

INTRATHECAL BACLOFEN FOR SEVERE SPINAL SPASTICITY

RICHARD D. PENN, M.D., SUZANNE M. SAVOY, M.N.S., DANIEL CORCOS, PH.D., MARK LATASH, M.S.,
GERALD GOTTLIEB, PH.D., BARBARA PARKE, M.D., AND JEFFREY S. KROIN, PH.D.

Abstract We studied the effect of the intrathecal infusion of baclofen, an agonist of gamma-aminobutyric acid, on abnormal muscle tone and spasms associated with spinal spasticity, in a randomized double-blind crossover study. Twenty patients with spinal spasticity caused by multiple sclerosis or spinal-cord injury who had had no response to treatment with oral baclofen received an intrathecal infusion of baclofen or saline for three days. The infusions were administered by means of a programmable pump implanted in the lumbar subarachnoid space.

Muscle tone decreased in all 20 patients (mean $\pm$ SD) Ashworth score for rigidity, from 4.0 ± 1.0 to 1.2 ± 0.4 ; $P < 0.0001$), and spasms were decreased in 18 of the 19 patients who had spasms (mean $\pm$ SD) score for spasm frequency, from 3.3 ± 1.2 to 0.4 ± 0.8 ; $P < 0.0005$). Tests for motor function, neurologic examination, and assessments

by the patients correctly indicated when baclofen was being infused in all cases.

All patients were then entered in an open long-term trial of continuous infusion of intrathecal baclofen. During a mean follow-up period of 19.2 months (range, 10 to 33), muscle tone has been maintained within the normal range (mean Ashworth score, 1.0 ± 0.1) and spasms have been reduced to a level that does not interfere with activities of daily living (mean spasm score, 0.3 ± 0.6). No drowsiness or confusion occurred, one pump failed, and two catheters became dislodged and had to be replaced. No infections were observed.

Our observations suggest that intrathecal baclofen is an effective long-term treatment for spinal spasticity that has not responded to oral baclofen. (*N Engl J Med* 1989; 320:1517-21.)

THE muscle spasms and increased muscle tone associated with severe spinal spasticity often respond poorly to oral medications. Until now, the only alternative treatments have been destructive surgical procedures that cut nerve roots or disrupt spinal-cord circuits.¹ In recent studies, the long-term infusion of baclofen, an agonist of gamma-aminobutyric acid (GABA), by means of a drug pump implanted in the lumbar subarachnoid space has been observed to reduce spasms and rigidity markedly.^{2,3} Since many previous treatments for spasticity have been thought to be dramatically effective according to the original reports, only to be discredited by later, more carefully controlled studies, we have undertaken a randomized, double-blind, crossover study using this new technique.

METHODS

Patients

Twenty patients with severe disabling spasms, caused by multiple sclerosis in 10 patients and by spinal-cord injury in the other 10, received pumps for infusion of drugs into the lumbar subarachnoid space (Table 1). All patients had longstanding spasticity (for an average of 2.2 years) that greatly interfered with their activities of daily living and could not be controlled by oral doses of antispastic medications. They had marked rigidity (Table 2) (mean Ashworth score,⁴ 3.9 ± 1.0) and frequent severe muscle spasms (mean spasm-frequency score, 3.0 ± 1.1) in spite of doses of oral baclofen that averaged 97 mg per day (range, 40 to 200). Higher doses were not tolerated, because of drowsiness or confusion. The patients with multiple sclerosis had primarily spinal involvement with, at most, mild cerebellar or cognitive deficits. One patient (No. 3, Table 1) was able to walk short distances with crutches, but the rest were wheelchair-bound. The patients with spinal-cord trauma had injuries at the midcervical to midthoracic levels. One patient (No. 11, Table 1) was able to walk short distances with crutches, but the remainder were wheelchair-bound and had minimal volun-

tary motor control of the lower extremities. All study patients were functionally dependent, unable to dress or otherwise care for themselves. The spasms were painful in 10 patients and disrupted sleep in 9.

