July 2006

Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: A multicentre, double-blind, randomized, placebo-controlled, parallel-group study

Stephen D. Silberstein
Thomas Jefferson University, Stephen.Silberstein@jefferson.edu

H. Göbel
University of Kiel, Germany

R. Jensen
University of Copenhagen, Denmark

A. H. Elkind
Elkind Headache Center, Mount Vernon, NY

R. DeGryse
Allergan, Inc., Irvine, CA

See next page for additional authors

Authors
Stephen D. Silberstein, H. Göbel, R. Jensen, A. H. Elkind, R. DeGryse, J. M.C.M. Walcott, and C. Turkel

Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study

SD Silberstein[1], H Göbel[2], R Jensen[3], AH Elkind[4], R DeGryse[5], JMCM Walcott[5] & C Turkel[5]

[1]Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA, [2]Kiel Pain Clinic, University of Kiel, Kiel, Germany, [3]Danish Headache Center, Department of Neurology, University of Copenhagen, Copenhagen, Denmark, [4]Elkind Headache Center, Mount Vernon, NY and [5]Allergan, Inc., Irvine, CA, USA

Stephen D. Silberstein MD, FACP
Professor of Neurology and Director of the Jefferson Headache Center
Thomas Jefferson University Hospital
111 South 11th Street, Suite 8130
Philadelphia, PA 19107, USA
Tel. + 1 21 5955 2030
fax + 1 21 5955 1960
e-mail stephen.silberstein@jefferson.edu

Abstract

We studied the safety and efficacy of 0 U, 50 U, 100 U, 150 U (five sites), 86 Usub and 100 Usub (three sites) botulinum toxin type A (BoNTA; BOTOX®; Allergan, Inc., Irvine, CA, USA) for the prophylaxis of chronic tension-type headache (CTTH). Three hundred patients (62.3% female; mean age 42.6 years) enrolled. For the primary endpoint, the mean change from baseline in the number of TTH-free days per month, there was no statistically significant difference between placebo and four BoNTA groups, but a significant difference favouring placebo vs. BoNTA 150 was observed (4.5 vs. 2.8 tension headache-free days/month; $P = 0.007$). All treatment groups improved at day 60. Although efficacy was not demonstrated for the primary endpoint, at day 90, more patients in three BoNTA groups had ≥50% decrease in tension headache days than did placebo ($P \leq 0.024$). Most treatment-related adverse events were mild or moderate, and transient. BoNTA was safe and well-tolerated in the study.

Introduction

Tension-type headache (TTH) is one of the primary headache disorders—having an overall annual prevalence as high as 38%—with 2% of patients affected on a daily or almost daily basis (1). Sensitization of afferents within peripheral tissues (e.g. muscles) by local nociceptive mediators can give rise to increased nociceptive afferent fibre activity, leading to central sensitization, and may be a pathogenic marker in chronic tension-type headache (CTTH) (2–8). The exact role of peripheral and central sensitization in CTTH is still unclear (8–10).

At motor neurons, botulinum toxin type A (BoNTA; BOTOX®; Allergan, Inc., Irvine, CA, USA) inhibits exocytosis of acetylcholine from presynaptic nerve endings through proteolytic cleavage of a specific

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

target protein, SNAP-25 (synaptosomal protein) with a molecular weight of 25 kDa), that is essential for vesicle fusion with neuronal membranes leading to decreased muscle contractions (11). In preclinical studies, BoNTA has also been shown to block the release of nociceptive mediators such as substance P, glutamate, and calcitonin gene-related peptide (CGRP) at non-cholinergic, non-motor neurons via SNAP-25 cleavage (11–14). Cui and colleagues have demonstrated that local peripheral injection of BoNTA significantly reduces formalin-induced nociceptive behaviour in rats in a dose-related manner with an absence of obvious muscle weakness (13). A small, open-label preliminary study of the analgesic effects of BoNTA in humans found that while BoNTA did inhibit peripheral neuropeptide release from nociceptive nerve fibres, its analgesic effects were reported by the authors to be limited (15). These results may have been influenced by the model used in this study since an electrical stimulus was applied directly to stimulate the pain nerve. The BoNTA pretreatment was only able to inhibit the peripheral nociceptive peptide release (measured as neurogenic flare) in the volunteers. Since BoNTA does not cross the blood–brain barrier and is not transported centrally by the nerve, there was no effect of BoNTA on hyperalgesia or allodynia elicited by electrical stimulation. Therefore, BoNTA would not have the ability to block electrically induced pain. In the preclinical studies, BoNTA was effective in situations where sufficient peripheral sensitization (i.e. formalin or capsaicin) could be achieved, so BoNTA may inhibit the peripheral release of nociceptive signals and thus reduce sensory input into the central nervous system (CNS) (12). Further clinical studies of this effect in humans are needed to confirm the results of preclinical studies.

BoNTA modification of pain pathways may potentially inhibit the pain associated with headache disorders. The results of double-blind, placebo-controlled trials, open-label trials and retrospective chart reviews show mixed evidence of efficacy that focal injections of BoNTA significantly reduce the frequency, severity and disability associated with migraine, TTH and other types of headaches (16–30). The varying results may be due to patient selection, the number of BoNTA treatments administered, the injection protocol employed or the dosage range used.

The purpose of this trial was to evaluate the safety and efficacy of a single BoNTA treatment in five active treatment groups compared with placebo for the prophylactic treatment of CTTH.

Methods

Objective

The objective of this study was to examine the safety and efficacy of a single treatment of BoNTA for the prophylactic treatment of CTTH.

