Comparison of Efficacy and Immunogenicity of Original vs. Current BOTOX in Cervical Dystonia

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ABSTRACT

Background: With long-term use and expanding indications for clinical use of botulinum toxin (BTX) there is a growing concern about the possibility of immunoresistance due to development of blocking antibodies. The available evidence of immunoresistance treated with repeated BTX injections, however, is not known. We postulate that as a result of lower protein load, the current BOTOX (25 ng of neurotoxin/100 units) is less antigenic than the original preparation (25 ng of neurotoxin/100 units). We examine the hypothesis that current BOTOX with a high protein content is associated with a higher frequency of antigenicity than the current preparation that has a low protein content. We conclude that the former preparation decreased the risk of antibody formation by a factor of 6. Conclusion: In contrast to the original BOTOX, we have found no significant difference in efficacy and adverse effects between the two preparations. Most important, many patients who had received BTX and BOTOX simultaneously (original BOTOX every 6 or 9 months) were significantly more frequent in patients treated with the original BOTOX (p < 0.004). Some studies have suggested that up to 17% of patients treated repeated for cervical dystonia with BOTOX have antibodies has been reduced by a factor of 6.

RESULTS

The two preparations, the original and the current BOTOX, had similar efficacy (e.g. latency, peak effect, duration of response) [Fig. 1]. Although the total number of visits associated with adverse events were slightly higher with this current BOTOX than with the original BOTOX, there was no difference in the frequency of types of side effects such as dysphagia, local pain, neck weakness, dry mouth or malaise between the two preparations [Fig. 2]. Blocking antibodies, as determined by positive MPA, were significantly more frequent in patients treated with the original BOTOX as compared to those treated with only current BOTOX (4/42 or 9.5% of patients treated only with the original BOTOX, p < 0.004; odds ratio = 6.7; 95% CI odds ratio = 0.6 – 58.8). Thus, treatment with original BOTOX alone tended to increase the risk of antibody formation by a factor of 6 (Fig. 4).

INTRODUCTION

Focal chemodenervation produced by injection of botulinum toxin (BTX) represents an important advance in the treatment of a variety of movement as well as other neuromuscular and non-neurological disorders. In 1989, BTX type A (BOTOX) was approved by the Food and Drug Administration for the treatment of strabismus in ipsilateral ocular palsies, and in 2000 for the treatment of cervical dystonia. The use of BTX, however, has rapidly expanded beyond these approved disorders and now includes a variety of ophthalmologic, neurologic, and cosmetic indications. With the growing and chronic use of BTX there is the possibility of immunoresistance due to development of blocking antibodies. Some studies have suggested that up to 17% of patients treated repeated for cervical dystonia with BOTOX have developed blocking antibodies. This is the first study that has longitudinally examined the effects of original versus current BOTOX. The primary aim of the study was to test the hypothesis that the high protein load associated with the current BOTOX treatment may be associated with a higher risk of immunoresistance due to blocking antibodies than low protein load treatment (5 ng of neurotoxin/100 units in current BOTOX).

METHODS

Over 2,900 patients have been treated with BOTOX in the movement disorder clinic at Baylor College of Medicine since 1983. Between 01-01-1995 and 01-31-2001 we treated and prospectively followed 119 patients with cervical dystonia. Of these patients, 119 were treated initially with the original BOTOX (n = 42) between 01-01-1995 and 12-31-1997 and 88 subsequently continued their treatment with the current BOTOX. 119 patients were treated with the original BOTOX. All patients included in the study were followed for at least one year by the movement disorder specialists (JJ) who assessed the patients at each visit, and rated their response according to previously published scale. The treating physician determined the dose and site of injection based on clinical assessment of the patient’s dystonia and associated abnormal posture and movement, complaints of muscle stiffness and pain, predominant muscle involvement determined by examination including palpation, head displacement, and previously established injection pattern. All clinical information was recorded in the BTX database and included: patient identification number, date of initial visit, date of last follow-up visit, associated diagnoses, sites of injection, dose in muscle units (U) of BTX at each site, latency of response (days), peak effect (0 – 4 scale where 0 = no effect and 4 = marked improvement in severity and function), total duration of maximum effect (weeks), total duration of response (weeks), and complications. We used a mouse protection assay (MPA), which has been previously described to correlate well with the presence of blocking antibody. All patients who published negative mouse protection assay (MPA), to assess the likelihood of developing immunoresistance to BTX for those patients who received only original BOTOX. Only current BOTOX contained (p = 0.88, odds ratio = 6.7; 95% CI odds ratio = 0.6 – 58.8). Thus, treatment with original BOTOX alone tended to increase the risk of antibody formation by a factor of 6 (Fig. 4).

DISCUSSION

This is the first study that has longitudinally examined the effects of original versus current BOTOX. The primary aim of the study was to test the hypothesis that the high protein load associated with the current BOTOX treatment may be associated with a higher risk of immunoresistance due to blocking antibodies than low protein load treatment (5 ng of neurotoxin/100 units in current BOTOX).

To the extent that MPA measures blocking antibodies (“gold standard”), we found that 4/12 (33.3%) of patients treated only with the current BOTOX developed evidence of immunoresistance (n = 42). The observation that 4/5 of patients who developed antibodies were treated only with the original BOTOX, and the one patient who was treated with both preparations received lack of his treatments with original BOTOX provides strong evidence that the original BOTOX was markedly more antigenic than the current BOTOX. Although the result may not be definitive, the study shows that the risk of immunoresistance in the current BOTOX is lower than in the original BOTOX. This finding, however, must be interpreted cautiously because this was not a controlled study and we did not systematically test all patients for BTX antibodies. Nevertheless, we believe that this finding has important therapeutic implications since in 1998 we have observed only three patients who satisfy the clinical criteria for secondary unresponsiveness as indicated by poor or no response to BTX (peak effect of 0 or 1) on two subsequent treatment visits, on whom had been administered neurotoxin (BOTOX) and not current positive MPA. We believe that the lack of immunoresistance observed with current BOTOX is particularly noteworthy in the group of patients treated only with the original BOTOX was a higher risk for developing antibodies since the patients received a higher mean dose per visit, were treated for a longer period of time and had a higher number of treatment visits as compared to the group treated only with the original BOTOX. This suggests that the difference in the occurrence of immunoresistance is due to the fact that the current BOTOX contains 95% less neurotoxic complex protein than the original BOTOX, and, therefore, is likely to be less antigenic.

Although there are no differences in the frequency of individual adverse effects between the original and current BOTOX, the slightly higher occurrence of overall side effects could be attributed to a significantly higher mean dose of current BOTOX per treatment visit. This higher dose could also possibly account for the observed longer duration of response with the current BOTOX.

In this long-term follow-up study, there was no significant difference in efficacy and adverse effects between the two preparations. Most important, many patients who had received BTX and BOTOX simultaneously (original BOTOX every 6 or 9 months) were significantly more frequent in patients treated with the original BOTOX (p < 0.004). Some studies have suggested that up to 17% of patients treated repeated for cervical dystonia with BOTOX have antibodies has been reduced by a factor of 6.

This study provides evidence that protein loading is an important risk factor for the development of immunoresistance.