididymitis (0.5%)^{26,51}.

Studies in pediatric patients with internal anal sphincter achalasia

No RCTs, systematic reviews or technology assessment reports of internal anal sphincter achalasia were found in the literature.

Five non-comparative publications that reported the use of botulinum toxin A in children with internal anal sphincter achalasia were identified in the peer-reviewed literature^{12 10 11 13 14}. Two publications consisted of reports of four cases^{12 14}, one publication consisted of a non-comparative observational study involving 20 patients¹¹. One publication included 14 patients treated with botulinum toxin A for persisting obstructive symptoms after surgical Hirschsprung's disease treatment¹³. Another

publication consisted of 18 patients who received treatment with botulinum toxin A for persistent obstructive symptoms after surgical treatment of Hirschsprung's disease¹⁰.

The patients' ages in the studies identified varied between 3 months and 17 years^{10 11 12 13 14}.

Total doses varied between 15U and 100U per treatment for Botox®, and 12U/kg to 24U/kg for Dysport® divided into 4 injections, one in each of the four quadrants of the internal anal sphincter^{10 11 12 13 14}. One of the studies did not report dose or site of injection¹³.

Langer and Birnbaum advocate that botulinum toxin A is also of value in determining if the obstructive symptoms are due to internal anal sphincter achalasia which may be treated by botulinum toxin and/or myectomy, or if the obstructive symptoms are due to other conditions in which these treatments would not be effective and would still carry the risks of permanent complications^{13 14}.

According to an algorithm proposed by Langer¹³, persistent obstruction after surgical Hirschsprung's disease treatment should be managed according to the etiology of the obstruction¹³. For instance, botulinum toxin A should be used if 1) no stricture is present, 2) ganglion cells are present, and 3) if the motility workup is normal¹³.

Response rates (internal anal sphincter achalasia)

Most of the patients (67%-100%) showed a good initial response to the first botulinum toxin A injection^{10 11 12 13 14}. However, the effect of the toxin wears off after a few months. Thus the duration of the response ranged between one week and 18 months (mean 14 weeks) among the 20 patients evaluated by Ciamarra et al.¹¹, and 2-12 months in the study by Langer¹³. As a consequence, the majority of the patients required repeated treatment within a few months of the previous injection consisting of either another injection of botulinum toxin A or a surgical procedure^{10 11 12 13 14} as described below.

Among the four cases reported by Messineo et al., three (75%) patients still exhibited a good response at the end of follow-up, 6 – 14 months after the second or third injection of botulinum toxin A¹². One patient (25%) was diagnosed with Hirschsprung's disease and was treated with surgery¹².

Among the 18 patients (90%) with a good initial response in the study by Ciamarra et al., eight (40%) patients required a second or third injection of botulinum toxin A 2-6 months after the previous injection and eight patients (40%) required surgical treatment due to either relapse or failure of botulinum toxin A¹¹.

Langer reported that among the 14 patients (100%) with a good initial response to botulinum toxin A, nine (67%) patients required 1-4 additional injections, and one (7%) patient had an ileostomy at the parents' request¹³.

In another study where 12 (67%) patients had a good initial response to botulinum toxin A, nine (50%) patients required 1-5 additional injections either due to recurrence of symptoms or due to initial failure¹⁰. In these cases, a higher dose of botulinum toxin A was administered¹⁰.

Among the four patients reported by Langer and Birnbaum¹⁴, three had a good initial response to the treatment with botulinum toxin A, and two exhibited an ongoing response at the end of follow-up after one or two injections of botulinum toxin A¹⁴. One patient who initially responded to the treatment had a recurrence of symptoms at six months. This patient had previously received myectomy¹⁴.

The length of patient follow-up was not reported in any of the studies so it is not possible to determine if additional treatments would still be necessary beyond what was reported.

More details in Appendix 4.

Safety (internal anal sphincter achalasia in pediatric patients)

One episode (5%) of rectal pain that lasted for a few hours after the injection was reported in one study¹¹, and anal or abdominal pain lasting for several hours after the injection was reported in another study¹⁰. Mild transient incontinence was reported in four (22%) of the patients in the study by Minkes and Langer, two of which had undergone previous myectomy¹⁰, which also carries a risk of incontinence. Two of four cases (50%) patients in the study by Langer and Birnbaum experience incontinence¹⁴, it lasted for 3 weeks in one (25%) patient¹⁴. The second patient was already experiencing intermittent incontinence after a myectomy, and after the treatment with botulinum toxin A, no change in the number of episodes was observed¹⁴. The other two publications did not report the presence or absence of complications^{12 13}.

Appendix 4 gives additional details about these publications.

LOCAL EXPERIENCE AT THE MUHC CHILDREN'S HOSPITAL

Chronic anal fissures

The majority of the pediatric patients presenting with anal fissures are successfully treated with conservative treatment (dietary advice, stool softeners, and sitz baths). Refractory patients may be treated with topical nitrates or tacrolimus paste and only in extremely rare instances patients are surgical candidates. Botulinum toxin A would be used as an alternative for patients who have not responded to the above measures and in whom surgery is considered to carry too high a risk of comorbidities, particularly incontinence. One child with chronic anal fissure who was not eligible for surgery has been recently treated with botulinum toxin A at the MUHC with a favourable response (Dr. H. Flageole, personal communication).