Study design

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter study conducted from 4 January 2000 to 28 February 2001. There were 22 North American study centers (one in Canada and 21 in the USA) and seven European study centers (three in Germany, two in the UK, one in Belgium and one in Denmark). Prior to enrolment and subsequent randomization to BoNTA or placebo, patients entered a 30-day baseline period during which they were screened for eligibility. During the baseline

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

period patients were required to record data capturing specified characteristics of their headache episodes and headache medication use using a paper diary. All eligible subjects who continued to meet eligibility criteria at the end of a 30-day screening baseline period were randomized to one of six treatment groups.

Participant characteristics

Eligible participants were men or women aged 18– 65 years with a history of CTTH as defined by International Headache Society criteria (31) (Key inclusion and exclusion criteria are outlined in Table 1).

The investigator could discontinue participants prematurely from the study for adverse events, protocol violations, lack of efficacy, or administrative reasons (e.g. inability to continue, lost to follow-up).

Patients taking prophylactic headache medications were required to have been on a stable dose for at least 3 months prior to enrolment and had to maintain a stable dose throughout the study. The use of any concurrent prescription or over-the-counter medication and the reason for taking it were recorded.

Intervention and protocol

Each vial of BOTOX® (Allergan, Inc.) was stored in a freezer between −20°C and −5°C before use and contained 100 U of botulinum toxin type A, 0.5 mg albumin (human) and 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. BOTOX was reconstituted with 3 ml of the diluent, 0.9% sterile saline (without preservative). Reconstituted solutions were stored in a refrigerator until use (within 4 h). To maintain the blinding of the study and the investigator (injector) and other staff involved in assessing or reporting on the subject, an individual not involved with these activities was identified at each study center to perform the dilutions and draw up the study medication.

At the injection visit (day 0), patients received a single treatment of 10 intramuscular injections of BOTOX, placebo or both in five muscle groups (Fig. 1, Table 2). Depending on the muscle area, 0.20–0.80 ml (3.3–40 U) was injected. Three treatment groups received BOTOX (50 U, 100 U or 150 U) distributed in all five muscle groups; two treatment groups received BOTOX (either 86 U or 100 U) distributed in three muscle groups (and placebo in two muscle groups); and one group received placebo in all five muscle groups (Table 2). Total BOTOX doses were 50 U, 86 Usub, 100 U, 100 Usub and 150 U ('sub' identifies the groups in which only three muscle groups received active treatment); the number of BOTOX U per muscle for each treatment group was fixed. Post-injection follow-up evaluations were scheduled on days 30, 60, 90 and 120.

At each study visit, participants were given a week paper diary and instructed to complete it on a daily basis throughout the study. Patients recorded the occurrence, severity, maximum severity and location of TTH; associated headache symptoms (nausea, vomiting, increased sensitivity to light and/or noise, and worsening head pain with physical activity); percentage of each day with headache, as calculated from the hours awake with headache as a proportion of those hours; headache medications with dose and time of dose; and the occurrence of non-TTH. Patients were administered the Headache Pain Specific Quality of

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

Life Questionnaire, the Tension-Type Headache Impact Questionnaire and the SF-36 Health Survey to evaluate the impact of treatment. The diaries were collected at the scheduled monthly study visits.

This study was conducted in compliance with institutional review board regulations in each participating country, the Declaration of Helsinki, informed consent regulations of each participating country, the recommendations of the International Headache Society for studies in the prophylactic treatment of CTTH, and the International Conference on Harmonization guideline for Good Clinical Practice.

Outcome measures

Efficacy

The primary efficacy variable was the mean change from baseline in the number of TTH-free days per month for the 30 days prior to day 60 (postinjection) recorded by the patient in the paper diary. The clinical criterion for effectiveness was a 3 days/month difference between treatment groups in the mean change from baseline for the number of TTH-free days.

Secondary efficacy measures included the percentage of patients reporting at least a 50% decrease in TTH days; percentage of the day with headache, as calculated from the hours awake with headache as a proportion of the hours awake; average of headache severity, as recorded in the patient diary; and concurrent headache medication usage.

Information from measures collected during office visits included the subject's response to treatment [rated on a 9-point Global Assessment Scale from −4 (very marked worsening) to +4 (clearance of signs and symptoms)]; the subject's rating of worst, least and usual TTH-associated pain as measured on an 11-point scale (0 = no pain to 10 = pain as bad as can be); and the subject's score on a Beck Depression Inventory. Other efficacy measures documented in the patient's diary included days of current acute headache medication usage per 30-day interval, average maximal headache severity per 30-day interval, presence/absence of associated headache symptoms and non-TTH days per 30-day interval.

Safety

Adverse events. All reported adverse events were recorded, with information regarding the date of onset, resolution date (if applicable), severity (mild, moderate or severe), duration, frequency, relationship to study treatment, action taken regarding study treatment, treatment required (if any), and outcome included. The relationship between an adverse event and study treatment was assessed by the investigator as none, possible, probable or definite. A serious adverse event was defined as one that was fatal, life threatening, or permanently disabling, or that resulted in hospitalization or prolongation of existing hospitalization.

Laboratory variables. Blood specimens were collected at the first screening visit and the last scheduled visit (day 120 or study exit). Standard blood chemistry, electrolyte panel and haematology analyses were performed and reported.

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

Physical examination and vital signs. A physical examination was performed, and height, weight, blood pressure, pulse rate and body temperature were measured at the first screening visit and the last scheduled visit (day 120 or study exit). At all other study visits, pulse rate and blood pressure were measured.

Statistical analyses

Analyses were performed on data from the intent-to-treat population, which included all randomized subjects. Subjects were analysed as randomized, regardless of which treatment they actually received, for all except safety variables. For safety variables, subjects were analysed as actually treated. All tests were two-sided and utilized a type I error of $\alpha = 0.05$ to determine statistical significance, except that treatment-by-subgroup interactions were examined at the 0.10 level.
A key variable (mean change from baseline in TTH-free days) and visit (day 60) were identified. For the key variable and visit, protection against multiple comparison errors was accomplished by examining *P*-values for significance between any of the five BoNTA groups and placebo only if the calculated *P*-value was $<0.05/5 = 0.01$ (Bonferroni method). Other variables, visits and pairwise treatment comparisons were considered supportive.