Before the blinded study was begun, each patient received one to three bolus doses of baclofen infused into the lumbar intrathecal space (25, 50, or 75 μ g; Lioresal, supplied by Ciba-Geigy U.S.) to determine the response to the medication, to observe any adverse effects, and to gauge the individual sensitivity to the drug. In all patients tested, spasticity was reduced for six to eight hours, and the patients chose to undergo implantation of a drug pump. During local anesthesia, a programmable pump (SynchroMed, Medtronic, Inc.) was placed in the left abdominal wall and connected to a catheter that passed subcutaneously to the lumbar subarachnoid space. Postoperative complications of this procedure were limited to moderately severe spinal headaches in two patients, which resolved in seven days. After the implantation, the pump was filled with either saline or baclofen (100 μ g per milliliter) and programmed for continuous infusion of a daily dose $1\frac{1}{2}$ to 2 times the effective bolus intrathecal dose (typically, 100 to 150 μ g per day).

Protocol Review

The protocol was reviewed and approved by the institutional review board of Rush-Presbyterian-St. Luke's Medical Center. It was submitted to and approved by the Food and Drug Administration for investigational new drug and device applications. Informed consent was obtained from each patient.

Study Design

This investigation was a balanced, randomized, double-blind, crossover study in which each patient underwent one trial of baclofen and another of saline placebo. The first drug given (whether saline or baclofen) was placed in the pump reservoir. On the third day of infusion the patient was tested (as described below), and then the pump was emptied and refilled with the second drug to be given (saline or baclofen). The patient was then retested on the sixth day. The active medication was continued in an open trial, and follow-up testing was performed at six-month intervals. The dosage of baclofen was adjusted at the monthly refills of the pump, to keep muscle tone normal and to reduce spasms to a level that did not interfere with activities of daily living.

Testing of Patients

Testing consisted of four assessments: (1) evaluation by a physician for muscle tone and for muscle spasms, according to the Ashworth and spasm-frequency scales (Table 2); (2) laboratory analysis of motor control by a motor physiologist, which typically included electromyographic recordings of the functioning of quadriceps, hamstring, gastrocnemius, and anterior tibial

From the Departments of Neurosurgery (R.D.P., S.M.S., M.L., J.S.K.), Physiology (G.G.), and Physical Medicine and Rehabilitation (B.P.), Rush-Presbyterian-St. Luke's Medical Center, Chicago, and the Department of Physical Education (D.C.), University of Illinois at Chicago, Chicago. Address reprint requests to Dr. Penn at the Department of Neurosurgery, Rush-Presbyterian-St. Luke's Medical Center, 1653 W. Congress Pk., Chicago, IL 60612.

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muscles during passive stretching of the ankle and knee joints, extensor plantar response (mass reflex), direct muscle (M) and reflex Hoffmann (H) responses of the calf muscle group, and if present, voluntary movement of the ankle and knee; (3) neurologic examination by a neurosurgeon of the tone, reflexes, induced spasms, and voluntary control in both lower extremities; and (4) assessment by the patient of the "on" and "off" periods of baclofen treatment.

All four assessments were made independently and were based on data recorded during both infusions. Blinding was stopped after all patients had completed the testing and had been evaluated. In analysis, the trial was rated "on-off" or "off-on." The Ashworth score was the sum of the scores for the hip (flexion and abduction), knee, and ankle joints on both sides, divided by 8, since in some patients the level of spasticity was not equal on both sides or at all three joints. The spasm score was the average of the scores for the two sides. The motor-laboratory testing was adapted to the degree of the patient's disability. For example, if a patient had no voluntary control, only passive stretching was done, and usually only the extremity most affected was tested. The physiologic recordings were then compared, and the period with the least electrophysiologic evidence of spasticity was considered the period of drug infusion.

RESULTS

The Ashworth scores and the spasm-frequency scores in the group with multiple sclerosis and the

Table 2. Definition of Ashworth and Spasm-Frequency Scores.

