tivated by porous-load autoclaving at 136°C for 4 minutes under these rigorous test conditions. The UK standard which was based on these data is, therefore, extremely well founded and is certainly not less stringent than the Committee's recommendation.

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More on Ciladopa

Stuart R. Snider, MD

Aminoff and colleagues [1] should have provided the times post-ciladopa of their examinations and the ciladopa blood levels. The drug effect lasts about 3 hours and could have been missed on the twice-a-day dosing. Were there dopaminergic side effects [2] or subjective patient responses (positive or negative) to the drug? Did analysis of variance of data from *all* grouped visits permit statistical analysis? Nonparametric analysis would be more valid statistically than *t* tests of data based on nonparametric 0–4+ scales.

Flaws in the study design prevent any conclusion about ciladopa. This negative report should not discourage the search for a more selective antiparkinsonism drug.

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Reply

Michael J. Aminoff, MD, FRCP,
and Douglas S. Goodin, MD

Dr Snider's comments are somewhat surprising to us because he participated in the same multicenter study, using the same protocol (devised by Ayerst Laboratories, the manufacturers of ciladopa) that we did. According to the manufacturer, the effects of the drug last for considerably longer than 3 hours and a twice-daily dosage is appropriate. Indeed, Dr Snider also used a twice-daily dosing regimen in the protocol for open administration of the drug for which he claimed benefit in 1985 [1]. Subjective patient responses were noted among our patients but were hard to interpret because they also occurred when patients received placebo. The parametric statistical tests that we used are appropriate even if the 0–4+ scales are not perfectly parametric, because this could lead only to an increase in false positive results (i.e., the tests might detect differences that were not genuine). Since we found no difference between groups, our conclusions are valid. We concluded that ciladopa as an antiparkinsonian agent was ineffective. In no way did we suggest that a search for more selective antiparkinsonian drugs should be discouraged. We hope, however, that such drugs are subjected to rigorous scrutiny before claims are made as to their therapeutic efficacy.

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Does Papaverine Interact with Levodopa in Parkinson's Disease?

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Since the observations of Duvoisin [2] showing an antagonism of levodopa by papaverine, it has been claimed in many pharmacological textbooks or in drug dictionaries (for example, the French Vidal dictionary) that papaverine should not be administered to patients with parkinsonism, especially those receiving levodopa therapy. Moreover, Duvoisin [2] concluded that papaverine may be added to the list of iatrogenic causes of levodopa treatment failure. In fact, the five cases he reported were uncontrolled observations. To our knowledge there have been no published controlled trials of papaverine in Parkinson's disease.

Our study was carried out on 9 patients with idiopathic Parkinson's disease (7 men and 2 women, aged 54 to 79 yr; mean age 66.4 ± 2.6 yr; 1 on Stage I, 3 on Stage II, and 5 on Stage III according to Hoehn and Yahr [3]). The duration of their illness was 5.9 ± 1.5 years (range 2–15 yr), and they all suffered from insufficient action of levodopa. None of them was depressed, demented, or suffered from dyskinesia, dystonia, or on-off effects. All patients gave informed consent approved by the institutional ethics committee after full disclosure of the nature of the study and the attendant potential risks. All 9 patients completed the double-blind, placebo-controlled, randomized crossover trial of 3 weeks of papaverine following or followed by 3 weeks of placebo, in which one tablet of papaverine hydrochloride (150 mg) was taken each morning at 8 AM with the antiparkinsonian drugs.

During the trial, the previous antiparkinsonian treatment remained unchanged: all the patients were treated with levodopa, 362.5 ± 66.0 mg daily (range 100–750 mg) plus decarboxylase inhibitor; 2 of them also received bromocriptine (40 mg daily) and 2 trihexyphenidyl (15 mg daily). All the patients were followed by the same physician and were clinically assessed before beginning treatment and at the end of each 3-week period using the Columbia University Rating Scale to obtain global, tremor, rigidity, and akinesia scores [4]. Each new assessment with the Columbia University Scale was made blind. The results expressed as mean ± SEM were analyzed by two-way analysis of variance with repeated measurements of one factor followed by Wilcoxon's *t* test.

Papaverine failed to modify the neurological symptoms of the 9 patients with Parkinson's disease: we did not find any change in global (33.88 ± 1.38 with papaverine versus 33.88 ± 1.41 with placebo), tremor (7.00 ± 0.91 with papaverine versus 6.78 ± 0.74 with placebo), rigidity (4.22 ± 0.70 with papaverine versus 4.44 ± 0.65 with placebo), or akinesia (15.11 ± 1.45 with papaverine versus 15.22 ± 1.88 with placebo) scores. No side effects were observed during the trial.

The present controlled study clearly demonstrates that papaverine does not antagonize the antiparkinsonian effects of levodopa. In fact, although some experimental data have suggested that papaverine might affect brain dopamine levels, the clinical consequences of these animal data remain unclear. Our present clinical study does not support the hypothesis that brain dopaminergic activity is influenced by papaverine. It agrees with the study of Branconnier et al [1] showing that papaverine does not significantly affect serum prolactin levels. From a therapeutic point of view, one can conclude that papaverine can be used in parkinsonian patients without any effect on extrapyramidal symptoms.

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