Data were summarized with descriptive statistics and/or response frequencies, including sample size, mean, standard deviation, median, minimum and maximum. For variables with ordered response categories and variables with a continuous response range, simultaneous comparisons among all treatments were done with the Kruskal–Wallis test (via analysis of variance of ranks). Comparisons between pairs of treatment groups were done with the Wilcoxon rank sum tests, even if the among-treatment results were not significant. For the continuous variables, if the responses appeared to be normally distributed (via the Shapiro–Wilk statistic), one-way analysis of variance methods were considered to improve the efficiency of the inferential test. If there were significant baseline differences between the treatments in a primary or secondary efficacy variable, a baseline covariate was included in an analysis of covariance of the variable. For binomial data, comparisons between treatment groups were done with χ^2 tests, 2×6 among-group comparisons, and 2×2 pairwise treatment comparisons. If the expected value of any cell in a table was <5, the affected distribution was tested with Fisher's exact test.

Results

Patient demographics

The screening included 429 patients, 300 of whom [187/300 (62.3%) female; mean age 42.6 years (range 18–65 years)] were eligible for participation and enrolled. There were no significant demographic differences between the treatment groups. Forty-nine patients were randomized to BoNTA 150 U, 51 patients to BoNTA 100 U, 52 patients to BoNTA 100 Usub, 51 patients to BoNTA 86 Usub, 47 patients to BoNTA 50 U and 50 patients to placebo (Table 3). A total of 279/300 patients (93%) completed the study. The most common reason for discontinuation was loss to follow-up [13/300 (4.3%)]. Seven BoNTA patients discontinued the trial because of lack of efficacy. Of these patients, three were in the 150 U

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

treatment group, two were in the 100 Usub treatment group, one was in the 86 Usub treatment group and one was in the 50 U treatment group. One patient in the 100 Usub treatment group discontinued participation for other (personal) reasons. No patient discontinued the study due to adverse events.

Headache history and medication use

All patients had a diagnosis of CTTH. The mean time since onset of CTTH was 14.7 years (range 0– 54 years) and the mean age at onset was 28.3 years (range 1–61 years). There were no significant differences between the treatment groups in the CTTH history. Patients recorded a mean frequency of 23.0, 23.9, 23.8, 22.8, 25.5, and 25.2 TTH days per month in the BoNTA 150 U, 100 U, 100 Usub, 86 Usub, 50 U and placebo groups, respectively (Table 3). In addition to having CTTH, 95/300 (31.6%) patients reported having at least one migraine per month. Patients experienced a mean of 0.7 migraines per month with a mean duration of 1.2 days per month. A total of 13/300 enrolled patients had less than 15 headache days per month at baseline (seven in the 150 U group; two each in the 100 U, 100 Usub and 86 Usub groups) and should not have been enrolled as per the protocol criteria. Overall, patients reported a mean headache duration of 12.4 h per day. Most patients (87.9%) reported taking analgesic and/or prophylactic medications including aspirin, ibuprofen, acetaminophen, acetaminophen plus codeine, non-steroidal anti-inflammatory drugs, β-blockers, antidepressants and anticonvulsants for TTH pain. A total of 98 patients (32.7%) reported taking concomitant prophylactic headache medications. Patients in the BoNTA 150 U, 100 U, 100 Usub, 86 Usub, 50 U and placebo groups used acute headache pain medication for a mean of 8.7, 10.3, 9.8, 11.9, 8.8 and 8.5 days, respectively, during the 30-day baseline period. There were no statistically significant differences between the treatment groups in their use of acute headache pain medication at baseline. There were 111/300 patients (37%) who used headache pain medication for 16 or more days during the baseline period. At baseline, most patients [195/300 (65%)] did not report associated symptoms with their headaches; however, the rest [105/300 (35%)] reported one or more associated symptoms with some of their headaches. These symptoms included sensitivity to light [68/300 (22.7%)], sensitivity to sound [49/300 (16.3%)], nausea [15/300 (5%)] and vomiting [2/300 (0.7%)]. Pain associated with TTH was most often reported as bilateral [182/ 300 (60.7%)] and localized to either the front of the head [202/300 (67.3%)] or the back of the head [161/ 300 (53.7%)]. According to the investigator assessment, patients in the 100 U group (43.1%) had a significantly higher incidence of pain in the cervical region compared with patients in the other groups (14.0–29.8%; $P = 0.015$).

Efficacy

Primary variable: mean change from baseline in the number of TTH-free days

At baseline, two of the five BoNTA treatment groups, BoNTA 100 U (6.5 days; $P = 0.001$) and 86 Usub (5.3 days; $P = 0.008$), had a significantly higher mean frequency of headache-free days (3.3 days) than the placebo group (Table 4). For the primary endpoint, there was no difference between placebo and four of the BoNTA groups (50 U, 100 U, 86 Usub and 100 Usub) but a statistically significant difference favoring placebo compared with the BoNTA 150 U group was observed (4.5 vs. 2.8 tension headache-free days per month) (Fig. 2). All groups demonstrated improvement at the day 60 primary endpoint.

Secondary variables

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

Reduction of ≥50% of TTH days. No significant differences were found in the number of patients reporting a decrease of 50% or more headache days at day 60, the primary endpoint. However, at day 90, significantly larger percentages of patients in the BoNTA 100 U group [15/47 (31.9%); $P = 0.017$], the 100 Usub group [15/49 (30.6%); $P = 0.024$] and the BoNTA 86 Usub group [15/47 (31.9%); $P = 0.017$] reported a 50% decrease in TTH days compared with the placebo group [6/50 (12.0%)] (Fig. 3).