ASHWORTH SCORE		DEGREE OF MUSCLE TONE	
1		No increase in tone	
2		Slight increase in tone, giving a "catch" when affected part is moved in flexion or extension	
3		More marked increase in tone, but affected part easily flexed	
4		Considerable increase in tone; passive movement difficult	
5		Affected part rigid in flexion or extension	
SPASM SCORE		FREQUENCY OF SPASMS	
0		No spasms	
1		Mild spasms induced by stimulation	
2		Infrequent full spasms occurring less than once per hour	
3		Spasms occurring more than once per hour	
4		Spasms occurring more than 10 times per hour	

group with spinal-cord injury are shown in Figure 1. In each group and on each evaluation scale, the period of baclofen administration could be distinguished from that of saline infusion by the occurrence of an improvement in the scores ($P<0.01$

by Wilcoxon signed-rank test). In the entire study group the mean ($\pm$ SD) Ashworth score decreased by 2.8 points, from 4.0 ± 1.0 to 1.2 ± 0.4 ($P<0.0001$), and the spasm index by 2.9 points, from 3.3 ± 1.2 to 0.4 ± 0.8 ($P<0.0005$). The scores for each patient are shown in Figure 2. Baclofen infusion decreased the Ashworth and spasm scores in all patients, with the exception of the spasm scores in two with multiple sclerosis. One of these patients (Patient 9, Fig. 2) had no spasms before the trial, and the other (Patient 1, Fig. 2) had a similar score (3) before and during baclofen infusion. However, increasing the dosage after the double-blind trial eliminated spasms completely. The results of the Ashworth and spasm ratings, neurologic examinations, motor-control tests, and patient self-assessments agreed — i.e., all four independent assessments correctly identified the period of baclofen administration.

After the blinded crossover study, an open trial of intrathecal baclofen was conducted in all 20 patients, who have been followed for an average of 19 months (range, 10 to 33). Their Ashworth and spasm scores are shown in Figure 3 and Table 1. Their mean scores before the trial of intrathecal baclofen, when they were receiving the highest tolerated dose of oral baclofen, were 3.9 on

Table 1. Baclofen Dosages and Ashworth and Spasm-Frequency Scores during the Open Long-Term Trial of Baclofen.

PATIENT No.* — DIAGNOSIS†	AGE/SEX	MAXIMAL ORAL BACLOFEN	DATE PUMP IMPLANTED	INITIAL SCORES‡		FINAL SCORES§		INTRATHECAL BACLOFEN
				ASHWORTH	SPASM	ASHWORTH	SPASM	
		mg/day						µg/day
1 — MS	62/F	60	7/18/86	4.25	4	1	0	67.2
2 — MS	41/F	80	1/23/87	5	0	1	0	306
3 — MS	42/F	80	1/31/87	4.4	2	1	0	62
4 — MS	45/F	60	2/6/87	4.75	3	1	0	648
5 — SCI (T2)	43/M	160	3/6/87	5	4	1	0	476
6 — SCI (T9)	26/M	80	3/19/87	2	3	1.25	2	749
7 — SCI (T6-8)	37/F	120	4/30/87	5	3	1	0	680
8 — SCI (C7)	42/F	80	6/19/87	5	3	1	0	307
9 — SCI (C5)	51/M	80	7/10/87	2.25	3	1	1	748
10 — SCI (C5)	46/M	80	8/24/87	4	2	1	0	374
11 — SCI (T4-5)	50/M	200	9/4/87	2.4	2	1	0	234
12 — MS	41/M	100	10/9/87	2.8	4	1	1	201
13 — MS	43/M	60	10/23/87	2.9	4	1	0	86
14 — MS	49/F	40	11/13/87	4.4	4	1.5	0	184
15 — SCI (T6)	23/M	80	12/4/87	2.8	4	1	0	312
16 — SCI (C7)	29/M	160	1/28/88	4.4	4	1	0	288
17 — MS	59/M	80	1/29/88	4.1	4	1	0	219
18 — MS	31/F	65	2/19/88	3.5	3	1	1	276
19 — SCI (C7)	25/M	150	4/14/88	4.5	3.5	1	0	402
20 — MS	45/F	120	5/6/88	4	1	1	0	180

*Patient numbers do not correspond to patient numbers in Figure 2.

