

LETTERS TO THE EDITOR

Treatment of Outlet Obstruction Constipation in Parkinson's Disease With Botulinum Neurotoxin A

TO THE EDITOR: In addition to motor signs, patients with Parkinson's disease (PD) suffer from a variable degree of autonomic impairment. Constipation is one of the most common autonomic dysfunctions observed in PD and may precede the onset of motor signs by many years (1). Chronic constipation, defined as the occurrence of less than three bowel movements per week accompanied by straining at stool, may be due to either slow transit or to outlet obstruction, and in PD both causes usually coexist (2). It is still unclear how many constipated PD patients have slow transit, outlet obstruction, or a combination of the two. Outlet obstruction is associated with a failure of relaxation, or even with a paradoxical contraction of the puborectalis muscle during straining, accentuating the flap-valve action of the anorectal angle and resulting in an obstruction to the onward passage of stool. Surgical treatments aimed at weakening or dilating the puborectalis muscle are often unsuccessful (3), whereas injections of botulinum toxin directly into the puborectalis muscle have provided promising results (4).

In a PD patient with prominent signs of outlet obstruction-type constipation, we observed a dramatic improvement after injections of botulinum neurotoxin directly into the puborectalis muscle (5). This prompted us to perform a prospective study in PD patients with chronic constipation, to identify possible candidates for this treatment.

PD outpatients seen at the movement disorders clinic filled an inventory of GI function (evaluating the number of bowel movements and defecatory function) and received a proctological evaluation. A total of 138 patients met the inclusion criteria for chronic constipation; 18 of them (13%) had isolated or prominent outlet-type constipation. Ten patients (one woman and nine men, mean age $\pm$ SD] 69.1 $\pm$ 9.2 yr, mean duration of PD 70 $\pm$ 53 months, mean duration of constipation 35.3 $\pm$ 11 months) were studied. All the patients were treated with levodopa, dopamine agonists, and domperidone. They were evaluated by means of manome-

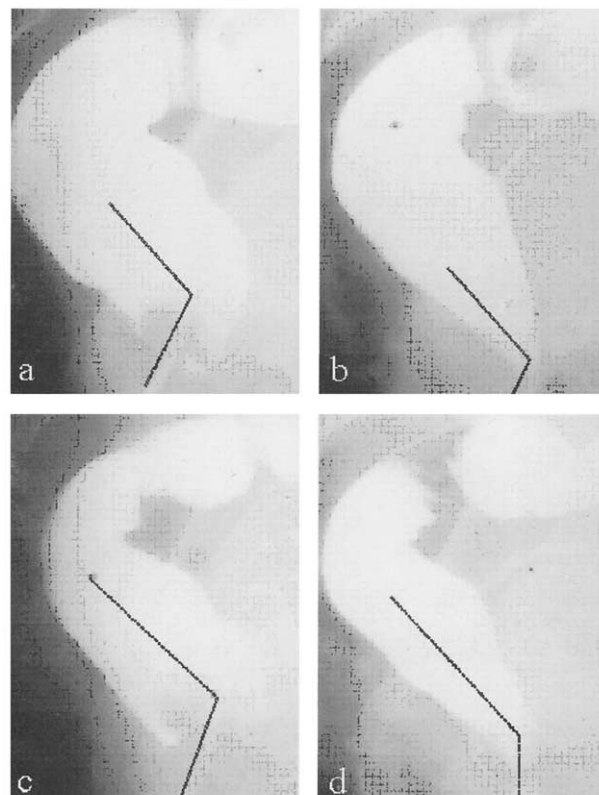


Figure 1. Treatment of outlet-type constipation in PD by injection of botulinum toxin in the puborectalis muscle, before (*a, b*) and after (*c, d*) treatment with botulinum toxin. Defecographies *a* and *c* represent the resting condition; defecographies *b* and *d* have been taken during straining. After treatment, during straining the pelvic floor descends about 3 cm and the anorectal angle becomes obtuse (compare *b* and *d*).

try, defecography, and electromyography before treatment and twice at monthly intervals after the injection. Botulinum neurotoxin (Botox, Allergan, Irvine, CA) was injected in the puborectalis muscle (two sites on either side of the muscle) under transrectal ultrasonographic guidance; the total dose per session was 100 U in each patient.