Percentage of the day with headache. There were no significant differences at day 60 in the percentage of the day with headache, calculated from hours awake and hours awake with headache as reported in the patient diary. The mean decrease from baseline was -6.8%, -3.0%, -6.5%, -4.0%, -5.0% and -4.7% for BoNTA 150 U, 100 U, 100 Usub, 86 Usub, 50 U and placebo groups, respectively.

Average usual headache severity. There were no significant differences in the average usual headache severity at any time point. At day 60, the mean decrease was -0.1, -0.1, -0.2, -0.2, -0.2, and -0.1 for BoNTA 150 U, 100 U, 100 Usub, 86 Usub, 50 U and placebo groups, respectively.

Other efficacy measures

At day 60, fewer patients in the BoNTA 150 U group reported a decrease of three or more TTH days compared with the BoNTA 86 Usub group [13/48 (27.1%) vs. 27/47 (57.4%); $P = 0.003$]. There were no significant differences between placebo and any BoNTA group in the other efficacy measures (subject's rating of headache pain, treatment assessment, global assessment, Beck Depression Inventory, days of concurrent headache medication usage, average maximal headache severity, associated headache symptoms and non-TTHs) at day 60 or any other follow-up visit. A decrease in phonophobia, photophobia (except BoNTA 50 U) and headache symptoms worsening with physical activity was noted for all groups. There were no significant differences between the groups in the Headache Pain Specific Quality of Life Questionnaire, the Tension-Type Headache Impact Questionnaire, and the SF-36 Health Survey (at day 60). There were no notable findings between the groups in the subgroup efficacy analyses.

Safety

Adverse events were reported for 61.7% (29/47) of BoNTA 150 U patients, 64.7% (33/51) of BoNTA 100 U, 63.5% (33/52) of 100 Usub, 54.9% (28/51) of BoNTA 86 U, 51.0% (25/49) of BoNTA 50 U and 52.0% (26/50) of placebo patients. The most frequently reported adverse events across all treatment groups were respiratory infection [10.7% (32/300)], neck pain [8.0% (24/300)] and muscular weakness [7.7% (23/300)]. Among 300 patients there were 41 adverse events reported as severe. Severe adverse events included seven, 11, five, four, seven and seven for the BoNTA 150 U, 100 U, 100 USub, 86 USub, 50 U and placebo groups, respectively.

Treatment-related adverse events were reported for 32.0% (96/300) of patients overall. There were no differences among the groups in the incidence of subjects reporting treatment-related adverse events (Table 5). The most frequently reported treatment-related adverse events were muscular weakness [20/300 (6.7%)] and neck pain [16/300 (5.3%)]. There were no significant differences between any BoNTA

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

group and placebo in the incidence of treatment-related adverse events except the overall incidence of the 100 U group [23/51 (45.1%) vs. 11/50 (22.0%); $P = 0.014$]. A consistent dose-response for these treatment-related adverse events was not apparent, but the BoNTA 100 U group did report the greatest incidence of muscular weakness, neck rigidity, neck pain, headache and pain. Most treatment-related adverse events were either mild or moderate in severity and transient in nature, and most patients had recovered without sequelae at the time that the study ended.

There was no significant difference in the analysis of all BoNTA groups combined vs. placebo in the incidence of all adverse events or treatment-related adverse events. There were no clinically relevant differences among the groups in changes from screening to study exit for laboratory variables or vital signs. No subject died during the study. The five serious adverse events were worsening of headache, re-dislocation of left shoulder, chest pain, palpitation (100 U group) and emotional lability (50 U). None of the serious adverse events was considered treatment related.

Discussion

The results of this clinical study suggest that BoNTA is a safe, well-tolerated intervention in patients with CTTH. No discontinuations due to adverse events occurred, nor were any treatment-related serious adverse events reported. The BoNTA patients, especially those treated with 100 U (but not those treated with 150 U) did have a greater percentage of transient, treatment-related, muscular weakness and neck pain, which are known to be associated with BoNTA injections.

As a result of this intervention most patients evaluated in this study had more TTH-free days. The efficacy of BoNTA in the prophylactic treatment of CTTH compared with a placebo treatment was not confirmed in this study at day 60, the primary efficacy endpoint. However, at day 90 there was a significant effect of BoNTA treatment on the percentage of patients reporting a 50% decrease in headache days for several BoNTA dose groups, suggesting that perhaps a longer primary endpoint than 60 days may be warranted. The results of secondary and other efficacy measures did not show that BoNTA was significantly more effective than placebo, although improvement in most secondary and other efficacy measures was observed. The ability to differentiate BoNTA from placebo may have been confounded due to the uneven randomization (32) or due to the fact that patients were allowed to take acute headache pain medication as needed to treat their headaches, thereby potentially aborting or diminishing their headache characteristics.

BoNTA has demonstrated antinociceptive activity in patients with cervical dystonia, spasticity and chronic musculoskeletal pain disorders in clinical trials (33–37), suggesting that BoNTA may have analgesic effects. BoNTA inhibition of the release of nociceptive molecules has been demonstrated in several preclinical studies (12–14) and BoNTA administration has been shown to attenuate pain behaviour in a rat model (13). These effects have yet to be demonstrated in humans (15). BoNTA efficacy as prophylactic treatment of TTH has been assessed in several small controlled trials, but the evidence of a treatment effect has thus far been mixed or lacking (17, 23, 25, 27, 30, 38). The reasons for the lack of efficacy of BoNTA treatment of CTTH in this trial may be related to the injection protocol, the BoNTA dosage range, the patient population or ineffectiveness in this patient population.

