Movement Disorders
Vol. 22, No. 15, 2007, pp. 2268–2273

Ipratropium Bromide Spray as Treatment for Sialorrhea in Parkinson's Disease

Teri R. Thomsen, MD,[1] Wendy R. Galpern, MD, PhD,[1] Abena Asante, MSc,[1] Tamara Arenovich, MSc,[2] and Susan H. Fox, MRCP(UK), PhD[1]*

[1]*Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada*
[2]*Biostatistical Consulting Service, Clinical Research Department, Centre for Addiction and Mental Health, Toronto, Ontario, Canada*

Abstract: Sialorrhea is a significant problem in advanced Parkinson's disease (PD). Current treatment options include systemic anticholinergics which frequently cause side effects. We hypothesized that sublingual application of ipratropium bromide spray, an anticholinergic agent that does not cross the blood brain barrier, may reduce drooling without systemic side effects. We performed a randomized, double blind, placebo-controlled, crossover study in 17 subjects with PD and bothersome drooling. Patients were randomized to receive ipratropium bromide or placebo (one to two sprays, maximum of four times per day) for 2 weeks followed by a 1 week washout and crossover for further 2 weeks of treatment. The primary outcome was an objective measure of weight of saliva production. Secondary outcomes were subjective rating of severity and frequency of sialorrhoea using home diaries, United Parkinson's Disease Rating Scale (UPDRS) part II salivation subscore, parkinsonian disability using UPDRS, and adverse events. Ipratropium bromide spray had no significant effect on weight of saliva produced. There was a mild effect of treatment on subjective measures of sialorrhea. There were no significant adverse events. Ipratropium bromide spray was well tolerated in subjects with PD. Although it did not affect objective measures of saliva production, further studies in parkinsonism may be warranted. © 2007 Movement Disorder Society

Key words: ipratropium bromide; sialorrhea; drooling; Parkinson's disease; randomized controlled trial.

Excessive drooling of saliva (sialorrhea) is a common and bothersome complication of Parkinson's disease (PD).[1] While saliva production may be reduced in PD,[2] sialorrhea is mainly due to dysphagia. Yet, current treatment options are aimed at reducing saliva release with either oral or patch anticholinergic medications.[3] Unfortunately, use of such medications is often limited due to systemic side effects, including confusion, hallucinations, or urinary retention. Other approaches used to treat intractable drooling include botulinum toxin A and botulinum toxin B injections into the parotid and/or submandibular glands to block acetylcholine release from autonomic parasympathetic neurons.[4,5] However, such treatments necessitate repeated injections, which are costly and may exacerbate dysphagia.

A simpler approach to reduce saliva production may be the local application of an anticholinergic into the mouth. Atropine drops in a dose of 1 drop b.i.d. (one drop containing 5 mg atropine in 1% wt/vol) were found to be effective in an open label study in six PD subjects; however, systemic side effects still occurred, including delirium and hallucinations.[6] An alternative may be to use an aerosol spray directly into the mouth. Ipratropium bromide spray is an anticholinergic agent currently used as a bronchodilator for patients with asthma and chronic obstructive pulmonary disease.[7] It blocks muscarinic receptors, thereby decreasing salivary secretion, up to 10% of patients using ipratropium bromide report dry mouth as a side effect.[8] This drug has a favorable side effect profile and is currently widely used and well tolerated in the treatment of pulmonary disorders. The risk of central

Current address for Wendy R. Galpern: NINDS/NIH, Bethesda, MD, USA.

*Correspondence to: Dr. Susan H. Fox, MCL7.421, Movement Disorders Clinic, Toronto Western Hospital, 399 Bathurst St, Toronto, Ontario, M5T 2S8, Canada. E-mail: sfox@uhnresearch.ca

Received 14 May 2007; Revised 15 July 2007; Accepted 15 August 2007

Published online 17 September 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21730

antimuscarinic effects is minimal as ipratropium does not cross the blood brain barrier.[9] Systemic absorption of ipratropium bromide aerosol spray is low, thus minimizing potential systemic anticholinergic side effects. We therefore performed a randomized, double blind, placebo-controlled, crossover study designed to assess the safety, tolerability, and efficacy of ipratropium bromide spray as a treatment of PD-related drooling.

