A CLINICAL TRIAL OF BENACTYZINE HYDROCHLORIDE ("SUAVITIL") AS A PHYSICAL RELAXANT

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A new drug has recently been introduced into this country for use in states characterized by emotional and physical tension. This drug, benactyzine hydrochloride ("suavital"), is the hydrochloride of 2-diethylaminoethyl benzilate. It is a member of the group of anticholinergic substances, and experimental work in Denmark suggests that it produces a state of emotional and physical relaxation without drowsiness. For convenience its name in this paper is shortened to benactyzine.

Previous Observations

Jacobsen and Sonne (1955) found that benactyzine, injected subcutaneously into rats, abolished states of tension previously induced by certain conditioned and unconditioned stimuli. When the rats were expecting a mild electric shock they tended to remain immobile in a characteristic attitude with arched backs, stiff legs, and raised tails. After the administration of benactyzine, not only did the rats become relaxed in their attitude but they also resumed normal activity, as if there was diminished anticipation of the coming stimulus.

Jacobsen and Skaarup (1955a, 1955b) considered benactyzine to be the most effective of a series of anticholinergic compounds in modifying or abolishing signs of stress induced by "conflict-situations" in cats. Some effect was also seen after alcohol, but scopolamine and chlorpromazine showed no effect by the technique employed.

The effect of the drug on the responses of the human autonomic system to emotional stimuli was next investigated (Jacobsen *et al.*, 1955a, 1955b). In general, the responses (as shown by changes of pulse and respiration rate and of skin temperature and resistance) were less pronounced when

the subject was under the influence of benactyzine, given orally, than without premedication or on control tablets.

Jensen (1955), in a clinical trial of the drug on a group of 110 neurotics, reported a beneficial effect in 75% of the cases. Both Jensen (1955) and I. Munkvad (1955, personal communication) found that the patients who are likely to respond most favourably to benactyzine are those with persistent anxiety or tension, especially when associated with preoccupation or rumination.

The general pharmacological effects of the drug have been reviewed by Jacobsen (1955), who emphasizes its low toxicity, lack of hypnotic effect, and the fact that no tendency to addiction has been observed in about 600 patients treated. He states that in normal human subjects doses of 4 to 6 mg. produce a feeling of relaxation of the voluntary muscles and a blockage of the spontaneous thought stream. Side-effects such as dizziness and ataxia were also noted.

Purpose and Methods of Present Investigation

The present paper concerns 80 patients who, with only four exceptions, regularly attended the neurological outpatient clinics at three hospitals (the Royal Northern, Chase Farm, and Luton and Dunstable) where we together observed them. Our main purpose was to investigate the possible effect of benactyzine in producing muscular relaxation both in purely organic types of rigidity and spasm, and in cases where underlying psychogenic factors might also be present. The latter included such conditions as facial tic, writers' cramp, and spasmodic torticollis. A few cases of intractable pain (unexplained facial pain and post-herpetic neuralgia) where an obsessional factor was believed to be present were also studied. The diagnostic classification of the patients is given in Table I.

We also wished to observe the incidence and nature of side-effects of benactyzine given to these patients in relatively small doses by mouth. Results were recorded in all of the 80 patients and also in two normal subjects who received gradually increasing oral doses up to 15 mg.

The method employed in 72 of the cases was to give a basic course of 2 mg. of benactyzine three times daily by mouth for two weeks. In a few early instances where tablets (known to us to be benactyzine) given in this way were without any effect, we prolonged the course for a further one or two weeks. In 10 of the cases an additional two weeks' treatment with 3 mg. three times daily was given, and in three cases the dose was increased to 4 mg. three times daily. In eight other cases 4 mg. three times daily for one week (preceded or followed by the same dose of

