EFFECTS OF METHYLPENTYNOL IN NOCTURNAL ATTACKS OF BRONCHIAL ASTHMA

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In chronic bronchial asthma the symptoms often occur at night-time. Some patients have an attack as soon as they retire to bed; some wake up wheezing and fighting for breath after one or two hours of sleep; and others have an attack early in the morning, making them get up. The symptoms may last a few minutes or a few hours. In any case, the disturbance of sleep brings anxiety to the patient and to his family. Loss of sleep and physical and mental exhaustion render the patient unfit for work or school next morning. Fear of another attack in the approaching night may develop a conditioning reflex, and thus the vicious circle is established.

Hypnotics in Bronchial Asthma

The purpose of hypnotics is to allay nervousness and to induce a natural sleep. Hypnotics in bronchial asthma are very important therapeutic measures, but they should be employed carefully, as some of them may depress the respiratory centre and cough reflex.

Morphine and its derivatives have been condemned by allergists because they depress the respiratory centre. The patient develops anoxia and passes into coma. Bronchial secretions are not coughed up and the patient dies of asphyxia. Recently Mitchell and De Jong (1954) showed that morphine potentiates the effect of acetylcholine on bronchial muscle by inhibiting cholinesterase, and therefore it has a second adverse effect in bronchial asthma.

The Barbiturates.—The patient suffering from nocturnal attacks of asthma due to nervous or psychic causes needs a heavy dose of a barbiturate to induce him to sleep. Such a dose will make him drowsy the next morning. Although there are many barbiturates available for therapeutic purposes, certain dangers are associated with them.

Side-effects of Barbiturates.—It is possible to produce chronic barbiturate intoxication by the frequent taking of these drugs. Mental impairment with changes in the daily habits of the patient, depression, forgetfulness, impaired judgment, carelessness, slow responses, irresponsibility—all of these have been noted by Morgan (1953). He pointed out that these side-effects may mimic organic disease of the central nervous system, such as neoplasm of frontal lobes, or senile dementia. Addiction is common, especially to those with medium action. Allergic manifestations, such as skin rashes, urticaria, or asthma, may develop after taking barbiturates.

Antihistamine Drugs produce a soporific effect, but this wears off after taking them for a few days. They also cause unpleasant side-effects—dryness of the mouth, drowsiness on waking, disorientation, ataxia, headaches.

Pharmacological Action of Methylpentynol

Allen and Krongold (1951) and Margolin *et al.* (1951) published their reports on the action of a new hypnotic which has no barbituric acid in its chemical formula.

Respiratory System.—Methylpentynol (3-methylpentynol-3) does not depress the respiratory centre and has no effect on respiration (Margolin *et al.*, 1951; Allen and Krongold, 1951). It does not exert antispasmodic action (Margolin *et al.*, 1951).

Cardiovascular System and Blood.—Methylpentynol does not alter the pulse rate or blood pressure, and no changes

are noted in blood morphology or chemistry after its prolonged administration (Margolin *et al.*, 1951; Allen and Krongold, 1951).

Cerebral Activity.—Tükel and Tükel (1952) studied E.E.G. patterns in children induced to sleep by this drug, and found them to be identical with those of normal physiological sleep. Patients can be easily awakened by sensory stimuli such as pain or noise.

Dosage.—The usual dose is 250 to 500 mg. by mouth, and for children from 1 to 12 years the average effective dose is 150 mg.

Hypnotic Effect.—Hirsh and Orsinger (1952) treated 276 patients with 100 to 500 mg. of methylpentynol and found that 93% of them fell asleep within one hour, and 92% slept for more than five hours.

Side-effects.—No side-effects were observed to follow methylpentynol administration (Allen and Krongold, 1951; Margolin *et al.*, 1951; Tükel and Tükel, 1952).

Contraindications.—There are no contraindications to the administration of this drug. Patients with hepatic, renal, pulmonary, and cardiac disease can take it without harm (Allen and Krongold, 1951; Margolin *et al.*, 1951).