It is estimated that approximately 1 pediatric patient per year may require treatment with botulinum toxin A for chronic anal fissures at the MUHC.

Internal anal sphincter achalasia

At the MUHC, pediatric patients with persistent obstructive symptoms after surgical treatment for Hirschsprung's disease undergo an investigation in order to identify the etiology of the obstructive symptoms. The children's hospital, under the leadership of Dr Dominique Levesque, has an advanced gastrointestinal motility laboratory and their studies are very helpful to determine which patients may benefit from botulinum toxin A injection. Patients in whom the symptoms are suspected to be due to internal anal sphincter achalasia are normally treated surgically with internal sphincter myectomy or sphincterotomy. However, these surgeries may not be effective in some cases as the obstructive symptoms may be caused by conditions other than internal anal sphincter achalasia, and these surgeries may increase the risk of incontinence in patients who had already undergone surgical treatment for Hirschsprung's disease. Botulinum toxin A injected into the internal anal sphincter can be used before the surgery as a test to identify the patients who would benefit from surgery, i.e., patients with a positive response to botulinum toxin A would be then referred to surgery as the effect of the toxin wears out after a few months. The botulinum toxin A injection may be repeated in patients who are ineligible to surgery or in whom surgery needs to be delayed.

The benefit of using botulinum toxin A in these patients would therefore be to avoid operating on patients in whom surgery would likely not be effective, but who would nevertheless be at risk for permanent complications such as incontinence, which has a strong negative impact in the patients' quality of life.

It is estimated that approximately 1-3 pediatric patients per year may require treatment with botulinum toxin A for internal anal sphincter achalasia at the MUHC.

COSTS

The treatment of chronic anal fissures and internal sphincter achalasia with botulinum toxin A injection is carried-out as a day surgery.

Table 2 summarizes the resources involved in the procedure. The resources involved and length of procedure were provided by Dr. Hélène Flageole, MD (personal communication). Physicians' fees were not included in the cost calculation since they are not paid by the MUHC. We have assumed that overhead costs would not be increased as a result of performing the procedure in a small number of patients and therefore these costs were not included.

Table 2 - Per patient cost of a single administration of botulinum toxin A in the internal anal sphincter

Resource Utilization	Unit Costs	Total Costs
Pre-procedure (1 hour)		
Nursing fees (1 hour)	\$39.59* / hour	\$39.59
Procedure (botulinum toxin A injection) (40 minutes)		
Nursing fees (40 minutes)	\$39.59* (per hour)	\$26.4 (40 minutes)
Botulinum toxin A (Botox®), 100U	\$340.00**	\$340.00
Post-procedure recovery (2 hours)		
Nursing fees (2 hours)	\$39.59* (per hour)	\$79.2
Total cost		\$485.2

*Source of the information: Finance department of the MUHC, Mr. Paul Tan

** Source of information: Régie de l'Assurance Maladie du Québec³³ .

The estimated cost per patient per treatment with botulinum toxin A injection for chronic anal fissures or internal anal sphincter achalasia is approximately \$500.00. One to two injections may be necessary per year.

The total cost to the MUHC assuming that 4 patients a year (1 with chronic anal fissure and 3 with internal sphincter achalasia) may vary between \$2,000 and \$4,000.

ISSUES REGARDING OFF-LABEL MEDICATION USE IN PEDIATRIC PATIENTS

A high proportion of approved drugs in different countries lacks specific prescribing information for pediatric patients⁵². In the absence of this information, physicians are left with the dilemma of either not providing potentially beneficial treatment to children^{53 54}, or prescribing a drug based on information from adult studies, without specific knowledge of therapeutic benefits and potential toxicity in children^{55 54}.

A review of the literature published in 2005 has shown that unlicensed or off-label drug prescription to pediatric patients represents 11% - 80% of the drug prescriptions in neonatal or pediatric hospital wards, and 11% - 37% of the prescriptions in the community in different countries in Europe, USA, Australia, and Israel⁵⁶. A publication from Canada⁵⁷ arrived at similar conclusions. Appendix 5 discusses these issues further.

DISCUSSION

Chronic anal fissures

Studies in adult patients treated with botulinum toxin A for chronic anal fissures have shown a relatively acceptable efficacy with few side-effects^{36 37 38 39 40 41 42 43 44}. However, no studies of botulinum toxin A in pediatric patients with chronic anal fissures have been identified.

Pediatric patients with chronic anal fissures are usually successfully treated with conservative treatment at the MUHC. Patients refractory to these measures are rare (one patient / year at the MUHC), and are usually treated with sphincterotomy at the MUHC, however, patients who cannot undergo surgery due to concomitant medical conditions might benefit from treatment with botulinum toxin A (Dr. H. Flageole, personal communication).

