Effect of Anticholinergic Compounds on Post Convulsive EEG and Behavior *

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In 1956 Ulett and Johnson reported to this society that large doses of atropine or scopolamine blocked the appearance of the high voltage delta activity usually induced by convulsive therapy. They also noted that the dose of atropine necessary to affect the EEG was such as to be associated with unpleasant systemic effects. The reports by Jenkner and Lechner describing diethazine as an anticholinergic compound with potent neurologic but minimal systemic effects led us to undertake studies similar to those of Ulett and Johnson; and these observations, in turn led to an investigation of other similar agents. It is the purpose of this report to describe the clinical and EEG correlations on the intravenous administration of various hallucinogens and anticholinergic agents in psychiatric patients at various stages of convulsive therapy; and to relate these observations to the recently expressed neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy and of hallucinogens.

Subject and Method:

Our subjects were consecutive referrals for convulsive therapy in an open ward voluntary psychiatric hospital. Patients have been studied at various stages of therapy, with observations being made in acute experiments in the EEG laboratory. Following a standard 8 channel EEG recording from 17 leads using needle electrodes, the compound under study was administered intravenously at a set rate per minute, until clinical behavioral or electrographic changes were observed. The compounds studied have been diethazine, Win 2299, LSD-25 and benactyzine.

Fig. I - Chemistry structure

Diethazine was administered at 25 mgm. per minute, for a total of 175-250 mgm; Win 2299 and benactyzine at 0.5 mgm per minute for 2-5 mgm; and LSD-25 at 10 gamma per minute for 50-150 gamma.

Observations:

On the administration of diethazine, in 15 patients prior to convulsive therapy, there was a decrease in voltage and a desynchronization of all frequencies. Prevailing rhythmic patterns became less prominent. In some instances, symmetric low voltage 6-7 cps activity appeared, most prominent in the frontal and anterior temporal leads. The alpha frequency was not altered, but the build-up in voltage and slower frequencies induced by hyperventilation was blocked.

Fig. 2, 3

Diethazine - EEG - Pre-convulsive Treatment

In 17 patients during convulsive therapy, with varying degrees of induced high voltage delta activity, there was a significant decrease both in voltage and in per cent time of slow wave activity. From an average per cent time delta of 45% in the fronto-occipital leads, there was a reduction to a mean of 20%. Both random and burst delta activity diminished and low voltage alpha and beta frequencies became prominent. The hyperventilation response was no longer apparent. These electrographic effects persisted for one to five hours.

Fig. 4, 5

Diethazine - EEG - Convulsive Treatment

Concurrent with these EEG effects, we observed distinctive behavioral changes. Patients became more irritable and restless and complained of sensations of unreality with dysesthesias of the extremities. Visual illusory phenomena and delusional thoughts about their illness, the setting of the test procedure or the examiner's identity were described. Their language patterns were characteristically altered in a fashion opposite to that previously described for amobarbital, so that verbal denial, minimization, cliches, third person mode and past tense became less prominent. These changes were concurrent with maximum electrographic change.

The behavioral observations with diethazine led to a review of the effects of hallucinogens on EEG activity. In 1955 Denber and Merlis had reported that mescaline altered EEG delta activity induced by electroshock, in a fashion similar to diethazine. They described a marked reduction in amplitude and per cent time of high voltage symmetric slow wave bursts with an increase in alpha per cent time and in low voltage, random slow wave activity.

Reports by Pennes that an experimental compound, Win 2299 manifested both potent anticholinergic activity and induced hallucinations in man led to our study of this compound. The effects were similar to that observed in the diethazine group. In patients pre-convulsive therapy, EEG

desynchronization and decrease in voltages of all frequencies were induced.

Fig. 6

Win 2299 - Pre-convulsive Treatment

In eleven patients with high voltage delta activity there was a decrease in amplitude and per cent time of slow wave activity with an increase in alpha and beta frequencies. The mean per cent time delta activity dropped from 50% to 23% in these subjects. Associated with these electrographic effects were clinical patterns of restlessness, excitement, and hallucinatory and illusory activity.

Fig. 7

Win 2299 - Post Convulsive Treatment

As the hallucinogenic activity of LSD-25 was well established, these studies were next repeated with this compound. Here, too, the behavioral and electroencephalographic effects, on intravenous administration, were similar to diethazine. There was a difference in the time constant in that the behavioral effects occurred 1½ to 2 hours after drug administration, but the electrographic changes were concurrent with the behavioral change. While there was less desynchronization with LSD, the delta activity was significantly repressed. Mean per cent time delta activity fell from 47% to 16% in five subjects.