Methylpentynol has been used in patients suffering from various diseases, and as premedication for general and dental anaesthesia. I was not aware if it had been used in chronic bronchial asthma, and therefore decided to carry out a controlled clinical trial in patients suffering from bronchial asthma whose sleep was interrupted by attacks of asthma.

Methods of Observation

Patients suffering from bronchial asthma who complained of frequent nocturnal attacks were selected for the trial. All 15 patients (eight males and seven females) have been fully investigated and were attending the allergy clinic for treatment. Their ages varied from 10 to 73 years.

A control group of 15 patients received inert capsules identical in shape and colour with those of methylpentynol. This series included seven males and eight females. Their ages varied from 12 to 63 years.

The treatment lasted from 6 to 18 months.

Methods of Treatment.—All patients were issued with hospital prescriptions for 250-mg. capsules of methyl-

TABLE I.—Patients Treated with Methylpentynol

Case	Sex	Age	Occupation	Duration of Symptoms	Remarks
1	M	53	Labourer	7 years	Wakes up every night between 2 and 3 a.m.
2	F	36	Housewife	19 "	Cannot go to sleep because of wheezing
3	M	63	Shipyard foreman	33 "	Wakes up at 4 a.m. coughing and wheezing
4	M	73	Retired commercial traveller	58 "	Wakes up every night between 1 and 2 a.m.
5	F	43	Housewife	23 "	Cannot go to sleep because of wheezing
6	M	56	Labourer	6 "	Wakes up coughing and wheezing at 4 a.m.
7	M	43	"	7 "	Cannot go to sleep because of coughing
8	M	63	"	4 "	Cannot go to sleep because of coughing and wheezing
9	M	14	Schoolboy	8 "	Cannot go to sleep because afraid of asthmatic attacks
10	M	61	Insurance agent	15 "	Cannot go to sleep because of coughing and wheezing
11	F	45	Housewife	4 "	Wakes up between 1 and 2 a.m.
12	F	31	"	5 "	Cannot go to sleep because of coughing and wheezing
13	F	38	"	3 "	Is afraid to go off to sleep because of asthmatic attacks
14	F	26	"	4 "	Wakes up every night between 2 and 3 a.m. coughing and wheezing
15	F	10	Schoolgirl	10 "	Wakes up every night between 1 and 2 a.m. wheezing

pentynol and were instructed to take one before retiring to bed. Two lists were kept at the hospital dispensary—one list with the names of the patients receiving the real drug and the second list with the names of the control series. I did not know which of the patients were receiving the real drug and which were taking the placebo. As the patients were coming every week to the clinic I questioned them about their sleep and the effects of the drug. If necessary the dose was increased. At the end of the trial I prepared a list of the 30 patients, and the hypnotic effect of the drug was estimated for each patient and any remarks made by the patients were noted. Then the chief pharmacist revealed the names of those who were taking the real drug or the placebo. For the sake of clarity I present my clinical observations in Tables I and II.

TABLE II.—Patients Treated with Placebo

Case	Sex	Age	Occupation	Duration of Symptoms	Remarks
A	M	49	Baker	30 years	Cannot go to sleep because of wheezing
B	F	63	Housewife	28 "	" " " " " " " "
C	F	19	Factory worker	10 "	Wakes up every night between 2 and 3 a.m. wheezing
D	F	52	Housewife	8 "	Is afraid to go to sleep because of asthmatic attacks
E	F	54	"	24 "	Wakes up between 2 and 3 a.m. wheezing
F	M	23	Labourer	4 "	Wakes up between 2 and 3 a.m. coughing and wheezing
G	F	43	Hospital ward maid	24 "	Wakes up between 1 and 2 a.m. wheezing
H	M	30	Labourer	7 "	Wakes up between 3 and 5 a.m. coughing and wheezing
I	F	38	Cook	31 "	Wakes up between 1 and 2 a.m. wheezing
J	F	33	Shop assistant	10 "	Wakes up between 2 and 3 a.m. wheezing
K	M	62	Labourer	7 "	Wakes up 3 or 4 times at night wheezing and coughing
L	F	17	Paper-mill worker	8 "	Wakes up 2 or 3 times at night wheezing
M	M	12	Schoolboy	10 "	Wakes up between 1 and 2 a.m. wheezing
N	F	22	Factory worker	18 "	Wakes up between 2 and 3 a.m. coughing and wheezing
O	M	52	Labourer	10 "	Wakes up 3 or 4 times at night coughing and wheezing