Internal anal sphincter achalasia in pediatric patients

Although most of the pediatric patients treated with botulinum toxin A for ***internal anal sphincter achalasia*** reported in the literature (N=60) exhibited an initial positive response to the treatment, many required repeated treatment^{10 11 12 13 14}.

At the MUHC, pediatric patients with obstructive symptoms that are suspected to be due to internal anal sphincter achalasia and who are refractory to conservative treatment are usually referred to surgery (myectomy). The use of botulinum toxin A before the surgery might help identify those patients who are more likely to benefit from myectomy and these patients can then be referred to surgical treatment as the

effects of the toxin wear off after a few months. It not only avoids that an unnecessary surgical procedure be performed in pediatric patients who would not benefit from it, but it also avoids possible complications such as permanent incontinence in these children. At the MUHC, it is expected that 1-3 patients with internal anal sphincter achalasia will need to be treated annually.

General

Low frequencies of adverse events were reported in the studies identified in both indications, most of them were local and were not serious^{10 11 12 13 14 36 37 38 39 40 41 42 43 44}. Nonetheless, systemic side effects with the use of botulinum toxin A have been reported in patients treated for other conditions^{16 23 30 31}.

Moreover, as these represent off-label uses of botulinum toxin A, informed consent should be obtained.

The yearly estimated budget impact of using botulinum toxin A in these children is approximately \$2,000 - \$4,000.

TAU RECOMMENDATIONS:

Given the sparse evidence of the efficacy and safety of botulinum toxin A in chronic anal fissures and internal sphincter achalasia in pediatric patients, recognition of these two applications of botulinum toxin A as routine or “accepted” technologies at the MUHC is not recommended at this time. However, recognizing that definitive studies of these relatively rare conditions are unlikely to be available soon, the small anticipated budgetary impact, and the possibility that their use may avoid some unnecessary surgery, the TAU recommends that:

1 - Botulinum toxin A could be used in the following exceptional circumstances (approximately 4 patients per year), and only after consultations with at least two specialists:

- In pediatric patients with ***chronic anal fissures*** refractory to conservative treatment and who are not eligible for surgery.
- In pediatric patients with ***internal anal sphincter achalasia*** refractory to conservative treatment, botulinum toxin A could be used as a means of identifying those patients who would benefit from surgical treatment, thus avoiding operating on patients who would likely not benefit from surgery and who might nonetheless be at risk of developing permanent complications.

2 - The patients' families should be informed that these are off-label treatment indications for botulinum toxin A that have not been approved by Health Canada.

3 - The efficacy and safety outcomes of these patients should be recorded and reviewed in a systematic fashion.

APPENDIX 1 – LITERATURE SEARCH METHODOLOGY

Literature Search

The literature search was performed by using the Pubmed, EMBASE and INAHTA databases, and the Cochrane Database of Systematic Reviews.

There were no restrictions for dates of publication (last search on September 20th 2005). The abstracts were searched for relevance and only articles in humans treated with botulinum toxin A, published in English and French and that fell in one of the following categories were reviewed for relevance:

- Studies comparing botulinum toxin A to other treatment alternatives,
- Studies comparing different doses of botulinum toxin A,
- Non-comparative studies if either long-term follow-up (> 2 years), or if they included patients refractory to other medical treatments, or if these were the only studies available in the peer-review literature for a given indication,
- Systematic reviews,
- Safety studies,
- Treatment guidelines,
- Economic studies.

Studies where the results of adult and pediatric patients were reported as one group were excluded.

The reference lists of the publications identified were also searched in an attempt to find additional clinical studies that might have been missed during the literature search.

Additional literature searches were also performed in order to identify publications in specific areas that were deemed necessary. The keywords used in the additional searches were:

- “botulinum toxin ” AND “children” OR “pediatrics”
- “botulinum toxin ” AND (“children” OR “pediatrics”) AND “internal anal sphincter”
- “botulinum toxin ” AND “systemic effect”
- “botulinum toxin ” AND “anal incontinence”

