THE EFFECT OF CHLORPROMAZINE ON THE INCIDENCE OF EPILEPTIC PHENOMENA DURING INSULIN COMA THERAPY

A STATISTICAL INVESTIGATION

By

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EPILEPTIC manifestations complicating insulin coma therapy (I.C.T.) were described by Sakel in his original paper (1937). In recent years the administration of chlorpromazine to patients undergoing I.C.T. has been common practice. Lancaster and Jones (1954), however, have commented on the resulting apparent increase in the incidence of epileptic fits.

The effect of chlorpromazine on the convulsive threshold has been the subject of a number of investigations, The conclusions derived from these are sometimes conflicting and will be reviewed below. While some experimental studies on this subject have been controlled, all the clinical reports have been based solely on clinical impressions.

AIM OF INVESTIGATION

In the following investigation, we set out to enquire whether chlorpromazine increased the incidence of epileptic manifestations during I.C.T. and furthermore whether the addition of anti-convulsant drugs reduced such incidence.

MATERIAL AND METHOD

Seventy consecutive non-epileptic schizophrenic patients admitted to the Insulin Unit of the Bethlem Royal and Maudsley Hospitals, between January, 1957 and December, 1958 were included in this study. The author had been responsible for the supervision of treatment in the above unit during this time and his duties included the supervision of the daily records of treatment kept by the nursing staff. Each day the various features of the coma were charted fully and amongst other information kept was the incidence of epileptic manifestations and the time of their occurrence. These notes were examined each day prior to prescribing the dose of insulin for the following day.

During the course of these 2 years, combined insulin and chlorpromazine therapy was introduced, and for a time all patients received this treatment. Chlorpromazine rendered the patients more manageable and improved the therapeutic atmosphere of the ward. Clinical observations, however, suggested that the combined treatment increased the frequency of epileptic manifestations. After an 18-year old schizophrenic patient had fractured a thoracic vertebra in a particularly violent fit, it was decided that anti-convulsants, in the form of sodium hydantoin 1½ gr. three times daily, should be administered routinely to all our patients.

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Our 70 patients therefore fell into three distinct groups:

1. 40 patients who received insulin alone.
2. 10 patients who received insulin and chlorpromazine.
3. 20 patients who received insulin, chlorpromazine and phenytoin (sodium hydantoin).

Results

Table I

Incidence of Epileptic Manifestations

	Insulin Alone	Insulin and Chlorpromazine	Insulin, Chlorpromazine and Phenytoin
Number of patients	40	10	20
Total number of comas ..	1,519	377	759
Total number of fits	72	37	16

When our findings, shown in the above table, are submitted to statistical analysis using the χ^2 technique, the difference in the incidence of epileptic manifestations in the three groups was found to be significant at a level greater than 1 per cent.

Examination of the distribution of epileptic manifestations in our three groups of patients gives further support to the above findings.

Table II

Distribution of Epileptic Manifestations

Number of Fits	Insulin Alone	Insulin and Chlorpromazine	Insulin, Chlorpromazine and Phenytoin
0	20	0	12
1–3	13	6	6
4–6	3	3	2
7	4	1	0
Total	40	10	20

There was no relationship between the dose of chlorpromazine or insulin administered and the incidence of fits. There was no tendency for epileptic manifestations to occur at any particular stage of the treatment in the different groups.

Discussion

The possibility that spontaneous epileptic attacks during I.C.T. were desirable and of good prognostic significance was entertained by Sakel (1937). Not all investigators, however, found themselves in agreement with him. Plattner and Frolicher (1938) stated that epileptic manifestations occurred in 1·6 per cent. of cases that recovered and in 4·3 per cent. of cases that did not. A higher incidence of epileptic manifestations was reported by Gross-May (1938): in his experience, 35 per cent. of patients undergoing I.C.T. had epileptic fits at some stage of the treatment. Tennent (1944) warned of the danger of fractures occurring as a consequence of epileptic fits in I.C.T. Leibermann and Hoenig (1953), however, concluded from their study that epileptic activity

witnessed either as seizures or as myoclonic jerks during insulin coma treatment was of good prognostic significance.

Epileptic manifestations in I.C.T. may occur in the early or late stages of hypoglycaemia or during the later stages of coma and are attributed to the individual sensitivity of the cortex to hypoglycaemia. Hill (1948) reported the case of a patient with a marked tendency to produce EEG abnormalities when activated by insulin. He studied this patient in detail over a period of 12 weeks and found that the amount of paroxismal activity was greatest at the beginning and at the end of stupor at which times two spontaneous convulsions occurred.