Results of Treatment

Methylpentynol Series.—Table III shows the results of treatment with methylpentynol. One patient (Case 4) slept only occasionally well on 500 mg. of the drug. On closer inquiry it was found that his wife was ill and the worry contributed a great deal to his attacks of asthma. Perhaps

TABLE III.—Results of Treatment—Methylpentynol Series

Case	Dose Required	Hypnotic Effect in Hours	Side-effects	Remarks
1	750 mg.	7-8	Nil	Sleeps well and feels fresh in the morning
2	250 "	6-7	"	Goes to sleep easily and feels stronger in the morning
3	500 "	8	"	Sleeps well and feels fresh in the morning
4	500 "	4-8	"	Sometimes he sleeps well; at times no effect
5	500 "	7	"	Goes to sleep easily and feels better in the morning
6	500 "	6-8	"	Sleeps well and feels fresh in the morning
7	250 "	8	"	Goes to sleep easily
8	500 "	Nil	"	Died suddenly (coronary thrombosis)
9	250 "	8	"	Goes to sleep easily within 15 minutes of taking the drug
10	500 "	6-8	"	Goes to sleep easily
11	250 "	7	"	Sleeps well
12	250 "	6-8	"	Goes to sleep easily
13	250 "	7	"	" " " " " "
14	250 "	6	"	Sleeps well now
15	250 "	8	"	Sleeps well now and does not scratch the eczematous lesions

if the dose was increased to 750 mg. he would have a regular good sleep. One patient (Case 8) died suddenly during the trial. The post-mortem examination revealed coronary thrombosis. The hypnotic effect of the drug was not estimated for this patient. The rest of the patients claimed that methylpentynol was of great help in promoting a good sleep and abolishing or reducing their nocturnal attacks of asthma. They were not afraid to go off to sleep, and were feeling fresh and strong in the morning and able to face their daily work. One patient (Case 3), whose frequent attacks of asthma at night-time kept him off work the following day, has lost only two days off work in the past 18 months while taking methylpentynol. A schoolboy (Case 9) used to be absent from school several days every term before treatment with methylpentynol, and has lost only 10 days in 12 months while taking the drug. A schoolgirl (Case 15) is suffering from Besnier's prurigo. Frequent attacks of asthma and intense itching of the eczematous lesions kept her awake through the night and made her too exhausted to attend school the next morning. She sleeps well now for eight hours on 250 mg. of methylpentynol, and does not scratch her skin at night-time.

Placebo Series.—Table IV illustrates the results of treatment with placebo. Only one patient (Case B) slept well.

TABLE IV.—Results of Treatment—Placebo Series

Case	Dose Given	Hypnotic Effect	Side-effects	Remarks
A	750 mg.	Nil	Nil	No difference in sleep
B	250 "	6-8 hours	"	Patient cannot sleep without the "drug"
C	500 "	Nil	"	No difference in sleep
D	500 "	"	"	No effect
E	500 "	"	"	"
F	500 "	"	"	Loses "a few days off work every month because of night attacks of asthma
G	500 "	"	"	No difference in sleep
H	500 "	"	"	No effect
I	750 "	"	"	"
J	750 "	"	"	"
K	500 "	"	"	"
L	500 "	"	"	Lost 2 weeks off work in the past 4 months because of night attacks of asthma
M	250 "	"	"	No difference in sleep
N	250 "	"	"	"
O	500 "	"	"	No effect " "

The rest of the patients did not show any improvement in sleep or reduction of nocturnal attacks of asthma while taking placebo capsules.