APPENDIX 2 – DESIGN AND CHARACTERISTICS OF THE STUDIES IDENTIFIED

List of studies identified in the literature search

Study N	Year	Study Design and Characteristics	Comparators	Botulinum toxin A dose
<u>SYSTEMATIC REVIEWS</u>				
Bell et al. ³⁰	2000	Systematic Review	Various	Various
Nelson et al.	2001	Systematic Review	Various	Various
Zhao and Parisha et al. ¹⁶	2003	Systematic Review	Various	Various
Friedenberg et al. ⁶¹	2003	Systematic Review	Various	Various
Clinical Evidence	2004	Systematic review	Various	Various
Nelson ⁶²	2004	Systematic Review	Various	Various
AHFMR ³⁴	2004	Technology Assessment Report	Includes previous systematic reviews	Various
<u>COMPARATIVE STUDIES (OTHER ALTERNATIVES)</u>				
Maria et al. ³⁶ / N=30	1998	RCT, blinded	Placebo	20U
Brisinda et al. / N=50 ³⁷	1999	RCT, blinded	Nitroglycerin 0.2%	20U
Lysy et al. / N=30 ³⁹	2001	RCT, not blinded	Botulinum toxin A + ID	15U
Colak et al. / N=62 ⁴⁰	2002	RCT, not blinded	Topical lidocaine	25U
Siproudhis et al. ³⁸ / N=44	2003	RCT, blinded	Placebo	Dysport* 100U
Mentes et al. ⁴¹ / N=111	2003	RCT, blinded	LIS	20 – 30U
Giral et al. ⁴² / N=21	2004	Not randomized	LIS	20U
Iswariah et al. ⁴³ / N=38	2005	RCT, not blinded	LIS	?
Arroyo et al. ⁴⁹ / N=80	2005	RCT, not blinded	LIS	25U
Massoud et al. ⁴⁴ / N=50	2005	Not randomized, blinded evaluator	LIS	20U
<u>STUDIES COMPARING DIFFERENT DOSES OR INJECTION SITES OF BOTULINUM TOXIN A</u>				
Jost et al. ⁶³ / N=50	1999	Randomized	Compares different doses	20U, 40U
Maria et al. ¹ / N=57	1998	Not randomized	Compares different doses	15U, 20U
Brisinda et al. ²¹ / N=150	2002	Randomized	Compares different doses	20U, 30U
<u>OBSERVATIONAL STUDIES</u>				
Minguez et al. ⁶ / N=69	1999	Not randomized	-	10U, 15U, 21U
<u>OBSERVATIONAL LONG-TERM FOLLOW-UP STUDIES</u>				
Minguez et al. ⁸ / N=57	2002	Not comparative	-	10U, 15U, 21U
Godovenos et al. / N=45	2004	Not comparative	-	20U
Arroyo et al. ⁶⁴ / N=100	2005	Not comparative	-	25U
<u>OBSERVATIONAL STUDIES IN REFRACTORY PATIENTS</u>				
Jost et al. ⁶³ / N=50	1999	Not comparative	-	5U, 10U
Madalinski e t al. ⁵¹ / N=14	2001	Not comparative	-	15U (+ nitroglycerin)
Lindsey et al. ⁵⁰ / N=40	2003	Not comparative	-	
Lindsey et al. ⁴⁷ / N=30	2004	Not comparative	-	25U

AHFMR = Alberta Heritage Foundation for Medical Research / RCT=Randomized controlled trials / ID=isosorbide dinitrate / LIS=lateral internal sphincterotomy

*Botulinum toxin units in Dysport are not equivalent to the ones in Botox®.

APPENDIX 3 – RESULTS OF THE CHRONIC ANAL FISSURE STUDIES IN ADULTS IDENTIFIED

Comparative studies (vs. other treatment alternatives)

Study (year) Comparators (N)	Total dose / Comparators	Study population	Fissure healing rate Bot. A vs. comparator)	Relapse rates Bot. A vs. comparator)	Re-treatment requirement Bot. A vs. comparator)	Incontinence scores / rates Bot. A vs. comparator)
Maria ³⁶ (1998) N=30 RCT Blinded	Bot. A 20U (N=15) 2 bilateral injections (posterior?) Placebo (N=15)	Adults Symptomatic chronic anal fissure Posterior location	1 month 8 (53%) vs. 2 (13%) p=0.05 2 months 11 (73%) vs. 2 (13%) p=0.003 4 months 15 (100%), 4 patients received a 2 nd dose	2 months Bot. A 1/8 (13%) vs. 0/2 Mean f-up: 16.6m (both groups) No additional relapses (includes patients with 2 nd treatment)	2 months Bot. A group 4 (27%) treatment: Bot. 25U Control group 13 (87%) treatment: Bot. 20U (10), LIS (3)	0 vs. 1(6.7%) (transient flatus incontinence)
Siproudhis ³⁸ (2003) N=44 RCT Blinded	Dysport* 100U (N=22) Two bilateral injections (verge of the fissure) Placebo (N=22)	Adults Chronic anal fissure diagnosed by pathology examination (diagnosis > 1 month) Posterior location	1 month 5 (23%) vs. 5 (23%) 2 months 7 (32%) vs. 7 (32%) 3 months 5 (23%) vs. 11 (50%)	Within 3 months 3 (43%) vs. 2 (29%)	4-12 weeks 5 (23%) vs. 5 (23%) treatment: LIS	-
Brisinda ³⁷ (1999) N=50 RCT Blinded	Bot. A 20 U (N=25) Two bilateral injections in the anterior midline Nitroglycerin 0.2% (N=25)	Adults Chronic anal fissure (medical examination) Symptoms > 2 months Posterior location	1 month 22 (88%) vs. 10 (40%) p<0.001 2 months 24 (96%) vs. 15 (60%) p=0.005	Mean f-up 15-16 m No relapses (both groups)	Bot. A group 1 (4%) treatment: topical nitroglycerin Control group 10 (40%) treatment: Bot. A (9), LIS (1)	No episode of fecal incontinence was reported in either group
Lysy ³⁹ (2001) N=30 RCT Not Blinded	Bot. A 20U + ID 7.5mg/day for 3m (N=15) Bot. A 20U (N=15) – Two bilateral injections (into the IAS) ID treatment offered at 6 weeks non- responders	Refractory to topical nitrate treatment over 6 weeks Adults	6 weeks 10 (66%) vs. 3 (20%) p=0.025 12 weeks (after ID treatment given) 11 (73%) vs 10 (66%)	4-6 weeks 1 (10%) vs. 1 (33%)	3 months 3 (10%) treatment: Bot. A 25U re-treated by LIS (other treatment failures refused to be operated on due to lack of or mild symptoms)	-
Colak et al. ⁴⁰ (2002) N=62 Not blinded	Bot. A 50U (N=34) Two bilateral injections Topical lidocaine BID for at least 4 weeks (N=28), excludes 6 drop-outs	Adults Chronic anal fissure diagnoses clinically Symptoms > 2 m	2 months (epithelization) 24 (70.6%) vs. 6 (21.4%) p=0.006	-	-	-