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

Injection protocol

The injection protocol of this trial followed a fixed-site approach for TTH. Blumenfeld and colleagues (39) recommend a follow-the-pain approach for BoNTA treatment of TTH injecting the frontalis (2.5 U each, five sites on each side), temporalis (2.5 U each, four sites on each side), occipitalis (2.5–5 U on each side), trapezius (7.5–15 U on each side), semispinalis capitis (7.5–15 U on each side) and/or splenius capitis muscles, as deemed appropriate (21).

The current study protocol did not include occipitalis injections and it did not use as many sites for BoNTA in various muscle groups (21, 26) (Table 2). With 60–75% of patients describing frontal head pain and 50–60% of patients describing pain in the back of the head, the addition of more frontalis injection sites, the addition of occipital injection sites and an increase in the total BoNTA U injected in these sites might also have had an impact on BoNTA efficacy. Only 147/300 patients (the BoNTA 50, 100 and 150 U groups) received BoNTA injections into all five muscle sites.

BoNTA dosage range

Recent large, randomized, placebo-controlled BoNTA studies in patients with chronic headache disorders suggest that repeated BoNTA treatment between 105 U and 260 U, a higher dose range than those used in this study, may lead to better results (28, 29), although there are no such indications in the present study as fairly low doses of 100 U or 86 U demonstrated a better treatment effect than 150 U.

Patient population

Given that a large number of patients in this study reported concurrent migraine symptoms, such as sensitivity to light and sound, nausea and vomiting, and the numbers of patients reporting migraine headaches (95/300), it is likely that the patients in this study were not suffering exclusively from CTTH but also had coexisting infrequent migraine headaches similar to other TTH populations. In addition, the patients in this study were required to be on stable doses of prophylactic headache medications for at least 3 months prior to the initiation of BoNTA treatment and could continue their prophylactic regimen throughout the course of the trial. The additional effect of concurrent prophylactic headache medication could have confounded the ability to assess a BoNTA treatment effect.

Conclusions

BoNTA treatment of CTTH in a dose range of 50 U to 150 U was shown to be safe and well tolerated. For tension headache-free days per month, all groups improved at the day 60 primary endpoint. There was no statistically significant difference between placebo and four BoNTA groups, but a significant difference favoring placebo vs. BoNTA 150 U was observed. At day 90, significantly more patients reported a 50% decrease in headache days in several BoNTA groups, suggesting that a longer period of evaluation may be needed to see a treatment effect. The failure of BoNTA to demonstrate efficacy in this trial may be related to the injection protocol, the BoNTA dosage range, the patient population, the use of concomitant

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

prophylactic headache medication or a lack of a clinically relevant effect in CTTH. BoNTA may not be an effective prophylactic treatment of CTTH, but further study may provide insight into appropriate study parameters and a possible treatment effect.

Dosing and results reported in this study are specific to the formulation of botulinum toxin type A manufactured by Allergan, Inc. (Irvine, CA, USA). The Allergan, Inc. formulation is not interchangeable with other botulinum toxin products and cannot be converted by using a dose ratio.

BOTOX CTTH Study Group

Andrew Blumenfeld, MD (California); Roger Cady, MD (Missouri); Joanna Cooper, MD (California); James Couch, MD (Oklahoma); Seymour Diamond, MD (Illinois); Hans-Christoph Diener, MD (Germany); Marek J. Gawel, MD (Canada); Peter Goadsby, MD, PhD (UK); Jerome Goldstein, MD (California); V. Daniel Kassicieh, DO (Florida); Jack Klapper, MD (Colorado); Ninan Mathew, MD (Texas); Alexander Mauskop, MD (New York); Volker Pfaffenrath, MD (Germany); Sid Rosenblatt, MD (California); Joel Saper, MD (Michigan); Jack Scariano, MD (Tennessee); Jean Schoenen, MD (Belgium); Elliott Schulman, MD (Pennsylvania); Fred Sheftell, MD (Connecticut); Timothy Smith, MD (Missouri); Egilius Spierings, MD, PhD (Massachusetts); Stuart Stark, MD (Virginia); Timothy Steiner, MB, PhD (UK); Paul Winner, DO (Florida).

References

1. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. JAMA 1998; 279:381–3.
2. Langemark M, Olesen J, Poulsen DL, Bech P. Clinical characterization of patients with chronic tension headache. Headache 1988; 28:590–6.
3. Schoenen J, Bottin D, Hardy F, Gerard P. Cephalic and extracephalic pressure pain thresholds in chronic tension-type headache. Pain 1991; 47:145–9.
4. Schoenen J, Gerard P, De Pasqua V, Sianard-Gainko J. Multiple clinical and paraclinical analyses of chronic tension-type headache associated or unassociated with disorder of pericranial muscles. Cephalalgia 1991; 11:135–9.
5. Jensen R. Pathophysiological mechanisms of tension-type headache: a review of epidemiological and experimental studies. Cephalalgia 1999; 19:602–21.
6. Jensen R. Mechanisms of tension-type headache. Cephalalgia 2001; 21:786–9.
7. Mørk H, Ashina M, Bendtsen L, Olesen J, Jensen R. Induction of prolonged tenderness in patients with tension-type headache by means of a new experimental model of myofascial pain. Eur J Neurol 2003; 10:249–56.
8. Bendtsen L. Central sensitization in tension-type headache—possible pathophysiological mechanisms. Cephalalgia 2000; 20:486–508.
9. Nardone R, Tezzon F. The trigemino-cervical reflex in tension-type headache. Eur J Neurol 2003; 10:307–12.
10. Ashina M. Neurobiology of chronic tension-type headache. Cephalalgia 2004; 24:161–72.