†MS denotes multiple sclerosis, and SCI spinal-cord injury (with cervical or thoracic level affected).

‡Scores before double-blind trial.

§Scores at last follow-up evaluation.

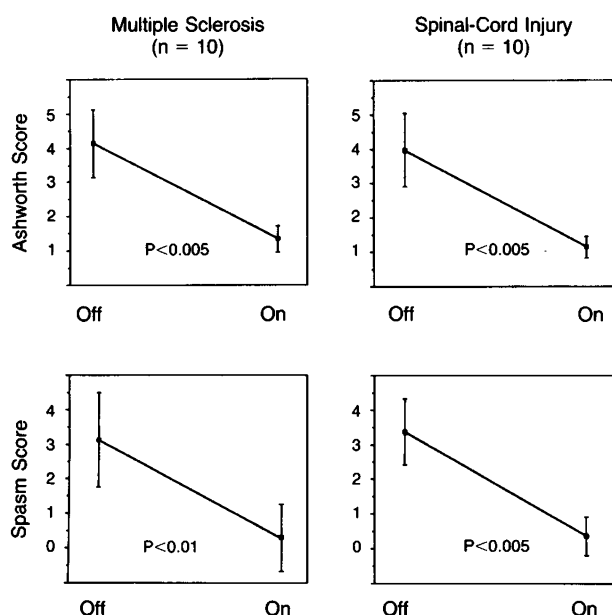


Figure 1. Ashworth and Spasm-Frequency Scores (Mean $\pm$ SD) with (On) and without (Off) Baclofen in the Patient Groups. Baclofen significantly decreased scores in both groups. P values were calculated with the Wilcoxon signed-rank test.

the Ashworth scale and 3.0 on the spasm-frequency scale. Their average scores at the last follow-up evaluation after intrathecal baclofen administration were 1.0 ± 0.1 and 0.3 ± 0.6 , respectively. Thus, the reductions in Ashworth and spasm scores observed in the blinded trial have been maintained. The sensitivity to intrathecal baclofen varied considerably from patient to patient. The dosages ranged from 62 to 749 μ g per day (mean, 340).

Several complications have occurred during the 26 months of follow-up: two catheters have been dislodged, one pump has failed at 4 months, and pain has occurred at the implantation site, requiring that the pump be moved medially, away from the iliac crest. These problems were corrected by operations performed under local anesthesia, and the patients continued to participate in the study. One patient with multiple sclerosis died of complications that followed aspiration pneumonia, six months after the pump was implanted. No side effects have occurred with the intrathecal baclofen, such as drowsiness or confusion. In patients who could use their extensor tone for walking or transferring from bed to chair, the dose had to be carefully adjusted so that tone was not reduced too much. In seven of the patients,

more baclofen was given at night to suppress spasms that interfered with sleep.

DISCUSSION

In this double-blind crossover study, all 20 patients with severe spinal spasticity responded to intrathecal infusion of baclofen into the lumbar area, with reductions in spasms or muscle tone or both, and all responded in an open trial. These patients had not responded adequately to oral medications. When they were receiving the highest dosage of oral baclofen that they could tolerate (mean, 97 mg per day), they still had considerably increased muscle tone, which made passive movement difficult and induced an average of 1 to 10 severe muscle spasms per hour. When intrathecal baclofen was administered as the sole treatment, the muscle tone was brought into the normal range and the spasms became clinically negligible. In previous studies of oral baclofen, the maximal change in the Ashworth score of any patient was only two grades.⁴ With intrathecal administration, the average change was an improvement of three grades. These results provided additional evidence that supported observations that intrathecal baclofen can markedly reduce severe spasms and increased muscle tone.^{2,3}

In the open trial conducted after double-blind testing, the reduction in spasticity could be maintained by continuous intrathecal administration of baclofen. The 20 patients have been followed for an