ID=isosorbide dinitrate / SD=standard deviation / * Botulinum toxin A units in Dysport® are not equivalent to the units in Botox®.

Bot. A = botulinum toxin A

Comparative studies (vs. other treatment alternatives) (cont.)

Study (year) Comparators (N)	Total dose / Comparators	Study population	Fissure healing rate (Bot. A vs. comparator)	Relapse (Bot. A vs. comparator)	Re-treatment requirement (Bot. A vs. comparator)	Incontinence scores / rates (Bot. A vs. comparator)
Iswariah ⁴³ (2005) N=38 RCT Not blinded	Bot. A (N=17) LIS (N=21)	Adults Chronic idiopathic fissure Refractory to conservative treatment and GNT	6 weeks 7 (41%) vs. 18 (86%) p=0.004 26 weeks 7 (41%) vs. 19 (91%) p<0.001	Bot. A group 1 relapse after delivery at 18 months	6 months 9 (53%) vs. 2 (9.5%) 1 other patient in Bot. group needed treatment with nitrate	Baseline 0.65 vs. 0.19 26 weeks 0.18 vs. 0 NS within and between groups
Arroyo ⁴⁹ (2005) N=80 RCT Not blinded	Bot. A 25 U (N=40) One injection into each side of the IAS and one into the anterior verge LIS (N=40)	Adults Chronic anal fissure (determined by medical examination and at least 6 weeks of conservative treatment)	2 months 34 (85%) vs. 39 (87.5%) NS 6 months 28 (70%) vs. 38 (95%) p<0.05 1 year 18 (45%) vs. 37 (92.5%) p<0.001 2-3 years No recurrences	6 months 6 (18%) vs. 1 (2.6%) 1 year 10 (36%) vs. 1 (2.6%) 2-3 years 0	-	Liquid - flatus 2 months (NS) 2 (5%) vs. 3 (7.5%) 6 months (NS) 0 vs. 1 (2.5%) 1 year (NS) 0 vs. 2 (5%) 2-3 years (NS) No changes
Giral ⁴² (2004) N=21 Not randomized	Bot. A 20U (N=10) Both sides of the fissure LIS (N=11)	Adults Chronic anal fissure (medical examination) Symptoms > 2 months	2 months 7 (70%) vs. 9 (82%) NS	6-12 months No relapses (mean f-up 14 months)	Bot. A group: 2 (20%), 1 refused LIS group: 0 (patients with unhealed fissures at 2 months excluded from f-up)	-
Mentes ⁴¹ (2003) N=111 RCT Blinded	Bot. A dose adjusted to patient weight, 20U for 60kg (N=61) One injection in the centre of the IAS LIS (N=50)	Adults Symptomatic chronic anal fissure > 2 months Severe chronic fissure	1 month 38 (62%) vs. 41 (82%) p=0.023 2 months 45 (74%) vs. 49 (98%) p<0.0001 6 months (after 2 nd treatment) 53 (87%) vs. 47 (94%) NS 12 months 46 (75%) vs. 47 (94%) p=0.008	6 months 0 vs. 2 (41%) 12 months 7 (13%) vs. 0	2 months Bot. A: 10 (43%) – 6 refused treatment: Bot. A LIS: 0	0 vs. 8 (16%) p<0.001 mostly transient flatus incontinence in the LIS group
Massoud ⁴⁴ (2005) N=50 Not randomized (patient preference) Blinded evaluator	Bot. A 20U (N=25) Two bilateral injections in the anterior midline LIS (N=25)	Adults CAF (medical examination) Symptoms > 2 months Posterior location	2 months 16 (64%) vs. 25 (100%) p<0.01 6 months 22 (88%) vs. 25 (100%) p<0.05	-	-	2 months (p<0.01) transient flatus incontinence 2 (8%) vs. 11 (44%) No complications after 2 months