Published version available at doi:10.1111/j.1468-2982.2006.01114.x

Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

11. Dolly O. Synaptic transmission: inhibition of neurotransmitter release by botulinum toxins. Headache 2003; 43 (Suppl. 1):S16–24.
12. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache 2003; 43 (Suppl. 1):S9–15.
13. Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain 2004; 107:125–33.
14. Durham PL, Dacy R, Cady R. Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. Headache 2004; 44:35–43.
15. Kramer HH, Angerer C, Erbguth F, Schmelz M, Birklein F. Botulinum toxin A reduces neurogenic flare but has almost no effect on pain and hyperalgesia in human skin. J Neurol 2003; 250:188–93.
16. Dodick DW. Botulinum neurotoxin for the treatment of migraine and other primary headache disorders: from bench to bedside. Headache 2003; 43 (Suppl. 1):S25–33.
17. Smuts JA, Baker MK, Smuts HM, Stassen JMR, Rossouw E, Barnard PWA. Prophylactic treatment of chronic tension-type headache using botulinum toxin type A. Eur J Neurol 1999; 6 (Suppl. 4):S99–102.
18. Silberstein S, Mathew N, Saper J, Jenkins S for the BOTOX® Migraine Clinical Research Group. Botulinum toxin type A as a migraine prophylactic treatment. Headache 2000; 40:445–50.
19. Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pogoda JM. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. Otolaryngol Head Neck Surg 2000; 123:669–76.
20. Barrientos N, Chana P. Botulinum toxin type A in prophylactic treatment of migraine headaches: a preliminary study. J Headache Pain 2003; 4:146–51.
21. Blumenfeld A. Botulinum toxin type A as an effective prophylactic treatment in primary headache disorders. Headache 2003; 43:853–60.
22. Troost BT. Botulinum toxin type A (Botox®) in the treatment of migraine and other headaches. Expert Rev Neurotherapeutics 2004; 4:27–31.
23. Kokoska MS, Glaser DA, Burch CM, Hollenbeak CS. Botulinum toxin injections for the treatment of frontal tension headache. J Headache Pain 2004; 5:103–9.
24. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. Cephalalgia 2004; 24:60–5.
25. Schmitt WJ, Slowey E, Fravi N, Weber S, Burgunder JM. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. Headache 2001; 41:658–64.
26. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine—a randomized, double-blind, placebo-controlled study. Cephalalgia 2004; 24:838–43.
27. Padberg M, de Bruijn SF, de Haan RJ, Tavy DL. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. Cephalalgia 2004; 24:675–80.
28. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C and the BOTOX CDH Study Group. Botulinum toxin type A (Botox®) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache 2005; 45: 293–307.

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

29. Silberstein SD, Stark SR, Lucas SM, Christine SN, DeGryse RE, Turkel CC. Botulinum toxin type A (BOTOX®) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clinic Proc 2005; 80:1126–37.
30. Relja M, Telarovic S. Botulinum toxin in tension-type headache. J Neurol 2004; 251:I12–4.
31. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988; 8 (Suppl. 7):S1–96.
32. Linde M, May A, Limmroth V, Dahlof C; Headache Masters Programme. Ethical aspects of placebo in migraine research. Cephalalgia 2003; 23:491–5.
33. Jankovic J. Medical therapy and botulinum toxin in dystonia. Adv Neurol 1998; 78:169–83.
34. Brashear A, Gordon MF, Elovic E, Kassicieh VD, Marciniak C, Do M et al. for the Botox Post-Stroke Spasticity Study Group. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med 2002; 347:395–400.
35. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. Neurology 2001; 56:1290–3.
36. Cheshire WP, Abashian SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. Pain 1994; 59:65–9.
37. Lang AM. A pilot study of botulinum toxin type A (Botox®), administered using a novel injection technique, for the treatment of myofascial pain. Am J Pain Manage 2000; 10:108–12.
38. Freund BJ, Schwartz M. Relief of tension-type headache symptoms in subjects with temporomandibular disorders treated with botulinum toxin-A. Headache 2002; 42:1033– 7.
39. Blumenfeld AM, Binder W, Silberstein SD, Blitzer A. Procedures for administering botulinum toxin type A for migraine and tension-type headache. Headache 2003; 43:884–91.

TABLES & FIGURES

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

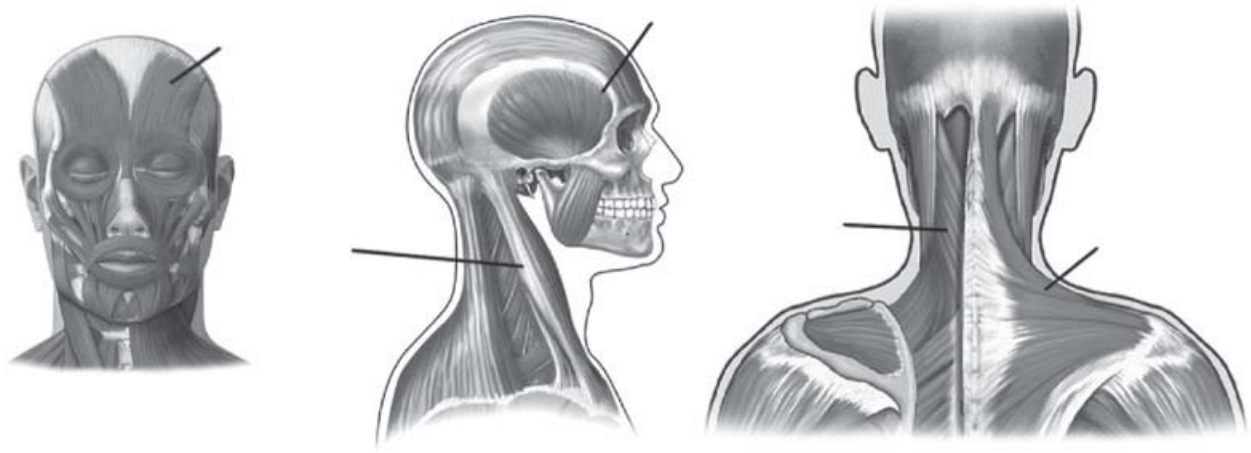

Figure 1
Location of injection sites. Adapted, with permission, from Nucleus Medical Art (http://www.nucleusinc.com).

