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The higher doses of botulinum toxin and the potentiate effect of its action after nitric oxide donors application for the treatment of chronic anal fissure

To the Editors:

We read with interest the article by Brisinda et al[1] confirming our previous observations on good effectiveness and tolerability of higher doses of botulinum toxin type A (BTX-A). We presented our data last year at the 17th World Congress of Neurology[2] and the year before at the National Congress of Polish Society of Gastroenterology.[3] We concluded that higher than 20 IU doses of Botox in the treatment of benign anal disorders are safe and do not produce serious adverse events. Mild incontinence, the major adverse reaction, was noticed in only 5% of sessions,[2] an incidence similar to Brisinda et al's 7%. Brisinda et al,[1] citing Lysy et al,[4] stated that the overall effect of BTX-A injections can be potentiated in patients with refractory chronic anal fissure by topical isosorbide dinitrate, an observation of ours as well[5] and that of Lysy et al.[6] In 2001, we presented[7] our observations that higher doses of BTX-A (Botox 50 and 100 IU) may modify the results of chronic anal fissure therapy, and that the monotherapy with high doses generally results in better improvement than a combination of lower doses of BTX-A and topical nitroglycerin.

In refractory cases, high doses repeated after short intervals (eg, 4 weeks) may lead to the problem of cumulative effect. The first lower dose, despite the produced denervation within the muscle, may not have reached a clinically evident improvement, and a secondary dose should be calculated as 25 IU plus 50 IU. There is also the possibility of a "saturation" or "ceiling" effect and the risk of an adverse reaction. Secondary nonresponsiveness due to formation of neutralizing antibodies may be another problem in patients with refractory fissure after repeated injections; the solution is to avoid "booster injections." The optimal dose of BTX-A is not established, and there is a relatively wide range of possible doses. In our opinion, there are no predictors of responsiveness in different patients, and one should start the therapy with lower (but not subclinical) doses and increase the dose if necessary at next sessions.[7]

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Reply

To the Editors:

We thank Drs Madalinski and Slawek for the interest in our article. Results of recent reports confirm that the management of chronic anal fissure has undergone extensive reevaluation with renewed emphasis during the past few years because of the tendency to treat the disease on an outpatient basis.

Botulinum neurotoxin can be used to treat anal fissure. The optimal dose of botulinum toxin has not been established, but the therapeutic efficacy of different doses of botulinum neurotoxin in chronic fissure have been reported recently.[1-4] A prospective comparison between 2 dose regimens (15 and 20 Botox units) showed negligible side effects and no complications; symptomatic improvement was achieved in both groups of patients, but the healing rate was higher in the group treated with 20 units.[3] The healing rate did not differ when the total dose and the number of injection sites were varied. 83% in patients treated with 10 units, 78% in those treated with 15 units, and 90% in the group treated with 21 units.[1] The injections were administered through the intersphincteric groove in the direction of the internal anal sphincter; however, 1 month after treatment, the mean squeeze pressure was reduced more than resting pressure, suggesting diffusion of the toxin to the external anal sphincter. Based on the theory that low anodermal perfusion at the base of the fissure contributes to the pathophysiology, additional infiltration of botulinum neurotoxin has been performed. In our experience, patients with a posterior chronic fissure have bet-

ter results, shown by a lowering of resting anal tone and early development of a healing scar when botulinum neurotoxin is injected anteriorly into the internal anal sphincter.[2,5-7] Anteriorly placed injections induce a greater decrease in resting pressure and improve clinical outcome. Fibrosis of the internal sphincter, which is more prominent in the site of the fissure than elsewhere in the smooth muscle, may reduce the compliance of the internal sphincter and limit diffusion of the botulinum neurotoxin. The myenteric plexus is located between the circular and longitudinal smooth muscle layers along the entire extent of the internal anal sphincter. A chronic reduction of perfusion in the posterior part of the anus may affect the myenteric nervous fibers at this location and make them less sensitive to the toxin.

In our study, the influence of different dosage regimens injected anteriorly in the internal anal sphincter on the clinical outcome of patients with a posterior chronic anal fissure was investigated.[2] Higher doses led to a higher success rate.[1] Resting anal pressures were lower than pretreatment values in both groups, and although maximum voluntary pressure was unchanged in patients treated with 20 units, it was lower than pretreatment value in patients treated with 30 units, probably related to a diffusion of botulinum neurotoxin to the external anal sphincter. Five of these patients reported mild incontinence of flatus that lasted 2 weeks after treatment and later disappeared. We believe that diffusion of the botulinum neurotoxin in the tissues is a dose-dependent phenomenon: histochemical staining of acetylcholinesterase suggested that higher doses produced a biologic effect throughout the entire muscle, whereas smaller doses produced a gradient down the length of the muscle studied. The combined treatment of botulinum toxin with local application of nitrate appears to be more effective than toxin alone.[8]

We do not believe that higher doses (50 to 100 units) are necessary, as we were able to produce an adequate effect using lower doses (30 units). With increasing doses of botulinum neurotoxin, the degree of denervation at the injection site increases. Furthermore, higher doses will increase costs and increase the incidence of undesired effects.

Complications of the treatment have been reported.[2,9] Reported side effects, other than mild and transitory incontinence for flatus or feces, involve perianal thrombosis and hematoma.[7,9] However, the development of the potential complications does not seem to influence the overall efficacy of the treatment. Minguez and coworkers[10] analyzed the long-term outcome (42 months) of 57 patients in whom an anal fissure had healed after botulinum neurotoxin injections. The late recurrence rate of chronic anal fissure was high when the effect of the toxin disappeared. Fissure recurrence was noted in 22 patients (42%); the highest risk of recurrence occurred with anterior location of the fissure, prolonged illness, and the need for reinjection and high doses to achieve healing.[10]

In conclusion, botulinum neurotoxin is a safe treatment for patients with anal fissure. It is also more efficacious than nitrate therapy and is not related to the patient's willingness to complete treatment. In the patients with a posterior chronic fissure, better results are achieved when the toxin is injected anteriorly into the internal anal sphincter. We propose that botulinum neurotoxin treatment should be considered as the first-line therapy in patients with chronic anal fissure.

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