LIS=lateral internal sphincterotomy / NS=not statistically significant

Bot. A = botulinum toxin A

CAF refractory to topical nitrates

Study (year) (N)	Treatment (total dose)	Previous treatments	Study population	Fissure healing rate	Relapse rate	Re-treatment requirement	Incontinence scores / rates
Lindsey ⁵⁰ (2003) N=40	Bot. A (20U) Two injections on either side of the IAS but at some distance	GTN 0.2% for 8 weeks	Adults Persistent symptomatic CAF	17 (43%)	-	11 (27%) - surgery	7 (18%) – minor transient incontinence symptoms flatus: 5 liquids: 2 (prior manual dilation and ulcerative colitis)
Lindsey ⁴⁷ (2004) N=30 Fissurectomy + botulinum t. A (internal anal sphincter)	Bot. A 25U One injection into the IAS	19 (63%) – GTN 11 (37%) – Bot. A (2 patients had previously failed surgery)	Adults Persistent symptomatic CAF Anterior / Posterior	4 months 28 (93%)	-	0	2 (7%) – transient flatus incontinence (scores 6-8)
Madalinski ⁵¹ (2001) N=14	Bot A (50U) if unhealed Two injections into the external anal sphincter, on each side of the fissure edge, halfway between the anterior and posterior midlines	Nitroglycerin and Bot. A treatment	Adults CAF	8 (57%) or 9 (64%) including 1 patient with a 3 rd Bot. A injection	12 months 1 (13%)	1 (7%) – needed a 3 rd injection of Bot.A	-

CAF= chronic anal fissure / GTN=glyceryl trinitrate / Bot. A = botulinum toxin A / IAS=internal anal sphincter

Refractory CAF / different doses

Study (year) (N)	Treatment (total dose)	Study population	Fissure healing rate	Relapse rate	Re-treatment requirement	Incontinence scores / rates
Jost ⁶³ (1999) N=50 Not randomized	Group 1 - Bot. A 5U (n=20) Group 2 – Bot A. 10U (n=30) Two bilateral injections into the external anal sphincter	Adults CAF (check)	3 months Group 1 - 14 (70%) Group 2 – 19 (63.3%)	-	-	Group 1 – 0 Group 2 – Transient fecal incontinence – 2 (6.7%)

Bot. A = botulinum toxin A

Different botulinum toxin A doses

Study (year) (N)	Treatment (total dose)	Study population	Fissure healing rate	Relapse rate	Re-treatment requirement	Incontinence scores / rates
Jost ⁶⁵ (1999) N=50 Randomized	Dysport® formulation used* Group 1 – Bot. A 20U (n=25) Group 2 – Bot. A 40U (n=25) Two injections just lateral to the fissure margins	Adults CAF > 3 months	3 months Group 1 – 19 (76%) Group 2 – 20 (80%)	3 months Group 1 – 1 (4%) Group 2 – 2 (8%)		0 (transient incontinence)
Minguez ⁶ (1999) N=69 Not randomized	Group 1 – Bot. A 10U (n=23) Group 2 – Bot. A 15U (n=27) Group 3 – Bot A 21U (n=19) 1 injection into the Intrasphincteric groove in the direction of the IAS	Adults CAF (medical examination) Symptos > 2 months	2 months Group 1 – 16 (70%) Group 2 – 20 (74%) Group 3 – 13 (68%) NS 6 months (includes repeated treatment) Group 1 – 19 (83%) Group 2 – 21 (78%) Group 3 – 17 (90%) NS	6 months Group 1 – 9 (17%) Group 2 – 4 (15%) Group 3 – 1 (5.2%)	Group 1 – 12 (52%): reinjection 4 (17%): LIS Group 2 – 8 (30%): reinjection 5 (19%): LIS Group 3 – 7 (37%): reinjection 1 (5%): LIS NS	Mild transient flatus incontinence Group 1 – 5 (22%) Group 2 – 2 (7.4%) Episodes lasted < 3 days and occurred 2x/month in the 1 st 2 months. Soiling reported in 2 (3%) of these patients

* Botulinum toxin A units in Dysport® are not equivalent to the units in Botox® .

NS= not statistically significant

Repeated injections / Long-term studies

Study (year) (N)	Treatment (total dose)	Study population	Fissure healing rate	Fissure healing rate (2 nd injection)	Overall fissure healing rate	Relapse	Symptom / pain relief	Re-treatment after 2 nd injection	Incontinence scores / rates
Maria ¹ (1998) N=57 Not randomized	Group 1 – 15 U / +20 U if unhealed (N=23) Group 2 – 20 U / + 25 U if unhealed (N=34) Two injections into the IAS on either side of the fissure 2 nd injection at 2 months	Adults CAF (medical examination) Symptoms > 2 months Posterior location	2 months Group 1 – 10 (43.5%) Group 2 – 23 (67.6%)	2 months Group 1 - 3/5 (60%) - 8 refused treatment Group 2 – 7/7 (100%) – 4 refused treatment	4 months after 1 st injection Group 1 - 13/15 (87%) Group 2 – 30/30 (100%) (excludes patients who refused re-treatment)	Follow-up 20-25 months No relapses	-	-	Group 1 – Mild transient flatus incontinence – 1 /15 (6.7%) Group 2 - 0
Brisinda ²¹ (2002) N= 150 RCT / double blind	Group 1 – Bot. A 20 U (+30 U if persisting) (N=75) Group 2 – Bot. A 30 U (+50 U if persisting) (N=75) Two injections into the IAS 2 nd injection at 2 months	Adult CAF Symptomatic 2m Posterior location	1 month Group 1 - 55 (73%) Group 2 - 65 (87%) 2 months Group 1 - 67 (89%) Group 2 - 72 (96%)	2 months Group 1 – 8/8 (100%) Group 2 – 3/3 (100%)	4 months after 1 st injection Group 1 – 75 (100%) Group 2 – 75 (100%)	After 1 st injection Group 1 - 6 (8%) Group 2 - 0 (?) No additional relapse (f-up ~ 20m)	-	-	-
Godevenos ⁴⁵ (2004) N=45 Not comparative	Botulinum toxin A 20U (+25U or LIS) Two injections into the IAS (lateral and below the fissure)	Adults CAF Symptoms > 2 months Posterior location	2 months 8 (18%)	2 months 27/37 (73%)	4 months after 1 st injection 35/45 (78%) Patients preferred a 2 nd injection to LIS	Mean follow-up: 22 months 2/35 (5.7%)	-	LIS - 11 (24%) (10 patients who failed a second injection + 1 relapse) Bot. A – 1(2.2%) – relapse	Transient flatus incontinence + soiling of underwear – 2 (4.4%) (after 2 nd injection)