SUBJECTS AND METHODS

Subjects

Seventeen subjects were recruited from the Movement Disorders outpatient clinic at the Toronto Western Hospital, after institutional ethics review board and Health Canada approval. The study was registered at ClinicalTrials.gov; NCT00296946. Written informed consent was obtained from each subject. Inclusion criteria included a diagnosis of idiopathic Parkinson's disease (PD) according to the UK Parkinson's Disease Society Brain Bank criteria,[10] age over 18 years and bothersome drooling [United Parkinson's Disease Rating Scale (UPDRS) part II, item 6, salivation score rating of two or higher]. Subjects had to be on stable PD and concomitant medications for the preceding 1 month. In addition, subjects or a caregiver had to be able to complete a daily home diary and subjects had to be able to tolerate oral dental rolls for 5-minute periods for saliva measurements. Exclusion criteria were a known hypersensitivity to ipratropium bromide; the concurrent use of acetylcholinesterase inhibitors, cholinergic agents, or anticholinergic agents; botulinum toxin for drooling within the past 4 months; a history of glaucoma; the presence of clinically significant urinary retention or outflow obstruction as evidenced by patient history or documented urodynamic studies; active psychosis with hallucinations (a prior history of hallucinations or on current treatment with no active evidence of psychosis was not an exclusion criteria); or allergy to peanuts or soybeans. Pregnant and nursing mothers were also excluded.

Study Design

The study was a randomized, double blind, placebo controlled, crossover design. At the screening visit (Visit 1), enrolled patients underwent a complete history and physical examination including documentation of UPDRS scores (Parts I–IV). All patients and caregivers received detailed instruction and training in how to complete daily home diaries in which severity and frequency of drooling were recorded (see below). Patients undertook two practice days completing the diaries before the next visit.

At Visit 2, 1 to 2 weeks after Visit 1, subjects were randomized to receive ipratropium bromide or matching placebo, in a double-blind, crossover design using randomisation tables. Study drug was dispensed as a metered-dose spray bottle of ipratropium bromide or identical placebo prepared by the Toronto Western Hospital Clinical Trials Pharmacy. Subjects were instructed to use one to two metered doses (sprays) sublingually of study drug (21 μg of ipratropium bromide per metered dose spray) or matching placebo, as needed, up to a maximum of four times per day (maximum daily dosage 168 μg ipratropium bromide). The minimum interval between doses was 4 hours. The total length of treatment was 2 weeks. At the end of the treatment period, subjects returned for Visit 3 followed by a 1 week wash-out period. Subjects then received either ipratropium bromide or placebo in a cross-over design at Visit 4. Study procedures were identical in the second arm, and subjects returned for the final visit (Visit 5) after completion of the second 2 week treatment period. Midway through each treatment arm, subjects were contacted via telephone to review any adverse events. All nonstudy medications were continued without changes during the course of the study. The total study period was 6 to 7 weeks.

Outcome Measures

The primary outcome measure was an objective measure of saliva production.[11] Cotton dental rolls (3.5×0.5 cm^2) were inserted into the mouth for 5 minutes. The number of rolls used was the maximum tolerated by the subject (average three to five rolls) and was identical at each assessment. Subjects were instructed to sit upright and refrain from swallowing or speaking while the rolls were in place, in addition, they were advised not to eat or drink for 1 hour before testing. Measurements were performed at the same time of day for each visit. Patients were all in the "on levodopa medication" state. The difference between the weight of the dental rolls before and after insertion was calculated as an objective measure of saliva production. Assessments were performed before (baseline) and at the completion of each treatment arm (Visits 2, 3, 4, and 5). At the end of each treatment arm, (Visits 3 and 5), a measurement 1 hour after treatment with two sprays of study drug was performed. A 1 hour time interval was chosen as peak effect of ipratropium bromide is 1 to 2 hour post dose.[12]

Secondary outcome measures included subjective assessment of saliva production using UPDRS part II, item 6, salivation score, at baseline and after each treatment arm (Visits 2, 3, 4, and 5). In addition, subjects or their caregivers documented the number of sprays adminis-