Fig. 8, 9, 10

LSD - EEG

Recalling reports that benactyzine, a potent anticholinergic compound, induced EEG desynchronization we next administered this compound intravenously in eleven subjects, and again observed similar clinical and electrographic patterns. Both in the well modulated alpha record and in the record with high voltage delta activity, desynchronization was prompt. Delta activity decreased from a mean per cent time of 39% to 17% in 8 subjects.

Fig. 11, 12

Benactyzine - EEG

These electrographic patterns were accompanied by clinical restlessness and excitement. While we did not observe illusory or hallucinatory activity, we did note that the language patterns were altered in the same fashion as with the other agents tested.

Thus, four compounds have been shown to have similar electrographic and behavioral effects. Each has definitive anticholinergic activity. Each induces hallucinogenic or excitatory activity; and these behavioral changes are accompanied by EEG desynchronization. Furthermore, these compounds have a similar chemical structure as may be seen in the next figure. The tertiary amine in a substituted diethylaminethanol is prominent, corroborating the recent reports by Denber on the hallucinogenic

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Repeat Fig. 1

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activity of tertiary amines, and amplifying his studies by the common concurrent electrographic patterns.

These observations amplify our understanding of the convulsive therapy process. In earlier studies we indicated that the development of high voltage slow wave activity was the neurophysiologic correlate of behavioral change in convulsive therapy, and a necessary, thought not sufficient, condition for clinical improvement. During the past ten years, studies by Bornstein, Tower and McEachern, Ward, Sachs, Ruge and others have noted similarities in the biochemical changes in convulsive therapy to craniocerebral trauma. They reported an elevation of free acetylcholine and pseudocholinesterase in the spinal fluid during convulsive therapy. In addition, topical administration of acetylcholine induces high voltage bursts and spike activity. Ulett and Johnson emphasized the blocking of these cholinergic effects by the anticholinergic activity of atropine and scopolamine. The observations on this report on

diethazine, Win 2299, LSD-25 and benactyzine support their observations. Each of these compounds has potent anticholinergic activity and the clinical behavioral and language effects are opposite to those described for convulsive therapy. We may thus amplify the earlier conclusion that the neurophysiologic basis for behavioral change in convulsive therapy is the development of high voltage slow wave activity by noting that this EEG change reflects an alteration in the acetylcholine-cholinesterase relations of the nervous system, probably in the direction of increased cholinergic activity.

These observations lend themselves to application in studies of craniocerebral trauma. Ward's reports of the efficacy of high doses of atropine in altering the clinical manifestations of head trauma also indicated that effective doses brought with them severe systemic effects. It would be advisable to repeat these studies, utilizing such more potent, more neurologically specific anticholinergic compounds as used in these experiments.

Finally, these observations, and our earlier reports on the significance of EEG delta activity in convulsive therapy, support the observation of Wikler (1954) who concluded his report on mescaline, n-allylnormorphine and morphine with the comment that: "... regardless of the drug administered, shifts in the pattern of the electroencephalogram in the direction of desynchronization occurred in association with anxiety, hallucinations, fantasies, illusions or tremors, and in the direction of synchronization with euphoria, relaxation or drowsiness." This conclusion, supported by our observations, permit a more meaningful generalization of

the recently expressed neurophysiologic-adaptive hypothesis of the mode of action of somatic therapies in psychiatry. We may infer that agents that synchronize EEG frequencies, like barbiturate and meprobamate in the beta frequency range and chlorpromazine, promazine and perphenazine in the delta frequency range, tend to be sedative, euphoriant and relaxant; while agents that evoke EEG desynchronization tend to be excitant and hallucinogenic, as was noted for diethazine, LSD-25, Win 2299, benactyzine and mescaline.

In summary, we have observed the effects of various hallucinogenic and anticholinergic compounds on the electroencephalogram and behavior in psychiatric patients at various stages of convulsive therapy.

Behaviorally, these compounds induced increased restlessness, haptic and visual illusory sensations and delusional thoughts about the subject's illness or the examiner's identity. The syntactic language patterns described for convulsive therapy and barbiturate were reversed. Concurrent with these changes were a decrease in voltage and a desynchronization of all frequencies in the EEG. In patients with high voltage delta activity, the per cent time and voltage of the delta activity were markedly decreased.

These observations have been discussed in the framework of the common biochemical structure and anticholinergic properties of these agents with the conclusion that:

(a) The biochemical basis for convulsive therapy and for high voltage EEG delta activity may be an alteration in the acetylcholine-cholinesterase relation of the nervous system, probably in the direction of increased cholinergic activity.

(b) The recently expressed neurophysiologic-adaptive hypothesis of the mode of action of somatic therapies in psychiatry is amplified to encompass the action of hallucinogens.

It is recommended that further studies of the effects of anti-cholinergic compounds in craniocerebral trauma to be undertaken, utilizing more neurologically specific compounds as diethazine, benactyzine and Win 2299.