ACTION OF "TESSALON" ON THE DYSPNOEA OF PATIENTS WITH CHRONIC LUNG DISEASE

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Michelson and Schiller (1957) investigated the effect of intravenously administered "tessalon"—a polyethylene glycol derivative of *p*-aminobenzoic acid—on the lung volume and ventilation in patients with obstructive pulmonary disease. They found that 2.5–10 mg. of tessalon produced symptomatic relief with an increase in both depth and volume of respiration in most instances and an increase in the minute-volume up to twofold. There was no significant change in lung volumes or expiratory flow rate. Their favourable report suggested that the drug should be tried in patients in whom chronic lung disease had produced a disabling grade of dyspnoea.

The investigation was divided into two parts: the acute effect of intravenous administration and the prolonged action of oral therapy using a double-blind clinical trial.

"Acute" Trial

Method

The effect of intravenous tessalon upon the minute-volume, intrathoracic pressure, air flow, and respiratory rate, pulse rate, and blood pressure was measured. All the subjects were volunteers. The nature of the experiment was explained to them, but no indication of the possible effects of the drug was given apart from the statement that it had been recommended for use in patients with chest disease.

The subject sat in a comfortable chair, connected by a soft rubber mouthpiece to a Lilly pneumotachograph. This was connected to a respiratory anemometer which

was designed to read air outflow in litres. A "polythene" tube attached to a thin rubber balloon was passed through one nostril into the lower third of the oesophagus and was held in place by a nose-clip, which also prevented any air flow through the nose. Changes in intrathoracic pressure and rate of air flow through the pneumotachograph were continually recorded on a Cambridge multi-channel recorder. Normal saline was slowly infused through an intravenous needle attached to a blood-transfusion giving set introduced into a vein in the right arm. Around the left arm was placed a sphygmomanometer cuff, and blood pressure was recorded using the criteria of the Cardiac Society (1939).

The volume of air expired was recorded at half-minute intervals throughout the investigation. When steady readings were being obtained, the tracings of the flow rate and pressure were started. Tessalon was injected into the rubber tubing of the giving set and washed into the circulation by increasing the rate of the saline transfusion. No indication was given to the subject that the administration was taking place. At intervals before and after injecting tessalon, measurements of the pulse rate and blood pressure were recorded and all readings and tracings were continued until five minutes after the last dose was given.

Tessalon, 5 or 10 mg., was administered at intervals of two to five minutes. The total amounts ranged from 5 to 20 mg. (Table I). After the final injection the patient was asked if he had noticed any symptoms.

Results

Observations were made on four normal people and seven patients with chronic lung disease.

Minute-volume, respiratory rate, pulse rate, blood pressure, air flow, and intrathoracic pressure showed no significant change during periods of up to 21 minutes from the initial injection of tessalon in patients at rest or exercising on a bicycle ergometer (Table I). One patient (No. 10) suffering from spasmodic asthma said that her breathing felt easier at the end of the investigation and her desire to cough had disappeared. The only adverse effect was a severe headache lasting 12 hours reported by a patient with diffuse interstitial pulmonary fibrosis (No. 9). The effect of increasing the dosage to a maximum value of 45 mg. was tested on another patient not included in the above investigation. The respiratory rate, blood pressure, and pulse rate did not change, and the patient experienced no symptoms.

TABLE I.—Effect of Intravenous Injection of Tessalon in 11 Subjects. Statistical Analysis Shows that the Minute-volume after Injection did not Differ Significantly from that before Injection ($P=0.5$)