Leibermann and Hoenig (1953) studied the photometrazol threshold in a group of catatonic schizophrenics and found that this was lower than in the normal population, the lowest levels being found during emergence from stupor. They put forward a hypothesis as a result of their study, to the effect that there is a dynamic relationship between the tendency to discharge on the part of the diencephalic mechanisms as measured by the convulsive threshold, and the clinical state. Leibermann and Hoenig's hypothesis is in agreement with Gellhorn (1943). The latter, from observations of an A.N.S. regulating centre following successful physical treatment of schizophrenia, deduced that in this disease there is a variation in the reactivity of a central mechanism which functions through the sympathetic-adrenal and vaso-insulin systems. Both Gellhorn and Hill (1957) suggest that this central mechanism is a diencephalic autonomic centre.

Chlorpromazine, the earliest phenothiazine derivative to be used widely in neuropsychiatry, is said to exert its action through a depression of the spontaneous activity of the brain-stem reticular formation, which may be related to its anti-adrenaline properties (Hiebel *et al.*, 1954; Longo *et al.*, 1954; Bradley and Hance, 1957).

Courvoisier *et al.* (1953) stated that in animal experiments chlorpromazine showed anti-convulsant properties but, though some later investigators confirmed their findings, others reported that chlorpromazine lowered the epileptic threshold in animals (Heming *et al.*, 1956). Tedeschi and his co-workers (1958) report that chlorpromazine affects the "minimum E.C.T." threshold of mice over a narrow range of dosage only, i.e. oral doses of between 9 mg./Kg. and 27 mg./Kg. They state moreover that these properties are particular to chlorpromazine and are not shared by other phenothiazine derivatives. Studies by Lehmann and Hanrahan (1954) had demonstrated a lowered convulsive threshold following administration of chlorpromazine to psychiatric patients.

More recently Bradley and Jeavons (1957) studied the effect of chlorpromazine and reserpine on the "convulsant" and "sedation" threshold of 12 chronic schizophrenics. Neither drug proved to have any demonstrable effect on the convulsive threshold as measured by the hexazol method (Ulett *et al.*, 1955). They discuss their findings and put forward possible explanations to account for them. According to the authors it is possible that the mechanism through which experimental and spontaneous convulsions are produced, may not be the same. This hypothesis would explain the discrepancy between their findings and previous clinical observations. It does not explain, however, the essential difference between their results and those of previous investigators who have studied the same problem.

From the clinical angle the findings of Lomas *et al.* (1955), Kinross-Wright (1955), Schlichter *et al.* (1956), Tarjan (1957) and others, revealed an increased incidence of epileptic seizures in established epileptics and the occurrence of fits for the first time in hitherto non-epileptic patients, following administration of

chlorpromazine. The above authors recommended that the drug should not be regarded as a substitute for anti-convulsants, a warning of particular importance since Bonafede (1955) and others had reported favourably on the use of chlorpromazine in the treatment of behaviour disorders in epileptics.

The epileptogenic properties of this drug which may lead to the development of manifest fits in susceptible people, can be counterbalanced by the potentiating effect on anti-convulsant drugs as well as by a reduction in emotional tension (Meszaros and O'Reilly, 1956; Rudy *et al.*, 1956; Feldman, 1957; Vogele and May, 1957). In a paper on the use of chlorpromazine in the management of patients with head injury, Shea *et al.* (1955) found that convulsions could be controlled by halving the previous dose of cortical depressants once chlorpromazine was added to them.

Electro-encephalographic studies after administration of chlorpromazine are inconclusive. Terzain (1952) reported an increase in amplitude or normal rhythm and the re-appearance of well-organized alpha rhythm, Azima (1954) could find no specific changes and Lehmann and Hanrahan together with Shagass (1955) only found changes secondary to drowsiness. Fabisch (1957) states that in patients with an unstable inter-seizural record there is an increase in abnormal EEG phenomena after administration of intravenous chlorpromazine. This effect is similar to that produced by hyperventilation or photic stimulation. Szatmari (1956) reports increased sensitivity to hyperventilation as well as decreased metrazol threshold after chlorpromazine in epileptic patients.

The relationship between chlorpromazine and epilepsy can be seen to be an extremely complicated one, complicated further by the assumption put forward by Gibbs (1951) that there is an antithesis between seizures and non-ictal psychiatric disorders.

The value of our own study is limited in that our patients were schizophrenic and undergoing insulin therapy; two additional variables were thus introduced. Our results, however, demonstrate convincingly that in such patients chlorpromazine has epileptogenic properties and that the combination of chlorpromazine and sodium hydantoin greatly reduces the incidence of fits in treatment. We are unable to deduce from our data whether the combination of chlorpromazine and sodium hydantoin is more effective than the latter drug alone in diminishing the incidence of fits.

Summary

The incidence of epileptic manifestations occurring as a complication of Insulin Coma Therapy is compared in three groups of patients receiving (*a*) insulin alone, (*b*) insulin and chlorpromazine, and (*c*) insulin, chlorpromazine and sodium hydantoin. Our results, statistically significant at the 1 per cent. level, show that in such patients chlorpromazine has epileptogenic properties.

The literature on the relationship between epilepsy and chlorpromazine is discussed.

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