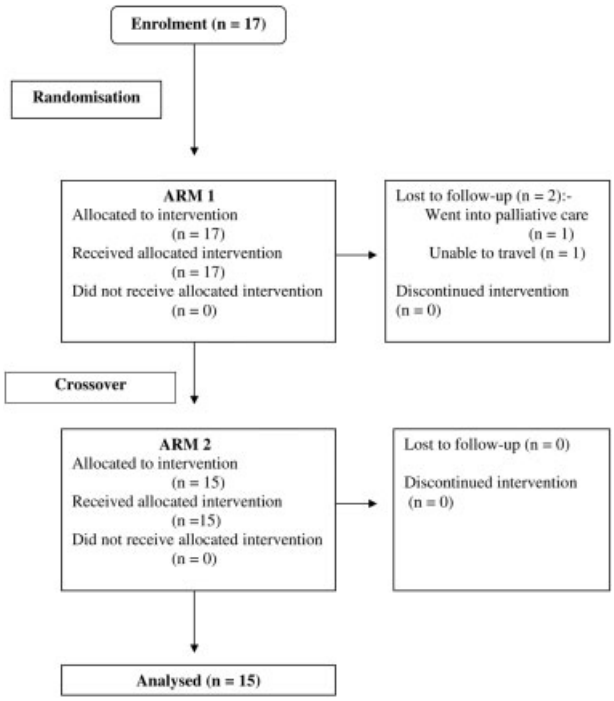

FIG. 1. Flow diagram from screening through completion of the study.

tered in a home diary for each day of the 2 week treatment periods. Subjects or their caregivers also recorded the severity and frequency of drooling saliva before and 1 hour after the spray using a validated subjective rating scale for drooling.[13] Thus drooling severity was rated on a scale of 1 to 5: 1: dry, never drools; 2: mild, only lips wet; 3: moderate, wet on lips and chin; 4: severe, drools to extent that clothing becomes damp; 5: profuse, clothing, hands, tray, and objects become wet. Drooling frequency was rated on a scale of 1 to 4: 1: never drools, 2: occasionally drools, 3: frequently drools, 4: constantly drools. Motor function and parkinsonism was measured at each study visit using total and part III motor scores of the UPDRS (on levodopa medication). Tolerability was assessed by questioning subjects and caregivers about side effects at each study visit and during telephone contact. Also, subjects or caregivers noted any adverse events on home diaries.

Statistical Analysis

The scores for objectively measured saliva production before and following ipratropium bromide and placebo treatment were compared using parametric repeated measures analysis of variance (ANOVA). Results from the scales assessing the subjective measures of saliva production and UPDRS ratings were compared using Friedman's nonparametric analysis of variance (ANOVA) followed by post-hoc Dunn's multiple comparison test. Diaries were analyzed for number of sprays used over the total 2 week treatment arm as well as change in subjective drooling severity and frequency ratings pre- and 1 hour post-study sprays using appropriate *t* tests. No prior studies have assessed use of ipratropium bromide in PD patients to perform formal power calculations; 15 to 20 patients were therefore estimated, depending on drop-out rate.

RESULTS

Seventeen patients were enrolled and 15 completed the study. Two randomized patients did not complete the study due to nonmedical reasons (see Fig. 1). Patient demographics are in Table 1. No patient had previously been treated with botulinum toxin for drooling. There was no significant difference in weight of saliva measured at baseline or at the end of 2 weeks treatment with ipratropium bromide compared with placebo ($P > 0.05$, Repeated Measures ANOVA $F_{(3-56)} = 0.8250$, $n = 15$) (Fig. 2a). There was also no significant difference in weight of saliva before and 1 hour after dosing with study spray at the end of each treatment arm ($P > 0.05$, Repeated Measures ANOVA, $F_{(3-56)} = 0.9745$, $n = 15$) (Fig. 2b).

There was an effect of treatment on UPDRS part II, question 6 salivation subscore ($P < 0.05$, Friedman test, $F_{(4-70)} = 9.041$, $n = 15$) (see Fig. 3). However, post-hoc analysis showed no significant effect between ipratropium bromide and placebo (Dunn's Multiple Comparison Test, all $P > 0.05$) (see Fig. 3). There were no carry-over effects during the cross-over period. Thus, there was no significant difference in the weight of saliva or UPDRS II part 6 salivation scores at each baseline visit (Figs. 2a and 3).