No.	Sex and Age	Diagnosis	Dose (mg.) and Divided Doses of Tessalon	Mean Readings Three Minutes Before First Injection				Mean Readings Following Intravenous Tessalon			Mean Reading of Minute-volume (l./min.) During Three-minute Intervals Following Tessalon							
				B.P.	P.R.	R.R.	l./min. M.V.	B.P.	P.R.	R.R.	1-3	4-6	7-9	10-12	13-15	16-18	19-21	
1	M 28	Normal	5	160/95	80	22.1	17.8	150/95	78	21.4	18.4	16.6	16.5	16.4				
2	M 25	"	10	170/80	120	21	18.2	170/80	120	23	16.5	17.2	16.7	17.0				
3	M 38	"	15 (5, 5, 5)	140/90	76	17.5	15.5	140/95	84	17.8	17.3	16.1	17.6	14.9				
4	M 51	Chronic bronchitis and emphysema	10	140/90	96	16	14.3	145/95	94	16	13.3	14.3	13.8					
5	M 37	Cor pulmonale ..	10	125/80	120	20	15.1	120/80	120	21	16.8	17.4						
6	M 22	Normal	10		100	19.5	19.9		100	19.2	21.9	20.4	23.0					
7	M 54	Chronic bronchitis and emphysema	15 (5, 5, 5)	150/80	96	15	16.4	160/80	92	16.6	18.1	21.0	18.3	18.4	22.6			
8	M 58	"	15 (5, 5, 5)	220/110	120	26	25.4	195/90	128	27.4	27.8	26.3	26.6	27.0				
9	M 56	Interstitial pulmonary fibrosis	15 (10, 5)	150/80	76	15	17.8	150/90	74	16.8	18.6	18.6	18.3	22.1				
10	F 29	Spasmodic asthma	20 (5, 5, 5, 5)	120/70	100	22	15.0	120/70	100	22	16.6	17.7	16.0	14.0	15.2	18.2	17.2	
11	F 51	Chronic bronchitis and emphysema	20 (10, 5, 5)	120/80	88	21	13.9	125/70	86	22.6	16.9	16.2	16.7	16.6	16.8	18.9		

Maximum Breathing Capacity.—Two further patients suffering from diffuse interstitial pulmonary fibrosis were given a control injection intravenously followed five minutes later by an injection of 5 mg. of tessalon. The maximum breathing capacity and respiratory rates were measured at intervals of one, three, and five minutes after each injection, using a spirometer. No significant change was found after tessalon was injected.

Clinical Trial

The tessalon used in this trial was prepared in 100-mg. capsules. Identical placebo capsules were also supplied by the manufacturers. Each patient acted as his own control. Either the placebo or tessalon capsules were given for one week in a random order, and the allocation was the responsibility of the hospital pharmacist. At no time during the investigation were the medical staff told whether the patient was receiving tessalon or the placebo. At the end of the trial every patient had had one week on tessalon and one week on the control capsules.

Two groups of out-patients were investigated. Tessalon, 100 mg. t.d.s., was tried on 20 patients (14 male, 6 female) who were dyspnoeic on effort as a result of chronic lung disease. At the beginning of the trial each subject was examined and the respiratory system was assessed clinically. The forced vital capacity and the volume expired in the first 0.75 second were measured, using a Gaensler spirometer: the expired volume of air in three consecutive minutes was determined with a respiratory anemometer and the respiratory rate was counted. A week's supply of capsules, in addition to any treatment he might already be receiving, was given to the patient. The following week the clinical examination and respiratory function tests were repeated and a further supply of capsules was dispensed. A final examination, and measurements, were made at the end of the fortnight. All the clinical examinations were made by the same observer.

In six further patients (four male, two female) suffering from diffuse interstitial pulmonary fibrosis the effect of the therapy on the ability to exercise was observed by stepping 20 times on and off a 9-in. (23-cm.) step. Each patient was asked to report any change in symptoms.

Results

Of the 26 patients in the trial, 3 were excluded from the analysis. Of these, a man with chronic bronchitis and emphysema stopped taking the capsules after four days because of increasing dyspnoea and cough. The capsules were the placebo. A second man was admitted to hospital on the 13th day with an exacerbation of his chronic bronchitis, and a third patient, a female, had to be admitted to the ward at the final examination with a functional laryngeal stridor, so that it was impossible to complete the respiratory function studies.

Of the 23 patients finally included in the trial, 14 were given tessalon in the first week and placebo capsules during the second week: the remaining nine received the capsules in the reverse order.

Respiratory Function Tests.—Although slight changes in the values of the minute-volume, respiratory rate, forced vital capacity, and timed vital capacity (0.75 second) were observed following a course of tessalon, similar changes were produced by the placebo, and none of them was statistically significant (*P* varying from 0.5 to 0.8).