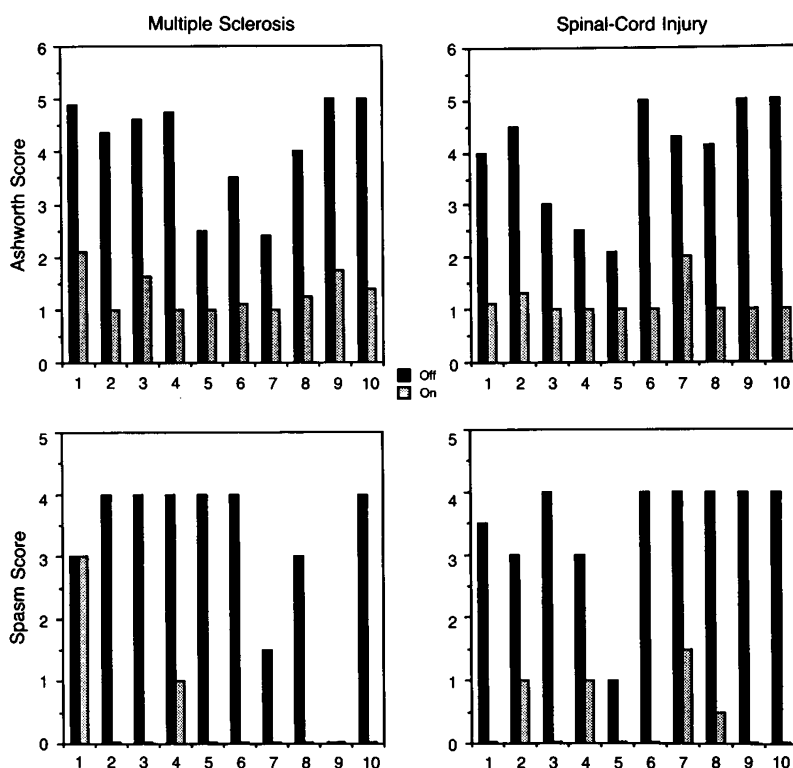


Figure 2. Ashworth and Spasm Scores with (Gray Bars) and without (Black Bars) Baclofen in Each Patient.

The absence of spasms (a score of 0) is represented by a thick line on the horizontal axis.

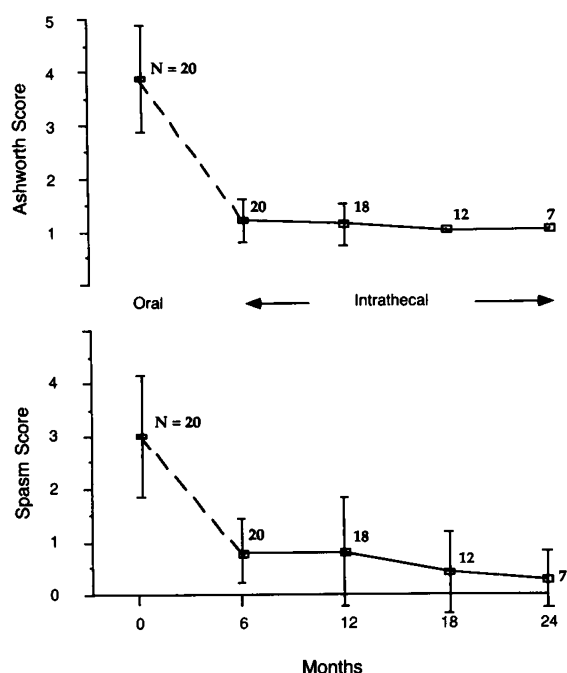


Figure 3. Ashworth and Spasm Scores (Mean $\pm$ SD) during the Open Trial of Baclofen and Long-Term Follow-up.

Averaged scores are shown for the period of maximal dosage of oral baclofen (0 months) and for the period of intrathecal baclofen. The numbers of patients decrease because the drug pumps were implanted at different times.

average of 19 months. In our first open trial of intrathecal baclofen, nine patients were followed for an average of 28 months, with similar reductions in their spasticity⁵; three of these patients have now been treated for over 4½ years. Thus, it appears from these two studies that the immediate effects of intrathecal baclofen on spasticity can be maintained over the long term. During maintenance treatment, many of the patients have had improvement of their activities of daily living, especially in self-care, transferring, sleeping, and urinary continence.⁶ The effect of baclofen on bladder function appears to be due to not only a reduction in the severity of spasms but also a decrease in the tone of the external sphincter and detrusor.⁷ Thus, intrathecal baclofen reduces both skeletal and visceral hyperactivity.