CAF= chronic anal fissure / GTN=glyceryl trinitrate / Bot. A = botulinum toxin A

Different site of injections / Repeated injections / Long-term studies

Study (year) (N)	Treatment (total dose)	Study population	Fissure healing rate	Fissure healing rate (2 nd injection)	Overall fissure healing rate	Relapse	Re-treatment after 2 nd injection	Incontinence scores / rates
Maria ⁹ (2000) N=50 RCT / blinded F-up: 18-20m	Group 1 – Bot. A 40U (+50U if persisting) (N=25) bilateral injections posterior midline Group 2 - Bot. A 40U (+50U if persisting), (N=25) bilateral injections anterior midline	Adults CAF (medical examination) Symptoms > 2m Posterior fissure	1 month Group 1 – 12 (48%) Group 2 – 22 (88%) p=0.0027 2 months Group 1 – 15 (60%) Group 2 – 22 (88%) p=0.025	2 months Group 1 – 5/6 (83%) 4 patients were treated with LIS Group 2 – 3/3 (100%)	Group 1 – 20 (85%) Group 2 – 25 (100%) p=0.025	F-up 18-20 months Groups 1 and 2: 0	Group 1 – 1 (4%) Group 2 - 0	None reported

Bot. A = botulinum toxin A

Long-term studies

Study (year) N / follow-up	Patient characteristics	Total dose	Relapse 1 year (cumulative)	Relapse 2 years (cumulative)	Relapse 3 years (cumulative)	Relapse 4 years (cumulative)	Treatment after relapse	Incontinence
Minguez ⁸ (2002) N=57 / 42 months Losses to f-up 4 (7%) not randomized	CAF Posterior and anterior location	Group 1- 2 sides of anal sphincter / 10 U total (N=19) Group 2- as above + below the fissure / 15 U total (N=21) Group 3 – 1 in each side of the fissure / 21 U total (N=17) Reinjection between 1 and 3 months after initial dose in patients with unhealed fissure	6/56 (10.7%)	18/54 (33.3%) (lower in posterior fissures)	21/53 (35.8%) (lower in posterior fissures)	22/53 (41.5%) 12/41 (29.3%) with posterior fissures	LIS – 12 patients Bot. – 2 patients Medical treatment – 8 patients	-
Arroyo ⁶⁴ (2005) N=100 / 2 years Losses to f-up 1 (1%) not randomized	Adult CAF Resistant to conservative treatment Posterior and anterior location	Bot. A 25 U Two injections into each side of the IAS and one into the anterior verge	52 (52%) (includes patients not healed) 2m – 12% 6m – 28%	53 (53%)	53 (53%)	-	-	2 months 6 (6%) – transient flatus - feces No reports /persistence after 2 months