The daily home diaries were completed by all subjects/caregivers. There was no significant difference in total number of sprays used between ipratropium bromide and placebo treatment. The mean (± s.d.) total number of sprays of ipratropium bromide per patient over 2 weeks was 66.3 ± 28.5 compared with 63.7 ±

TABLE 1. *Patient demographics*

Sex	15 M/2 F
Age (yr); mean (range)	70 (54-85)
Time since diagnosis (yr) mean (range)	10.8 (3-21)
On levodopa medication UPDRS III; median (range)	27 (10-65)
On levodopa medication UPDRS II salivation part 6; median (range)	3 (2-4)
Duration of levodopa (yr) mean (± s.d.)	8.8 (±5.5)
Levodopa-dose equivalent (mg) mean (± s.d.)[14]	903.3 (±491.3)
Use of botulinum toxin for drooling	0/17

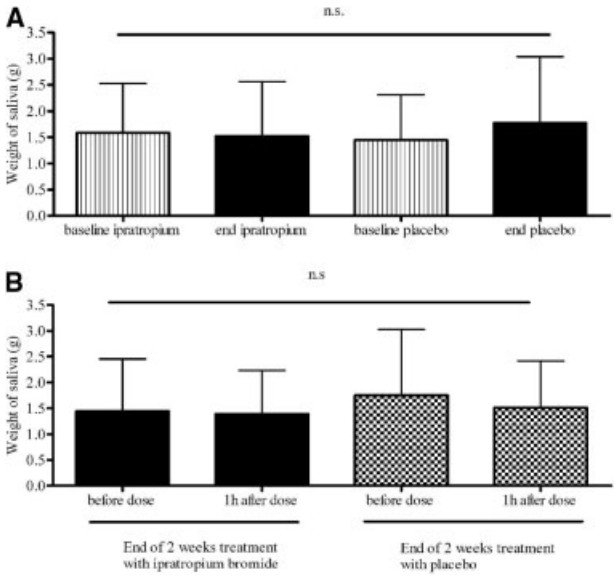

FIG. 2. (**a**) Saliva production before (baseline) and at the end of 2 weeks treatment with ipratropium bromide spray (ipratropium) or placebo spray in PD. Data show mean weight of saliva (g) (± s.d.); $n = 15$; n.s. = non-significant using Repeated Measures ANOVA. (**b**) Effect of ipratropium bromide and placebo on saliva production at the end of the 2 week treatment period measured before and 1 h after dose of study drug (two sprays). Data show mean weight of saliva (g) (± s.d.); $n = 15$; n.s. = non-significant Repeated Measures ANOVA.

26.8 with placebo ($P > 0.05$, paired t test). With both ipratropium bromide and placebo, there was a significant effect of treatment on severity ratings recorded in the daily home diary before (pre) and 1 h after (post) use of the spray. Thus, the mean (± s.d.) severity rating preipratropium bromide spray was 2.3 ± 0.8 and 2.0 ± 0.7 posttreatment ($P < 0.01$, paired t test) and 2.1 ± 0.7 preplacebo spray and 1.9 ± 0.7 after ($P < 0.01$, paired t test). However, there was no significant difference in the decrease in postspray scores between ipratropium bromide and placebo; thus, the decrease in scores (pre–post) with ipratropium bromide was 0.3 ± 0.7 compared with 0.2 ± 0.7 with placebo ($P > 0.05$, unpaired t test). Similarly, there was a decrease in frequency of drooling pre- and posttreatment with both ipratropium bromide and placebo as recorded in the daily home diaries ($P < 0.01$, paired t tests). However, there was also no significant difference between the decrease in frequency score (pre–post) with ipratropium; 0.2 ± 0.6 and placebo, 0.2 ± 0.6 ($P > 0.05$, unpaired t test).

There was no change in PD symptoms as measured using total and motor UPDRS part III. Thus mean (± s.d.) "on-levodopa" UPDRS III scores were 28.87 ± 14.11 at baseline before ipratropium bromide and 28.80 ± 14.93 after treatment; and 27.70 ± 12.65 before and 28.33 ± 14.63 after placebo ($P > 0.05$, Friedman test followed by Dunn's multiple comparison test, $F = 4.330_{(3–56)}$, $n = 15$). Mean "on-levodopa" total UPDRS scores were 50.44 ± 24.02 before and 48.25 ± 25.03 after ipratropium bromide; and 49.22 ± 22.06 before and 49.81 ± 23.45 after placebo ($P > 0.05$, Friedman test followed by Dunn's multiple comparison test, $F = 4.50_{(3–56)}$, $n = 15$).