Why does intrathecal baclofen have such a profound effect on spasticity? One reason is that much higher cerebrospinal fluid levels of the drug are achieved by intrathecal administration. Knutsson et al.⁸ measured plasma and cerebrospinal fluid concentrations of baclofen in 11 patients taking the drug by mouth. The highest level of baclofen in the cerebrospinal fluid was 95 ng per milliliter, recorded in a patient taking 90 mg per day, but the level was below 12 ng per milliliter in most patients. In contrast, Müller et al.⁹ found that a continuous intrathecal infusion of 400 μ g of baclofen per day produced a cerebrospinal fluid level of 380 ng per milliliter; the plasma levels in these patients were less than 5 ng per milliliter. As com-

pared with the oral route, intrathecal administration produces at least four times higher cerebrospinal fluid levels with 1/100 the systemic dose, and 1/100 the plasma level. The second reason for the effectiveness of intrathecal administration is that infusion into the lumbar area concentrates the baclofen at specific receptor sites in the spinal cord. The GABA receptors to which baclofen binds (GABA_B receptor sites) are found in the superficial layers of the dorsal gray matter.¹⁰ Physiologic studies suggest that baclofen acts presynaptically to reduce motor-neuron excitability by inhibiting the release of excitatory transmitters.¹¹ The baclofen perfused into the lumbar cerebrospinal fluid has to diffuse only 1 to 2 mm into the tissue of the spinal cord to reach its site of action. By the time that the baclofen reaches the cervical and brain regions, it is present in much lower concentrations. The lumbar-to-brain gradient that is created by continuous intrathecal infusion minimizes the central nervous system side effects of baclofen, such as drowsiness and confusion, while maximizing the antispastic effects at the level of the spinal cord.

An implanted programmable drug pump is essential to this therapy. It allows continuous administration of the drug, precise adjustment of the dose, and variation of the dosage schedules, such as the circadian rhythm used to reduce nighttime spasms. Once implanted, the pump requires percutaneous refilling every three to six weeks. No self-care or home nursing assistance is required to maintain pump function. Dose adjustments are made with use of an external programmer linked by radio frequency to the pump. The pump's in-line filter (0.22 μ m) acts as a barrier to bacterial contamination of the cerebrospinal fluid. The use of systems without such protection has been frequently reported to lead to meningitis.¹² No infections occurred in our series of patients.

Although our study has provided evidence of the efficacy of baclofen, it does not completely answer the questions about the long-term effectiveness and risks of this treatment. More patients will have to be followed for a longer time. Two multicenter trials have been initiated, one in the United States and one in Europe, for this purpose.

There are many types of spasticity. We chose to study spinal spasticity, since oral baclofen is thought to be the most effective drug in patients with this type. Other types of spasticity, such as cerebral, hereditary, and neonatal (cerebral palsy), might also respond to such treatment; Müller and coworkers³ have presented several case reports of patients with these disorders who have benefited. However, the degree of response may well vary according to the underlying pathologic process, and each type of spasticity will have to be studied separately. Our study demonstrates that in at least one type of severe spasticity, lumbar intrathecal infusion of baclofen produces dramatic results.

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A RANDOMIZED, CONTROLLED TRIAL OF THEOPHYLLINE IN PATIENTS WITH SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

DANIÈLE MURCIANO, M.D., MARIE-HÉLÈNE AUCLAIR, M.D., RENÉ PARIENTE, M.D.,
AND MICHEL AUBIER, M.D.