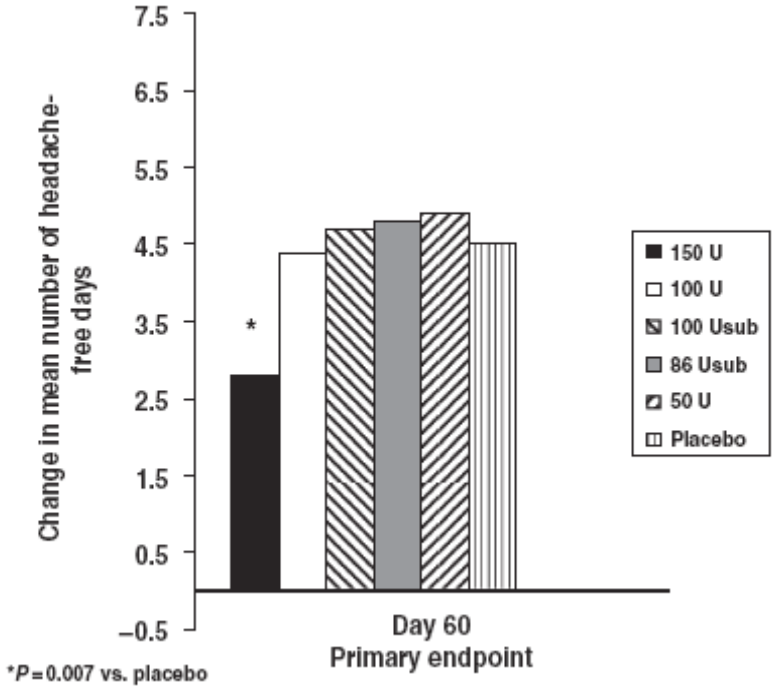

Figure 2
Mean change from baseline in the number of tension-type headache-free days at day 60.

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

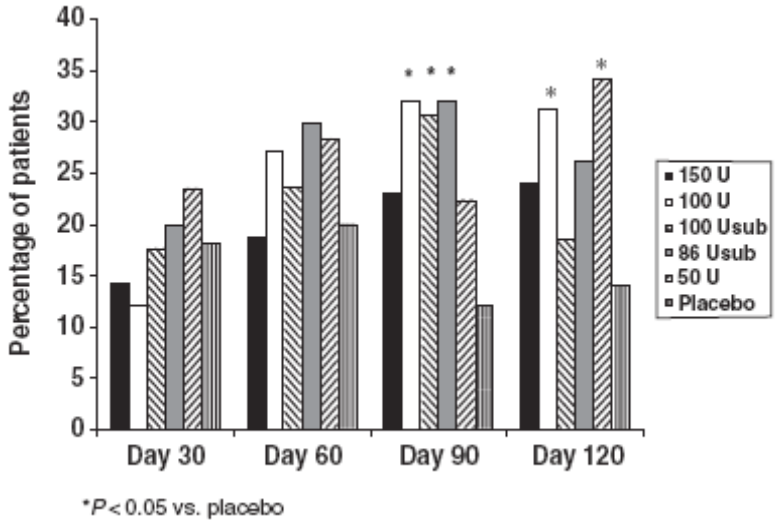

Figure 3
Percentage of patients with a decrease of 50% or more in tension-type headache days.

Table 1
Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

Patients who experienced a stable headache frequency and severity for 6 months prior to and including the screening period	Any medical condition or the use of any agent that may put the participant at risk with exposure to BoNTA (e.g. neuromuscular disorders, aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function)
Patients who for 6 months prior to and including the screening period experienced an average headache frequency of 15 days or more per month, as confirmed by their history and by their headache diary	Symptomatic medication overuse (defined as use of acute headache analgesics on more than 15 days per month and in excess of 100 aspirin-equivalent tablets per month or use of butalbital or ergotamine combinations on more than 3 days per week or regular use of narcotic analgesics or excessive use of caffeine-containing products)
Participants who were able to distinguish tension-type headaches from non-tension-type headaches and follow study instructions	More than 1 migraine headache per month for the 6 months prior to screening or during the 1-month screening period or the presence of cluster headache or cranial neuralgias including postherpetic neuralgia
	Consistently refractory to multiple acute therapies for the treatment of CTTH
	On prophylactic headache medications for less than 3 months immediately prior to the day-30 visit
	Injection of anaesthetics or steroids into the muscles to be injected in the month immediately prior to the day-30 visit
	Previous therapy with botulinum toxin of any serotype
	Women who were pregnant, nursing, or planning a pregnancy during the study or who are unable or unwilling to use a reliable form of contraception during the study
	A condition or situation that, in the investigator ’s opinion, may have put the patient at significant risk, confound the study results, or significantly interfered with the patient participating in the study

Table 2
Injection protocol

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

	Muscle				
Treatment group	Frontalis (2 sites)	Sternocleido-mastoid (2 sites)	Upper trapezius (2 sites)	Splenius capitis (2 sites)	Anterior temporalis (2 sites)
BoNTA 50 U	3.3 U 0.20 ml	13.3 U 0.80 ml	12 U 0.72 ml	12 U 0.72 ml	9.3 U 0.56 ml
BoNTA 86 Usub	10 U 0.20 ml	40 U 0.80 ml	36 U 0.72 ml	0.0 U 0.72 ml	0.0 U 0.56 ml
BoNTA 100 U	6.7 U 0.20 ml	26.7 U 0.80 ml	24 U 0.72 ml	24 U 0.72 ml	18.7 U 0.56 ml
BoNTA 100 Usub	0 U 0.20 ml	0 U 0.80 ml	36 U 0.72 ml	36 U 0.72 ml	28 U 0.56 ml
BoNTA 150 U	10 U 0.20 ml	40 U 0.80 ml	36 U 0.72 ml	36 U 0.72 ml	28 U 0.56 ml
Placebo	0 U 0.20 ml	0 U 0.80 ml	0 U 0.72 ml	0 U 0.72 ml	0 U 0.56 ml