CAF=chronic anal fissure

Bot. A = botulinum toxin A

APPENDIX 4 – STUDY RESULTS – BOTULINUM TOXIN A IN THE TREATMENT OF INTERNAL ANAL SPHINCTER

ACHALASIA IN CHILDREN

Study	Patient characteristics	Total Dose	Healing rate (bowel movements)	Repeated bot. A injections	Other treatments necessary	Complications
Messineo et al. ¹² (2001) N=4	Age: 3 months – 12 years	Dysport®, 12U/kg 2 nd injection: 24U/kg Divided into 4 injections, 1 in each IAS quadrant	3/3 (100%) 1 patient was later diagnosed with short aganglionic segment HD*	2 injections: 2 (67%) 3 injections: 1 (33%)	0 Response maintained with the last injection for at least 6-14 months (end of follow-up)	Not reported
Ciamarra et al. ¹¹ (2003) N=20	Age (mean): 5.8 years (5m – 17 yrs) IAS achalasia Severe constipation	Bot. A, 60 - 100U Divided into 4 injections, 1 in each IAS quadrant	18 (90%) within 72 hours Duration of response (mean): 14 wks (1 wk – 18 m) Patients were prescribed laxatives after treatment	2 injections: 6 (30%) duration of response (mean): 3.5m (2-6m) 3 injections: 2 (10%) response for almost 2 months	Relapses: 8 (40%): surgery 1 patient had to repeat the surgery due to failure with the 1 st one	Transient rectal pain for a few hours after the injection: 1 (5%) No other complications including incontinence
Langer ¹³ (2004) N=14 (subset of patients diagnosed with IAS achalasia as obstructive symptoms persisted after surgical treatment for HD)	Age (median): 4 years	Not reported	14 (100%) – IAS achalasia defined based on improvement in obstructive symptoms after treatment with Bot. A	2-5 injections: 9 (64%) duration of response: 2-12 months	1 (7%): ileostomy at the parents' request	Not reported
Minkes and Langer ¹⁰ (2000) N=18	Age (median): 4 years (1-13 years)	15-60U	12 (67%) 3 patients were later diagnosed with neuronal dysplasia	2-5 injections: 9 (50%)	-	Transient anal or abdominal pain for a few hours: several Mild transient (3 weeks) incontinence: 4 (22%) - 2 of these patients had undergone previous myectomy
Langer and Birnbaum ¹⁴ (1997) N=4	Age: 4-8 years	15U Divided into 4 injections, 1 in each IAS quadrant	1 injection 3 / 4 (75%) Duration of response 6-9 months	1 injection 1 (25%) Ongoing response 3 months afterwards	0 Patients doing well after bot. A: 2 (50%) Initial improvement with recurrence: 1 (25%) No improvement: 1 (25%)	Transient episodes of incontinence: 1 (25%) Another patient with previous intermittent incontinence had no change after the Bot. A injection

HD=Hirschsprung's disease / Bot. A = botulinum toxin A

APPENDIX 5 – OFF-LABEL MEDICATION USE IN CHILDREN

A high proportion of approved drugs in different countries lacks specific prescribing information for pediatric patients in their label⁵². For instance, it is estimated that three-quarters of the drugs available in the United States do not have information for pediatric patients in the label^{53 66}, although as another author pointed out, not all medications would be intended to be used in children⁶⁷.

Pediatric patients may differ from adults with regards to the pharmacodynamic and pharmacokinetic responses to drugs, and differences may even exist between different pediatric age groups⁵³. Therefore, specific information on dosing regimens and safety profile in pediatric patients is important. In the absence of this type of information, or even if specific pediatric formulations are unavailable, physicians are left with the dilemma of either not providing potentially beneficial treatment to children^{53 54}, or prescribing a drug based on information from adult studies and without specific knowledge on both therapeutic benefits and potential toxicity in children^{55 54}. The development of formulations that can be used in pediatrics is also important as younger children cannot swallow solid formulations and as some inactive components in the formula may be toxic to children⁶⁸. Unfortunately, medications available in formulations suitable for pediatric patients are infrequent^{69 52}.

Physicians are not legally forbidden from off-label prescriptions in the US⁶⁶ and UK/Europe⁷⁰. Although off-label prescriptions may be evidence-based⁵⁶, a higher likelihood of adverse drug reactions is expected^{71 72} due to lack of sufficient pharmacokinetic or safety information in children, or because the information has to be extrapolated from data in adults⁷⁰.

The use of drugs in pediatric patients without specific prescribing and safety label information for this group of patients is common⁵⁶. A review of the literature published in 2005 has shown that unlicensed or off-label drug prescription to pediatric patients represents 11% - 80% of the drug prescriptions in neonatal or pediatric hospital wards, and 11% - 37% of the prescriptions in the community in different countries in Europe, USA, Australia, and Israel⁵⁶. The children's ages varied between 1 day and 18 years⁵⁶. A literature review published earlier⁵³ and publications from Canada⁵⁷ other countries⁷³ arrived at similar conclusions.

Clinical research in pediatric patients poses additional difficulties when compared to adults, these difficulties arise from practical, technical and ethical considerations^{56 54}.

In the United States, efforts have been made in order to increase the number of studies in pediatric patients, such as extending the period of patent protection by six months for products that were tested in children^{56 54}. Europe and other countries are also starting to recognize the importance of such initiatives⁵⁶. The FDA and the International Conference on Harmonization (ICH), an organization that

regulates clinical research practices in North America, US, and Japan, may allow the extrapolation of efficacy information from adults for indications that have been studied and approved in adults, providing that both the course of the disease and the outcomes of therapy are similar between adults and children (21CFR314.55, ICH E11)^{74 75}. These studies must nevertheless be complemented with pharmacokinetic and safety studies in pediatrics^{74 75}.

According to the ICH, studies in children, unless in drugs for serious or life-threatening conditions or for predominantly pediatric indications, should not start before the late phases of research in adults, i.e., at least phases 2 or 3, or even before it is already approved in some instances, in order to ensure that efficacy has been shown and that safety has been established in adults (ICH E11, ICH M3)⁷⁵. This is part of the ICH guidance on clinical investigation of medicinal products in the pediatric population (ICH E11)^{74 75}, which has been adopted by Health Canada^{76 77}.

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