Table 1. Anal Pressures and Anorectal Angle Before and After Botulinum Neurotoxin Treatment

	Before Treatment	1 Mo	2 Mo
Resting anal tone (mm Hg)	59.2 $\pm$ 21.2	49.4 $\pm$ 13.9	56.8 $\pm$ 20.9
Maximum voluntary contraction (mm Hg)	60.1 $\pm$ 30.5	52.4 $\pm$ 30.3	61.7 $\pm$ 22.5
Pressure during straining (mm Hg)	97.4 $\pm$ 19.6	40.7 $\pm$ 11.5	38.2 $\pm$ 10.4
Anorectal angle at rest (degrees)	115.5 $\pm$ 7.5		114 $\pm$ 9.1
Anorectal angle during straining (degrees)	99 $\pm$ 7.9		122.2 $\pm$ 15

Data are expressed as mean $\pm$ SD.

After treatment, anal tone during straining was reduced from 97.4 ± 19.6 mm Hg at baseline to 40.7 ± 11.5 mm Hg 1 month after treatment ($p = 0.00001$); no further change was observed at the 2-month evaluation (38.2 ± 10.4 mm Hg; $p = 0.00001$ vs baseline values). Resting anal tone and maximum voluntary contraction were unchanged compared with baseline values (Table 1). The anorectal angle during straining (as measured with defecography) increased from a mean of 99 ± 7.9 degrees before treatment to 122.2 ± 15 degrees ($p = 0.0004$); nine patients evacuated the barium paste without the need for laxatives or enemas (Figure 1).

This observation indicates that outlet obstruction is the main cause for constipation in a minority of PD patients and provides evidence that botulinum toxin may be a remedy for them. The duration of efficacy of the injections remains to be measured, and repeated treatments are probably necessary. The optimal dose of botulinum toxin also remains to be determined; a placebo-controlled study with long-term follow up is warranted.

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Resveratrol and Red Wine Extracts Inhibit the Growth of *CagA*+ Strains of *Helicobacter pylori* In Vitro

TO THE EDITOR: In 1994, *Helicobacter pylori* was classified as a group I carcinogen and a definite cause of gastric cancer in humans by the International Agency for Research on Cancer (1). Since then, *H. pylori* has been epidemiologically linked to adenocarcinoma of the distal stomach (2, 3), and a recent study has also found a positive association between *H. pylori* infection and colorectal adenomas (4). *CagA* is the strain-specific *H. pylori* gene that has been linked to the development of premalignant and malignant histological lesions (5). Thus, susceptibility of *cagA*+ *H. pylori* strains is of note because, as compared with *cagA*- strains, infections caused by *cagA*+ strains significantly increase the risk for developing severe gastric inflammation, atrophic gastritis, and noncardia gastric adenocarcinoma (5). Previously, we have demonstrated that resveratrol, a stilbene from red wine, inhibited the growth of 15 clinical strains of *H. pylori* *in vitro* and suggested that the anti-*H. pylori* activity of resveratrol may play a role in its chemopreventative effects (6). In this investigation, the antibacterial activities of two red wine extracts (Pinot Noir) and resveratrol were assessed against five *cagA*+ *H. pylori* strains: accession numbers M23-3, GTD7-13, G1-1, SS1 (Sydney Strain *cagA*+), and the ATCC 43504 (Rockville, MD) possessing the *cagA*+ gene and expressing vacuolating cytotoxin. The *H. pylori* *cagA*+ strains were obtained from Drs. Richard Peek and Dawn Israel, Department of Pathology, Vanderbilt University School of Medicine, Nashville, TN. Susceptibility testing was performed with the agar dilution procedure, and all other methods were as previously described (6). Red wine extracts (Pinot Noir) were prepared, one by concentrating and drying under reduced pressure, and the second by separating the alcohol-soluble and -insoluble components. The second extract was prepared by dissolving 1500 ml of red wine in 3 L of methanol, concentrating under reduced pressure, filtering, and collecting both the filtrate (alcohol soluble) and the particulate matter (alcohol insoluble). The filtrate was termed a *methanol-soluble extract*, and the particulate matter was termed a *methanol-insoluble extract*. The methanol-soluble extract was not active in our assay at concentrations up to 500 $\mu\text{g/ml}$. However, both the methanol-insoluble and the concentrated red wine extracts were active against all *cagA*+ HP strains, with minimum inhibitory concentrations (MIC) of 25 $\mu\text{g/ml}$ and 50 $\mu\text{g/ml}$, respectively (range of 25-50 $\mu\text{g/ml}$). Resveratrol was also active against all five strains, with an MIC of 12.5 $\mu\text{g/ml}$ (range of 6.25-25 $\mu\text{g/ml}$). The control drug, amoxicillin, had an MIC range of 0.0039 to 0.25 $\mu\text{g/ml}$. These data demonstrate that both red wine and resveratrol inhibit the growth of *H. pylori* *cagA*+ strains *in vitro* and further support their role as chemopreventive agents.