Abstract To assess the effects of theophylline in chronic obstructive pulmonary disease, we conducted a randomized, placebo-controlled, double-blind, crossover trial in 60 patients with severe but stable disease. The patients (mean age, 61 years) were studied before and after two months of placebo and two months of treatment with a sustained-release preparation of theophylline (10 mg per kilogram of body weight per day), administered orally. The two treatments were administered in a random order and separated by an eight-day washout period.

After taking theophylline for two months (mean plasma concentration, 14.8 mg per liter), as compared with the two months of placebo, the patients had significant improvements in dyspnea, pulmonary gas exchange (partial pressure of arterial oxygen, 66 vs. 61 mm Hg [$P < 0.0001$]; partial pressure of arterial carbon dioxide, 44 vs. 49 mm Hg [$P < 0.0001$]), vital capacity (63 percent vs. 58 per-

cent of the predicted value [$P < 0.0001$]), and forced expiratory volume in one second (36 percent vs. 32 percent of the predicted value [$P < 0.0001$]), with no significant change in airway resistance or functional residual capacity. Minute ventilation increased by a mean of 18 percent ($P < 0.0001$) in the patients taking theophylline because of increased tidal volume, with no change in respiratory frequency. The respiratory-muscle performance of the patients taking theophylline improved by approximately 29 percent ($P < 0.0001$), as indicated by a decline in the ratio of inspiratory pleural pressure during quiet breathing to maximal pleural pressure.

We conclude that theophylline improves respiratory function and dyspnea in patients with severe chronic obstructive pulmonary disease and that these improvements are probably due to better respiratory-muscle performance. (*N Engl J Med* 1989; 320:1521-5.)

METHODS

Sixty patients with chronic obstructive pulmonary disease (mean age $\pm$ SD, 61 $\pm$ 8 years) were studied in a clinically stable condition. Fifty-two were men; 15 were smokers, 43 former smokers, and 2 nonsmokers. In each patient, the cause of the disease was chronic bronchitis. The mean values obtained at base line for pulmonary-function indexes and arterial blood gases are listed in Tables 1 and 2. All the subjects gave their informed consent, and the study protocol was approved by our ethical committee.

All measurements were made with the subjects in the sitting position. In each subject, several flow-pressure curves and absolute lung-volume measurements were made with a constant-pressure plethysmograph, to determine airway resistance and functional residual capacity. Flow-volume curves were also obtained with a Hewlett-Packard spirometer in order to determine forced expiratory volume in one second (FEV₁), forced vital capacity, and maximal midexpiratory flow rate. The measurements were repeated 15 minutes after the patients inhaled albuterol (400 μ g), to establish that all patients had a fixed airway obstruction (defined as a change in FEV₁ of less than 15 percent after the administration of albuterol).

The subjects breathed through a mouthpiece connected to a No. 3 Fleisch pneumotachygraph. The inspiratory and expiratory lines were separated by a Hans-Rudolph one-way valve. The dead space of the circuit was 40 ml. The resistance of the inspiratory and expiratory lines was 1.4 and 1.8 cm of water per liter per second, respectively, at a flow of 1 liter per second. Volume was measured

It has been shown that theophylline, a compound of methylxanthine, has a positive inotropic effect on diaphragmatic strength and reduces muscle fatigue in vitro,¹ as well as in animals.²⁻⁴ Several studies have shown that theophylline has a beneficial effect on diaphragmatic function in normal subjects^{5,6} and patients with severe chronic obstructive pulmonary disease.⁷ In the latter, however, the effect of theophylline on the diaphragm was relatively small, and any resulting clinical benefit remained questionable.⁷ In patients with chronic obstructive pulmonary disease, some studies showed improvement in dyspnea and exercise capacity as a result of theophylline treatment,⁸⁻¹⁰ whereas other did not.¹¹⁻¹³

We undertook to evaluate the benefits of theophylline on the degree of dyspnea, on arterial blood gases, and on respiratory-muscle performance in a large group of patients with severe chronic obstructive pulmonary disease.

From the Clinique Pneumologique, INSERM U 226, Hôpital Beaujon, 100 Blvd. du Général Leclerc, 92110 Clichy, France, where reprint requests should be addressed to Dr. Aubier.