One patient developed dry nasal passages and an associated nose bleed that was assessed as being possibly related to the study drug. This did not necessitate change in treatment. There were no effects on bladder function and no cognitive or psychiatric problems. There were no other adverse events reported.

DISCUSSION

Ipratropium bromide spray did not significantly reduce the weight of saliva production but may have a mild effect on subjective measures of sialorrhea in PD. Of importance, the treatment was well tolerated without any anticholinergic side-effects. Six subjects continued with open-label ipratropium bromide spray after the study had completed.

The potential for ipratropium bromide spray to reduce sialorrhea relates to antagonism of parasympathetic control of salivary glands and thus reduced saliva release. However, the exact dosage or timing of the spray required is not known. The lack of significant effect on weight of saliva between ipratropium bromide and placebo use was unrelated to amount of spray used, as the total number of sprays recorded was similar between the two treatments. It is currently unknown if in PD patients, dosing may need to be increased or continued for a longer duration to be more effective against drooling. However, small, unblinded, case series have assessed the use of ipratropium bromide spray in clozapine-induced hypersalivation and have reported some success with lower dosing schedules of one to two sprays/day.[15,16] The timing of ipratropium bromide used here was estimated from recommended use of such sprays in chronic bron-

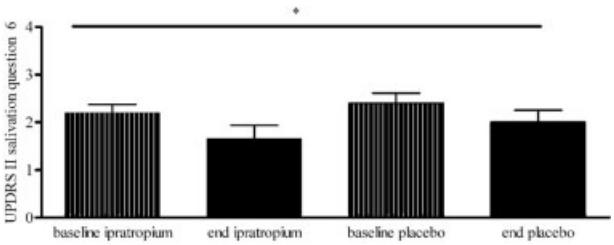

FIG. 3. Effect of treatment with ipratropium bromide and placebo spray on UPDRS II, part 6 salivation subscore at baseline and at the end of 2 weeks treatment. Data shows mean (± s.d.); $n = 15$. $^*P < 0.05$ Friedman test.

chitis. Thus speed of onset is 5 to 15 minutes with peak effect at 1 to 2 hour and duration up to 6 hour.[12] However, the timing of effects on salivary gland function is not known. In addition, compliance with accurate use of the spray directed towards the salivary glands rather than swallowed is unknown. Patients were observed using the spray and corrected if inaccurate, when seen at each visit.

Timing of the objective salivary measurements also may have impaired the ability to detect a significant difference. Although the assessments were kept to the same times as far as possible in both relation to meals and medications, saliva production varies throughout the day, and is influenced by multiple factors. Measurements were performed in the 'on medication state' for ease of patient access to the clinic, but frequently PD patients report sialorrhea as on off-period symptom. However, in more advanced PD the benefits of L-dopa on sialorrhea are frequently less than in early disease.

In PD, sialorrhea is primarily due to dysphagia as well as a tendency to keep the mouth open and a stooped posture; salivary production is actually reduced.[2] Thus, measuring the volume of saliva produced as a means of assessing sialorrhea in PD may not detect the impact of a treatment on drooling, as would rating impact on overall quality of life. However, this study was designed as a phase II study primarily to determine preliminary signs of efficacy of ipratropium bromide in reducing salivary production, and, as such, quality of life scales were not included. Such ratings would be appropriate for a larger phase III study. In addition, clinical studies in PD are frequently compromised by large placebo effects, particularly with subjective measurements. Therefore, an objective measurement of saliva levels was deemed the most sensitive way of measuring any potential change in drooling due to ipratropium. In fact, the "placebo " effect was seen in the significant decrease in subjective ratings of severity and frequency of drooling recorded by the patients/care givers in the diary cards, after use of *both* the ipratropium bromide and placebo sprays (although, there was no significant difference in the decrease between ipratropium bromide and placebo).