Discussion

The ideal treatment of bronchial asthma and its nocturnal attacks would be the removal of the various factors which bring on the attacks. This is not always possible as in a case of intrinsic asthma with strong psychological elements. In patients undergoing desensitization to inhalants and having disturbing nocturnal attacks of asthma, a good hypnotic will contribute greatly to successful treatment. Many asthmatic patients take their troubles to bed with them. A mild but rapid sedation eliminates the worry and anxiety, and a better sleep is possible until morning. In long-standing asthma complicated by chronic bronchitis and emphysema, sedation is very important and a difficult problem. In some old asthmatic patients both chronic bronchitis and ischaemic heart disease contribute to the symptoms of asthma. The choice of a hypnotic may present difficulty. Methylpentynol is very useful in such cases because it does not depress the respiratory centre. Methylpentynol is safe and well tolerated by children. It is dangerous to combine methylpentynol with barbiturates, and a death was recorded recently from such combined administration (*Lancet*, 1954).

The necessity for a control trial is well illustrated by Case B. This patient slept well on a 250-mg. capsule of placebo. It is widely recognized that some asthmatic patients improve on inert tablets or injections. The problem of clinical experiments and their control groups was recently discussed by

Reid (1954). He pointed out that some of the control groups are not properly selected and some of the experiments would be unethical to carry out. This investigation was simple and free from dangers. Although the number of patients was small—only 15 patients in each group—I found out that methylpentynol is a useful adjunct in the management of asthmatic patients.

Summary

Difficulties in choosing the right hypnotic for asthmatic patients are emphasized with special reference to morphine.

A brief description of pharmacological action of methylpentynol is given.

A clinical trial was carried out with methylpentynol on 15 patients suffering from bronchial asthma whose sleep was disturbed by asthmatic attacks. A similar group of 15 patients received a placebo. The results of treatment are presented.

The value of methylpentynol as an adjunct in the management of bronchial asthma is discussed.

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SICKLING PHENOMENON IN NORTHERN GREECE

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Recent investigations for sickling in Greece showed that the sickle-cell trait is not a rare finding. After the investigation by Makrycostas¹ of the first sickle-cell anaemia cases in people originating from an isolated village of the Sparta district, several cases of sickle-cell anaemia and trait were reported, affecting people from different districts of Greece.²⁻¹⁵ Choremis *et al.*^{10, 11} found a focus of sickling in Thebes, close to Athens; the frequency of the sickling phenomenon in this area is not known.

The Investigation

A few cases of sickle-cell anaemia in people originating from the Chalkidiki district of Northern Greece were reported by different writers.¹²⁻¹⁸ Several cases of sickle-cell anaemia admitted to our clinic from Chalkidiki gave us the opportunity for a wide and systematic investigation of the sickling phenomenon in Northern Greece, by examination of people of different origin living in this area.

The sodium bisulphite method was used because of its sure and rapid results and its simplicity (read after 30 minutes). We have several times repeated most of our exam-

inations, so that the findings can be looked upon as reliable. We examined mostly schoolchildren aged from 6 to 12 years, because we thought that they best represented a large number of the families of the area under investigation.

A total of 7,063 subjects were examined. Among these were 5,008 indigenous people from families who had lived in the villages for several centuries without mating with strangers, and 2,055 people of varied origin (254 natives speaking a Slav dialect, 208 refugees from Eastern Roumelia, 380 refugees from Eastern Thrace, 578 refugees from the Russo-Turkish border, 180 refugees from the Smyrna area, 163 Turks of Western Thrace, and 292 gypsies). In these 2,055 people the test was definitely negative except for two positive cases whose parents originated from Smyrna (Asia Minor).