TABLE I.—*Diagnosis and Therapeutic Response to Benactyzine of 80 Patients*

Diagnosis	No. of Cases	Improvement with Benactyzine, not with Control	Improvement with Control, not with Benactyzine	Equal or Almost Equal Improvement with Benactyzine and Control	No Improvement with Benactyzine or Control	No Improvement with Benactyzine Control not Used	Improvement with Benactyzine Control not Used	Self-contradictory (Though 2 Said No Improvement with Benactyzine)
Disseminated sclerosis (with spasticity)	29	4	1	7	3	9	4	1
Facial tic	11	2	2	2	3			2
Parkinsonism	8	2		2	2	1		1
Facial pain	6	1	2			1		2
Writers' cramp	4	*1	1		1	1		
Spastic dysarthria (cerebral arteriosclerosis) .. .	4				3	1		1
Post-herpetic neuralgia .. .	3	1			1			
Spasmodic torticollis .. .	3		2	1				
Dystrophia myotonica .. .	2					2		
Cerebral thrombosis (hemiparesis)	2			1	1			
Migraine (with tension) .. .	2			1	1			
Stutter	1		1					
Primary spastic paraparesis ..	1				1			
Muscle spasm after poliomyelitis	1					1		
Friedreich's ataxia	1			1				
Spinal meningioma (with flexor spasms)	1				1			
Myoclonus	1				1			
Totals	80	11	9	15	19	16	4	7

control tablets) was given as an initial dose. The lack of rigidity in dosage schemes was intentional, but we did not find any improvement in therapeutic effect from prolonging or increasing the dosage within these limits. On the other hand, as is described later, the increased incidence of side-effects with 4 mg. led us to use 2 mg. as our standard dose. At the beginning of the investigation and in some later instances benactyzine alone was given to 22 patients, only 4 of whom reported improvements. In certain cases the patients were specially observed for any change in the degree of spasticity or tendency to clonus during the first hour after taking benactyzine in single doses of 2 to 4 mg. Patients were always unaware of any change in the tablets, and in the majority (37) of these cases we ourselves were unaware whether benactyzine or control tablets were being prescribed. The patients were seen by both of us at the end of each fortnight's course—sometimes more often—and their response, if any, assessed on both a subjective and an objective basis. The occurrence of any side-effects from the tablets was noted, but we were careful to avoid asking any leading questions about the possible nature of these effects.

Results of Therapeutic Trial

The results of the investigation of therapeutic effects in the various diagnostic categories are given in Table I. The response of the whole group is summarized in Table II.

TABLE II.—*Summary of Results in 80 Patients*

Controlled Series (53 patients):	
26 reported improvement with benactyzine	
24 " " " control tablets	
Uncontrolled Series (27 patients):	
4 reported improvement with benactyzine	
18 " no improvement with benactyzine*	
5 were bad witnesses	

* Control tablets were deliberately not used in these cases.

From these figures it is evident that, so far as improvement in organic conditions is concerned, benactyzine was without significant effect. Some patients were enthusiastic in their reports of diminished nocturnal spasms and cramps, greater mobility and confidence in walking, and increased general activity, but these effects occurred almost equally, whether the patient was receiving benactyzine or control tablets. No immediate or transient therapeutic effects were observed in the patients who were kept under special observation during the hour following administration of benactyzine. The progress-reports of patients receiving tablets which turned out to be inert provide a telling illustration of the importance of control studies in an investigation of this sort.

Ten patients with disseminated sclerosis reported the disappearance or marked diminution of flexor spasms and jerks of the legs in bed at night. In five of these, improvement persisted either with or without control tablets. One man in particular who had been disturbed by frequent nocturnal jerks of the legs became completely free from them and said that he slept properly for the first time in years. He noted the improvement within two days of taking benactyzine, which he continued for two weeks. The striking feature, however, is that in the subsequent six months he has had no further nocturnal jerks, although taking only occasional control tablets. Some patients with severe nocturnal spasms have not benefited at all from the drug. Thus, in the case of spinal tumour (extradural meningioma) troublesome spasms were unaffected by benactyzine, but almost completely disappeared immediately after successful removal of the tumour.

In another case a persistent liability to painful spasms and cramps in the legs after an old attack of poliomyelitis was unrelieved by doses of 4 mg. of benactyzine, but responded afterwards to quinine.

Although we have not been able to demonstrate any immediate diminution of spasticity or clonus after administration of benactyzine, we cannot entirely exclude the possibility that certain patients may by some indirect means be relieved of troublesome nocturnal cramps and flexor spasms as a result of its use. At least, we feel that further investigation of this point is warranted.