The exercise tolerance was not affected in the six patients in whom it was measured.

Clinical Assessment.—Table II shows the clinical state in 16 subjects examined at all three attendances. No change was observed in eight of the patients throughout

TABLE II.—*Effect of Oral Tessalon and Placebo on the Clinical Signs in the Lungs in 16 Patients with Chronic Lung Disease*

No.	Sex	1st Attendance	2nd Attendance	3rd Attendance
			After Tessalon	After Placebo
2	M	Forced expiratory rhonchi	Chest clear	Chest clear
5	F	Generalized rhonchi	" "	Generalized rhonchi
6	F	"	Generalized rhonchi	"
7	F	Chest clear	High-pitched sibili	Chest clear
10	M	High-pitched sibili	Chest clear	High-pitched sibili
11	M	Expiratory rhonchi	Expiratory rhonchi	Expiratory rhonchi
12	M	"	Chest clear	Generalized rhonchi
16	M	Chest clear	Expiratory rhonchi	Forced expiratory sibili
18	F	Forced expiratory sibili	Forced expiratory sibili	" "
19	M	Chest clear	Chest clear	Chest clear
			After Placebo	After Tessalon
3	M	Generalized rhonchi	Generalized rhonchi	High-pitched sibili
4	F	"	"	Generalized rhonchi
8	M	Chest clear	Chest clear	Chest clear
13	M	Generalized rhonchi	Generalized rhonchi	Generalized rhonchi
14	M	Scattered rhonchi	Scattered rhonchi	Forced expiratory rhonchi
15	M	Generalized rhonchi	Generalized rhonchi	Generalized rhonchi

the trial. In six the administration of tessalon was followed by a reduction in adventitious sounds (Nos. 2, 3, 5, 10, 12, and 14). In two patients an increase in adventitious sounds was observed after a week on tessalon therapy (Nos. 7 and 16). These numbers are not large enough for valid statistical analysis.

Subjective Changes.—All 23 patients in the trial were asked at the second and third visits if they had noticed any changes in their symptoms and had had any adverse effects from the capsules. Improvement in symptoms was reported by seven. A gradual lessening in symptoms throughout the trial was noticed by three of these, without any apparent relation to the tessalon. The remaining four all stated there was some improvement at one visit but not at the other. Two were found to have had relief from tessalon and two from the placebo. The chest condition was unchanged at both attendances in 16 patients. Six of these complained of adverse effects, three developed headaches while on tessalon, and three developed symptoms while taking the placebo. At one attendance two patients reported an increased feeling of well-being. They had both had a week of placebo capsules.

Discussion

Animal experiments have shown that tessalon will selectively depress the peripheral nerve endings in the lung concerned with the regulation of normal respiration (Bein and Bucher, 1957). The observations of Michelson and Schiller (1957), however, suggested that the symptomatic relief obtained in asthmatic patients did not depend on this mechanism. They reported that tessalon induced a sensation of ease of breathing with increased minute-ventilation. We have found no change in either symptoms or objective measurements of lung function in patients with chronic lung disease after intravenous tessalon, or after oral treatment for a week. In the double-blind trial both adverse and favourable symptoms were reported equally with the placebo and the drug, but headache was noted only in patients taking

tessalon. A severe headache also occurred in a patient given intravenous therapy. Naegeli (1956) has also found this symptom in patients treated with tessalon.

We are unable to confirm the antitussive action of tessalon that has been reported (Giuliano and Rossa, 1955; Bucher, 1956; Herzog, 1956; Naegeli, 1956; Neumann, 1956; Simon, 1957; Shane *et al.*, 1957). One patient noticed considerable relief from coughing while taking both the placebo and the drug, and another lost the desire to cough after intravenous administration of tessalon. All our patients, however, had a severe grade of dyspnoea with a relatively minor degree of cough.

Summary

Tessalon—a polyethylene glycol derivative of *p*-aminobenzoic acid—has been given intravenously in doses up to 45 mg. without causing symptoms or having any measurable effect on minute-volume, air flow, intrathoracic pressure, maximum breathing capacity, respiratory rate, pulse rate, and blood pressure in four normal subjects and 10 patients with chronic lung disease.