A total of 37 villages of indigenous people were covered, in 22 of which some cases of sickling were found. In these 22 villages 3,583 persons were tested and 537 showed the sickling phenomenon. In the remaining 13 villages the investigation gave negative results. The highest incidence of sickling was found in the southern part of Chalkidiki district (Sithonia Peninsula). In the village of Sykia we tested 846 out of the 2,400 inhabitants and found 265 positive (31.3%). In the village of Parthenon the sickling rate was 32%, in St. Nicholas village 24%, in Nikiti 19%, and in Ormylia 18%. The incidence of sickling in the remaining part of Chalkidiki and generally in Northern Greece ranges from 2 to 14%, as is clearly seen on the map printed overleaf.

Incidence of Sickling in N. Greece

No.	Villages	No. Examined	Age in Years	Sickling Positive	%	Origin of People Examined
1	Sykia ..	846	1-76	265	31.3	Indigenous
2	Parthenon ..	153	5-12	49	32.0	"
3	Nikiti ..	143	5-13	27	19.0	"
4	St. Nicholas ..	101	2-12	24	24.0	"
5	Ormylia ..	103	5-12	18	18.0	"
6	Valta ..	196	1-60	25	12.8	"
7	Kallithea ..	90	6-12	8	8.8	"
8	Pazarakia ..	150	4-50	21	14.0	"
9	Furka ..	92	2-15	2	2.2	"
10	Kallandra ..	90	3-20	2	2.2	"
11	Polychronon ..	160	4-56	13	8.7	"
12	Kapsochora ..	96	6-11	1	1.0	"
13	Paliouri ..	160	2-80	16	10.0	"
14	Kassandrinon ..	46	6-12	0	—	"
15	Chanioti ..	62	5-30	0	—	"
16	St. Paraskevi ..	50	6-12	0	—	"
17	Nea Skioni ..	40	3-45	0	—	"
18	Stageira ..	—	—	—	—	"
19	Epanomi ..	183	7-14	5	2.7	"
20	St. Prodromos ..	177	6-12	0	—	"
21	Zangliveri ..	172	2-14	0	—	"
22	Hortiatiss ..	159	5-14	0	—	"
23	Xylopolis ..	90	2-60	0	—	"
24	Halastra ..	108	7-13	4	4.0	"
25	Klidi ..	67	7-14	4	6.0	"
26	Tsinaforon ..	151	3-17	14	9.2	"
27	Korifi ..	142	4-14	18	12.6	"
28	Loutros ..	102	7-18	6	6.0	"
29	Leptokaria ..	106	3-14	3	3.0	"
30	Fytia ..	150	4-13	0	—	"
31	Nigrita ..	—	—	—	—	"
32	Aidonochorion ..	136	8-15	4	3.0	"
33	Paleokomi ..	100	5-27	6	6.0	"
34	Prosotsani ..	220	6-12	0	—	"
35	Gratini ..	86	1-60	0	—	"
36	Kosmion ..	76	4-13	0	—	"
37	Soufli ..	205	1-50	0	—	"
		5,008		535		
38	Vrahia ..	92	7-12	0	—	Slav. dialect
39	Kimina ..	162	8-14	0	—	"
40	Trikalla ..	168	7-14	0	—	Refugees, E. Roumelia
41	Vathylakos ..	162	7-13	0	—	Refugees, Smyrna
42	Neon Petritsi ..	238	7-40	0	—	" mixed
43	Fitoki-Flamburon ..	181	7-16	0	—	Gypsies, Christian
44	Stavropolis ..	108	1-30	2	—	Refugees, mixed
45	Lekani ..	160	3-45	0	—	"
46	Kechrocamos ..	102	7-65	0	—	"
47	Paranestion ..	86	2-70	0	—	"
48	Komotini ..	143	4-8	0	—	Mixed people
49	Arisvi ..	82	6-12	0	—	Refugees, E. Thrace
50	Aratos ..	163	5-58	0	—	Turks, W. Thrace
51	Elafochori ..	97	2-14	0	—	Refugees, E. Thrace
52	Elafochori ..	111	3-38	0	—	Gypsies, Moslem
		7,063		537		

* Positive cases noted.