Side-Effects in Patients Treated

No major systemic toxic effects from large doses of benactyzine have been reported in the Scandinavian series, nor have any been observed after the comparatively small doses which we have given. Certain transient effects, mainly of a subjective kind, however, were common. We prefer not to call them toxic, for many of them are clearly the effects claimed as advantageous in the psychiatric studies. Out of 72 patients receiving the standard 2 mg. dosage, 29 (40%) reported such side-effects. All of eight patients receiving a dosage of 4 mg. reported side-effects. Of the 50 patients who received both benactyzine (2 mg. and 4 mg.) and control tablets, 30 (60%) reported subjective effects after the benactyzine and 9 (18%) reported subjective effects after the control tablets. (In 18 of the 50 cases the control tablets were given before the benactyzine, and 4 of these patients reported various symptoms after the controls alone.)

The two groups of side-effects most commonly described by patients were feelings of general apathy or detachment (for example, "everything is too much effort," "lazy," "far-away feelings") and altered sensations in the limbs (for example, hands and feet feel "heavy," "unsteady," or "dis-jointed"; "as if my legs weren't there"; "knees feel like jelly"; "my feet seem glued to the floor"; "insecure in walking"). These two main groups of symptoms (separately or together) each occurred in 20 patients. Feelings of dizziness were described by 13 patients. The dizziness and strange feelings in the limbs often became pronounced on first standing up. Slight nausea was reported by three patients, throbbing or tingling sensations by three patients, and blurred vision by one patient. One patient experienced micropsia and another described "a horrible frightened feeling." Among individual patients taking 2-mg. doses there was much variation in their susceptibility to the drug. If subjective effects occurred at all, they developed quickly and lasted from a few minutes to about one and a half hours. When the drug was taken immediately after a meal the liability to symptoms was less and their onset was delayed.

Effect of Larger Doses in Control Subjects

Single doses of 2 mg. by mouth before meals were given to several healthy medical observers without hint of the possible effects. Some of these described "slight far-away feelings," a sense of relaxation or detachment amounting sometimes almost to depersonalization, loss of alertness, difficulty in concentrating, and slight hesitancy in speech.

Two medical observers, who were given increasing single doses from 2 mg. up to 15 mg. at a time, noted an ever-increasing degree of thought blockage. When single doses of 7 mg. or more were given, the thought blockage began to show itself by repeated breaks in conversation with such remarks as "I don't know what we were talking about just then"; "I can't remember what I was going to say"; "What did I say?"; or "Have I said that before?" The larger doses resulted in some slowing and slurring of speech and impaired performance of simple mental tests such as serial sevens and Babcock sentence. Such remarks as "I can't be bothered to think or to articulate," "I feel lazy—not drowsy," were made. In each case the subject usually wanted to lie down and shut his eyes, or else gazed remotely into the distance. His thoughts were easily distracted (sometimes by flights of ideas and visual imagery), though full insight and awareness were preserved. There was, however, a striking flatness of affect. Altered sensations in the limbs occurred even after small doses—for example, hands felt "heavy," "a long way off," or "on the end of rods," and legs seemed to "sag at the knees." Objective inco-ordination was not pronounced. Clumsiness in complicated procedures, such as piano-playing, became evident after a dose of 9 mg., but this seemed more related to lack of attention, since simple finger-nose testing and handwriting were unaffected. Slight unsteadiness of gait was observed only after the highest doses.

The effects invariably began about 20 minutes after taking the tablets on an empty stomach. They developed quite suddenly, lasted for about one and a half hours, and then disappeared almost as quickly as they had come. The development of such symptoms suggests that it would be a wise precaution to warn any patients taking regular doses of more than about 4-5 mg. of benactyzine that they should not drive a car while under treatment.

No significant changes in pulse or respiration rate or in blood pressure occurred in the control subjects during the action of the drug. There was no notable pupillary dilatation or dryness of the mouth, and no alteration of normal muscle tone or power or of reflexes was observed. Deep and superficial pain sensibility remained unimpaired; indeed, both subjects were acutely aware of discomfort from a tight-fitting cap and hard head-rest used in the prolonged electroencephalogram (E.E.G.) recordings.