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

Table 3
Tension-type headache (TTH) characteristics at baseline

	BoNTA					
	150 U $n = 49$ (%)	100 U $n = 51$ (%)	100 Usub $n = 52$ (%)	86 Usub $n = 51$ (%)	50 U $n = 47$ (%)	Placebo $n = 50$ (%)
TTH days per month[a]	23.0 (20)	23.9 (25)	23.8 (25)	22.8 (22)	25.5 (30)	25.2 (26)
Use medication for TTH pain						
Yes	41 (85.4),	44 (88.0)	49 (96.1)	47 (92.2)	38 (80.9)	42 (84.0)
No	7 (14.6)	6 (12.0)	2 (3.9)	4 (7.8)	9 (19.1)	8 (16.0)
Use of prophylactic HA medication	16 (32.6)	19 (37.3)	14 (27)	19 (37.3)	15 (32)	15 (30)
Symptoms with headache						
Nausea	3 (5.6)	2 (3.4)	1 (1.8)	5 (9.4)	2 (3.7)	2 (3.7)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)
Light sensitivity	13 (24.1)	15 (25.9)	9 (16.1)	7 (13.2)	10 (18.5)	14 (25.9)
Noise sensitivity	8 (14.8)	7 (12.1)	8 (14.3)	10 (18.9)	8 (14.8)	8 (14.8)
No symptoms	30 (55.6)	34 (58.6)	38 (67.9)	31 (58.5)	33 (61.1)	29 (53.7)
Location of pain						
Front of head	37 (75.5)	37 (72.5)	37 (71.2)	29 (56.9)	32 (68.1)	30 (60.0)
Side of head	20 (40.8)	16 (31.4)	17 (32.7)	14 (27.5)	14 (29.8)	20 (40.0)
Back of head	26 (53.1)	28 (54.9)	26 (50.0)	26 (51.0)	28 (59.6)	27 (54.0)
Behind eye	19 (38.8)	16 (31.4)	13 (25.0)	7 (13.7)	14 (29.8)	16 (32.0)
Top of head	9 (18.4)	15 (29.4)	12 (23.1)	11 (21.6)	16 (34.0)	14 (28.0)
One side of head	6 (12.2)	6 (11.8)	7 (13.5)	8 (15.7)	3 (6.4)	5 (10.0)
Both sides of head	35 (71.4)	27 (52.9)	27 (51.9)	28 (54.9)	33 (70.2)	32 (64.0)
Migraine headaches						
Yes	16 (32.7)	14 (27.5)	13 (25.5)	18 (36.0)	23 (48.9)	11 (22.0)
No	33 (67.3)	37 (72.5)	38 (74.5)	32 (64.0)	24 (51.1)	39 (78.0)

HA, Headache.
[a]Mean (median) values provided for TTH days/month and TTH duration (hours/day).

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.

Table 4
Tension-type headache-free days at baseline

Treatment group	Mean	Median	*P*-value vs. placebo at baseline
BoNTA 150 U	5.4	2.0	0.065
BoNTA 100 U	6.5	6.0	0.001*
BoNTA 100 Usub	5.3	3.0	0.027
BoNTA 86 Usub	5.3	4.5	0.008*
BoNTA 50 U	4.8	2.0	0.133
Placebo	3.3	0.0	–

*P ⩽0.01.

Table 5
Treatment-related adverse events reported in at least 3% of patients in any treatment group, by number (%) of subjects

Preferred term	BoNTA 150 U *n* = 47	100 U *n* = 51	100 Usub *n* = 52	86 Usub *n* = 51	50 U *n* = 49	Placebo *n* = 50
Overall	13 (27.7)	23 (45.1)	16 (30.8)	17 (33.3)	16 (32.7)	11 (22.0)
Muscular weakness	3 (6.4)	10 (19.6)	2 (3.8)	3 (5.9)	1 (2.0)	1 (2.0)
Neck rigidity	1 (2.1)	5 (9.8)	0 (0.0)	0 (0.0)	2 (4.1)	0 (0.0)
Neck pain	3 (6.4)	4 (7.8)	2 (3.8)	3 (5.9)	3 (6.1)	1 (2.0)
Headache	0 (0.0)	4 (7.8)	2 (3.8)	2 (3.9)	2 (4.1)	2 (4.0)
Pain	1 (2.1)	4 (7.8)	3 (5.8)	0 (0.0)	0 (0.0)	1 (2.0)
Dizziness	0 (0.0)	4 (7.8)	1 (1.9)	0 (0.0)	1 (2.0)	0 (0.0)
Injection-site pain	1 (2.1)	1 (2.0)	1 (1.9)	1 (2.0)	1 (2.0)	3 (6.0)
Dysphagia	0 (0.0)	1 (2.0)	0 (0.0)	3 (5.9)	0 (0.0)	0 (0.0)
Paraesthesia	0 (0.0)	0 (0.0)	1 (1.9)	3 (5.9)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	2 (3.9)	0 (0.0)	3 (5.9)	2 (4.1)	0 (0.0)
Hypertonia	2 (4.3)	0 (0.0)	2 (3.8)	1 (2.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (4.1)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.1)	0 (0.0)
Injection-site burning	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)

Published version available at doi:10.1111/j.1468-2982.2006.01114.x
Silberstein SD, Göbel H, Jensen R, Elkind AH, DeGryse R, Walcott JMcM & Turkel C. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26:790–800.