To date, there are no well-validated scales of measuring drooling in PD. The UPDRS part II has a single question related to salivation. The subjective scale used in this clinical trial is validated for drooling in other neurological and medical conditions and is not specific for PD. Thus, potential benefits in the use of ipratropium bromide may not have been detected using the scale in this study. A recent study, published after completion of this clinical trial, has proposed a promising new scale for sialorrhea in PD, which awaits further validation.[17] This scale incorporates a range of aspects of sialorrhea including frequency of drooling, amount, and impact on daily life.

In conclusion, this randomized, double blinded, placebo-controlled clinical trial failed to show an effect of ipratropium bromide spray on objective measures of drooling in PD. It is important to note that the sample size was small and the study may have been underpowered. Nevertheless, the spray was well tolerated in this population, caused no serious adverse events and did not worsen PD. Six patients continued after the study suggesting they had derived benefit. Future studies of ipratropium bromide spray in PD using a higher dosage or longer treatment, with measures of quality of life, may be warranted, as well as studies in other parkinsonian syndromes with more bothersome drooling such as multiple system atrophy or progressive supranuclear palsy.

Acknowledgments: Funding for this study was provided by a Research Grant from the Parkinson's Disease Foundation (to S.H.F. and W.R.G.). The expertise and assistance of Ron Seto, Piri Babos Margaret McGrath-Chong, and staff in the movement disorder clinic is greatly appreciated. The original idea was from Jan Parsons, PD Specialist nurse, Walton Centre for Neurology, Liverpool, UK. Finally, this trial would not have been possible without the enthusiasm and commitment of the patients involved.

REFERENCES

1. Johnston BT, Li Q, Castell JA, Castell DO. Swallowing and esophageal function in Parkinson's disease. Am J Gastroenterol 1995;90:1741-1746.
2. Bagheri H, Damase-Michel C, Lapeyre-Mestre, M. et al. A study of salivary secretion in Parkinson's disease. Clin Neuropharmacol 1999;22:213-215.
3. Potulska A, Friedman A. Controlling sialorrhoea: a review of available treatment options. Expert Opin Pharmacother 2005;6: 1551-1554.
4. Mancini F, Zangaglia R, Cristina S, Sommaruga MG, Martignoni E, Nappi G, Pacchetti C. Double-blind placebo controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. Mov Disord 2003;18:685-688.
5. Ondo WG, Hunter C, Moore W. A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology 2004;62:37-40.
6. Hyson HC, Johnson AM, Jog MS. Sublingual atropine for sialorrhea secondary to parkinsonism: a pilot study. Mov Disord 2002; 17:1318-1320.
7. Beeh KM, Welte T, Buhl R. Anticholinergics in the treatment of chronic obstructive airway disease. Respiration 2002;69:372-379.
8. Mann KV, Leon AL, Tietze KJ. Use of ipratropium bromide in obstructive lung disease. Clin Pharm 1988;7:670-680.
9. Brown JH, Taylor P. Muscarinic receptor agonists and antagonists. In: Hardman JG, Limbird LE, and Gilman AG, editors. Goodman and Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; 2001. p 155-169.
10. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-184.
11. Pal PK, Calne DB, Calne S, Tsui JK. Botulinum toxin A as treatment for drooling saliva in PD. Neurology 2000;54:244-247.

12. Atrovent® (ipratropium bromide) nasal aerosol Product Monograph March 3, 2004. Boehringer Ingelheim.
13. Heine RG, Catto-Smith AG, Reddihough DS. Effect of antireflux medication on salivary drooling in children with cerebral palsy. Dev Med Child Neurol 1996;38:1030-1036.
14. Lozano AM, Lang AE, Galvez-Jimenez N, Miyasaki J, Duff J, Hutchinson WD, Dostrovsky JO. Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 1995;346:1383-1387.
15. Tessier P, Antonello C. Clozapine and sialorrhea: update. J Psychiatry Neurosci 2001;26:253.
16. Freudenreich O, Beebe M, Goff DC. Clozapine-induced sialorrhea treated with sublingual ipratropium spray: a case series. J Clin Psychopharmacol 2004;24:98-100.
17. Perez Lloret S, Piran Arce G, Rossi M, Caivano Nemet ML, Salsamendi P, Merello M. Validation of a new scale for the evaluation of sialorrhea in patients with Parkinson's disease. Mov Disord 2007;22:107-111.