E.E.G. Findings

The effect of benactyzine on the E.E.G. of the two control subjects was observed after subcutaneous injection of 5 mg. and 7 mg. respectively. Subsequent symptoms were more intense than when the same dosage was taken by

Suppression of normal E.E.G. rhythms by benactyzine in two control subjects (electrodes in transverse post-central position). Top: Records from subject A before and 20 minutes after subcutaneous injection of 5 mg. of benactyzine. Bottom: Records from subject B before and about one hour after subcutaneous injection of 7 mg. of benactyzine.

mouth, but their rate of onset and duration were similar. Continuous E.E.G. recordings (kindly arranged by Dr. B. G. Parsons-Smith) showed at first a well-marked stable alpha rhythm in each control subject and in one of them a considerable amount of underlying beta rhythm at 22 c/s. As the usual symptoms began to develop, both the alpha and the beta rhythms became suppressed, and thereafter for prolonged periods the records were quite flat (see Fig.). Random low-voltage 4-c/s waves in both frontal regions occasionally occurred. Short spells of low-voltage alpha rhythm reappeared at times, and this alternating suppression and return of the normal rhythm became more noticeable as the effects of the drug wore off and the normal E.E.G. pattern began to be restored. The same suppression of normal activity in the E.E.G. during this height of the subjective symptoms after subcutaneous injection of benactyzine has been noted but not yet reported in Denmark (G. Hess, 1955, personal communication). No such effect is produced by reserpine, chlorpromazine, or other compounds derived from the antihistamines.

Summary

The possible effect of the new drug benactyzine hydrochloride ("suavitil") in relieving muscular rigidity, spasm, or pain has been investigated in a group of 80 neurological patients.

No effect on muscle tone and no significant relief of symptoms were produced by a two-weeks course of 2 mg. of benactyzine three times daily by mouth.

No temporary reduction of rigidity or of tendency to clonus was observed after individual doses.

Although subjective improvement was reported after benactyzine by many of the patients, similar improvement after inert control tablets was reported by almost exactly the same number.

Some, though not all, patients who had previously been much troubled at night by flexor spasms reported that these had disappeared and that they were now able to sleep well. This possibly indirect effect warrants further investigation.

No systemic toxic effects were observed, but transient, mainly psychological, "side-effects" occurred in 40% of 72 patients who received a dosage of 2 mg. of benactyzine. All eight patients who received 4 mg. showed such side-effects.

These transient symptoms, though they may constitute part of the therapeutic effect in psychiatric cases, seem to us to be a disadvantage in the possible regular use of the drug in other types of case.

With single oral doses of more than about 6 mg. normal control subjects showed increasing thought-blockage, impairment of concentration, slowness and clumsiness in carrying out complicated procedures, and a general flatness of affect. Such symptoms developed within about 20 minutes and lasted up to about one and a half hours.

Because of these symptoms it seems to us unwise to allow any patient to drive a car if he is being treated by large doses of benactyzine.

A striking suppression of the normal rhythm of the E.E.G. after administration of benactyzine has been demonstrated.

We wish to express our thanks to Glaxo Laboratories Ltd. for supplying the suavilil and placebo tablets used in this trial, and also to Dr. B. G. Parsons-Smith for reporting on the electroencephalograms.

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A reference centre has been established at the Institute of Hygiene, Vienna University, to record the literature on virology. The centre is publishing an abstracting journal, *Mitteilungen der Virusdokumentationsstelle*, the first number of which appeared at the end of 1955. It deals mainly with the classification scheme to be adopted, and also gives specimen abstracts. Later issues will abstract articles on viruses appearing in Austrian journals from 1946 to 1954, and then recent American, European, and Australian publications. The journal will be published five times a year, costing 2s. an issue or 9s. annually. It can be obtained from Dr. Karl Chlud, Virus Reference Centre, Hygiene Institute, Kinderspitalgasse 15, Vienna 9.