A double-blind trial of tessalon in 23 patients with chronic pulmonary disease did not have any beneficial effect.

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DOUBLE CARDIAC ARREST WITH SURVIVAL

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During tracheobronchial manipulations cardiac arrest is a well-known complication. Such arrest may occur at separate operations on the same patient (Lampson, 1951), repeatedly at one operation (Knowles, 1953), or during angiocardiology (Holmdahl and Gyllenswärd, 1954). If during a non-urgent operation arrest occurs, it is probably safer to terminate the operation as soon as possible after the heart is restarted. However, if the operation is urgent, the possibility of further cardiac

impairment during or following a necessary operation, once the heart has been restarted, must be weighed against the functional impairment resulting if the operation is not completed. This problem is illustrated by the following case report.

Case Report

A man aged 24 years was involved in a factory explosion and suffered 10% third-degree burns of both hands, face, and left thigh.

On three occasions (March 12, 14, and 20, 1957) he was anaesthetized and orally intubated under "narkotal" (an ultra-short-acting barbiturate), suxamethonium, pethidine, nitrous oxide, and oxygen, for cleaning and dressing of the burns, without untoward results.

March 21.—He was anaesthetized by one of us (B. L. F.) for the first time. It was noticed that he suffered very great pain in his hands and was in a state of extreme anxiety, in spite of premedication with morphine, 10 mg., and scopolamine, 0.3 mg. While a vein was being found for intravenous injection, he was moaning, restless, and terrified of the repeated attempts at venepuncture. Owing to the rather extensive third-degree burn surface in this case no cut down of the vein had been made. Anaesthesia was induced with narkotal, 300 mg., and suxamethonium, 100 mg. A No. 10 Magill cuffed tube was inserted orally and connected to the anaesthetic machine, the patient being ventilated with nitrous oxide and oxygen. At this stage he rapidly turned white and the pupils became widely dilated. Spontaneous respiration had not returned after the suxamethonium. His pulse could not be felt and cardiac sounds were not heard. 100% oxygen was administered, and within two minutes of detection of cardiac arrest one of us (B. O. N.) made a left submammary intercostal incision, without bleeding from the skin vessels, and a hand was placed around the pericardium. Immediately before massage, spontaneous heart beats returned, the skin wound began spurting, the colour became pink, and the pupil returned to normal size. Blood pressure and pulse became stabilized at 110 and 80 respectively. The operation was postponed to allow the patient to awaken, which he did on extubation. Apart from even greater anxiety after being told the reason for his submammary wound, cerebral function seemed normal.

March 26.—A further excision of granulation tissue of the burnt hands was performed. Premedication was with promethazine, 50 mg., pethidine, 100 mg., and atropine, 0.5 mg. The patient was still very frightened. Induction was with nitrous oxide and oxygen, venepuncture being avoided until he was asleep. Narkotal, 300 mg., pethidine, 50 mg., and suxamethonium, 200 mg., in intermittent doses were administered, but without intubation, and the operation proceeded without incident. During the operation an infusion was set up in the foot and continued until the following day. In this way a venepuncture was not necessary while the patient was awake, and the cause for some of his fears would be removed.

March 27.—Because of the second/third-degree burns in his face and also because of his state of anxiety it was thought that the best anaesthesia would be by intubation. He was premedicated with chlorpromazine, 25 mg., morphine, 10 mg., and scopolamine, 0.3 mg. Induction was by chlorpromazine, 10 mg., pethidine, 50 mg., narkotal, 300 mg., suxamethonium, 50 mg., and local analgesic spray to the larynx and trachea. A No. 10 Magill cuffed tube was passed and maintenance was with nitrous oxide and oxygen. At this stage the pulse was 80 and blood pressure 110, the skin colour was pink, and the pupils were of normal size. Very rapidly over the next minute the pulse became increasingly faster until it was uncountable and then impalpable, the blood pressure dropped to zero, the skin became pale, and the pupils became widely dilated. No heart sounds were heard and the previous submammary incision was reopened. The heart was in asystole and cardiac massage was applied. After about 10 compressions