HIBICON

A NEW ANTICONVULSANT

By

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Introduction

In spite of the large increase in the number of anticonvulsant drugs in the three decades since the introduction of phenobarbitone, new remedies are constantly being sought. The present state of therapy of the epilepsies remains rather unsatisfactory. Drug therapy, which is still the most widely used form of treatment, is at best a maintenance treatment, i.e. the patient has to continue with it at least for many years to control the attacks. Even then a large number of sufferers continue to have seizures, often as frequently as once a month, which elude treatment. Surgery, which has found a wider application recently, is not radical either in many cases, and has to be followed up by medication over many years. The situation is further complicated by the fact that many anticonvulsant drugs, even when effective, produce unpleasant or dangerous side effects and have to be abandoned. One has also to consider the enormous psychological effects of the disease on the patient. The social stigma which epilepsy confers and the continual threat of an impending fit are often far more disabling than the actual seizures.

Lately three favourable clinical reports have appeared in American journals on a new anticonvulsant drug called "Hibicon" (Gotton *et al.*, 1951; Kaplan *et al.*, 1952; Hawkes, 1952). Lederle Laboratories Division, American Cyanamid Company have kindly put a quantity of Hibicon at our disposal for a therapeutic trial in this country. We are reporting our experiences with this drug on a group of forty patients suffering from various types of epilepsy.

Pharmacology

Lederle Laboratories Division, American Cyanamid Company had been experimenting with several compounds which contained a benzylamid residue, and which were found to have anticonvulsant properties when tested on rats. Kushmer *et al.*, (1951) from that Laboratory have reported on the preparation of 23 new benzylamides which they tested for anticonvulsant activity. One of them "Hibicon", was found to be clinically active in the treatment of grand mal epilepsy. The chemical formula is N-benzyl-β-chloropropionamide. It is a white crystalline solid with a molecular weight of 197·6 and a melting point of 90 to 92° C. It has a low solubility. It raises the electrical threshold in laboratory

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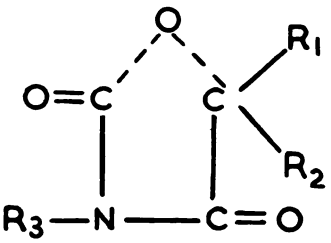
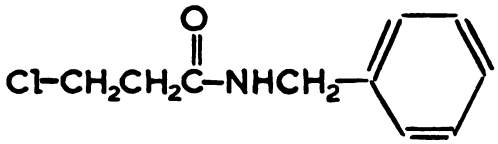
animals and is also effective in the metrazol test, but less so than tridione. It was tested for acute and chronic toxicity in various animals and was found to have a wide margin of safety. The peak of the action is reached two hours after administration and there is little accumulation.

Hibicon is particularly interesting chemically in that it does not contain the group which all other anticonvulsants hitherto used have in common (Toman *et al.*, 1948) (see Fig. 1).



This group appears in most anticonvulsant drugs (from Toman *et al.*, 1948).



Hibicon.

The capsules are rather large and have a dark brown colour. Later on Hibicon was supplied in small cachets of orange colour. This we felt was an improvement.

Material

The case material consisted of two groups of patients. At first one of us (J.H.) administered the drug to twenty-one out-patients attending the out-patient department of the Maudsley Hospital. They were all patients treated at Dr. Denis Hill's Clinic. There were twelve men and six women, their ages ranging from 18 to 56. The remaining three patients were children aged 6, 8 and 8½ years.

The diagnoses could be loosely grouped into three categories:

(1) Idiopathic epilepsy with major seizures: ten adults and one child.
(2) Psychomotor epilepsy with demonstrable epileptogenic foci in the temporal lobes, confirmed by electroencephalogram: three adults and one child.
(3) Focal epileptogenic areas in other parts of the cortex and taking clinical forms other than psychomotor seizures: five adults and one child.

One patient in Category 2 had Jacksonian attacks in addition to the psychomotor seizures. The suspected lesions responsible for the seizures in the patients of group 2 and 3 varied in their pathology. They included head injuries, encephalitides, lesions very likely due to birth injuries, etc. Of the children one dated his attacks from a cerebral thrombosis, the other had a history of whooping cough, with seizures beginning one week after the onset of the illness and persisting up to the present time.

The mode of selection of the patients for treatment with Hibicon was not uniform. Five patients were recent admissions to the clinic and had never been treated before; thirteen patients had been attending for some time but had not responded satisfactorily to other drugs, and three were included in the trial because, although their seizures had been fairly well controlled by other medi-

cation, they had shown side effects from these drugs. One of these patients had developed ataxia while on phenytoin, and two had hypertrophy of their gums due to prolonged treatment with hydantoinates.

The patients attended the clinic at regular intervals of one week to one month, as the case required. Before treatment began they had all been fully investigated and a diagnosis had been made. They all had several EEG's done.

The second group consisted entirely of in-patients of St. Francis Hospital, Haywards Heath, a mental hospital. All of these patients had very intractable seizures and some had marked personality disorders in addition, which made hospitalization necessary. They were all chronic patients and had been in hospital from two to fifteen years. They were chosen for treatment with Hibicon because they persisted in having at least one seizure per week in spite of treatment with other anticonvulsant drugs. As can be seen, they constituted a most difficult group of patients to treat and presented a formidable test for a therapeutic trial. There were ten women and nine men. Their ages ranged from 23 to 60 years of age. Their diagnoses fall into three categories: eleven patients had "idiopathic" epilepsy, seven had temporal lobe foci presenting with atypical attacks, and one patient had multiple cortical foci due to arteriosclerosis. Two of the temporal lobe foci were caused by head injuries, the others were of unknown pathology. The high proportion of temporal lobe epilepsies is in accordance with the findings of Liddell (1953) who analysed all epileptic patients in a mental hospital and found temporal lobe lesions in over half of them. Almost all patients had personality disorders in addition to intractable seizures. In the case of fourteen of these patients these disorders would necessitate hospitalization even if there were no fits.

The two groups are so different that we shall report them separately.

Dosage and Method

Most workers agree that a dose of one to two grams of Hibicon three to four times a day is effective in most adults, whereas in children 0·25 to 0·5 g. three to four times per day suffices. Kaplan (1952) was using smaller doses, but got equal if not better results. In his series the number of fits was reduced by more than 50 per cent. in just over half the patients. In a further 20 per cent. there was a reduction in the number of fits by 25 to 50 per cent. Hawkes (1952) could achieve "adequate control" in 66 per cent. of his group.

In the present series the adult patients were given 0·5 g. three times per day as the initial dose irrespective of whether they were already on anticonvulsant treatment or not. After one week the previous medication was very gradually reduced, withdrawing not more of the daily dose than 0·2 g. epanutin per week and other drugs were withdrawn in similar proportions. When the number of fits increased during this withdrawal period the daily dose of Hibicon was increased by 0·5 g. every week. The Hibicon dose continued to be increased at the same rate after all other drugs had been withdrawn until either all fits were suppressed or a maximum of 1·5 g. three times per day was reached. If fits still persisted in spite of the ceiling dosage, other drugs such as phenobarbitone or epanutin were added in the usual doses.

As far as the Maudsley Hospital group of patients is concerned this scheme was modified in that the maximum dosage was kept at 1 g. of Hibicon three times per day. This caution was adopted because the patients were out-patients and could therefore not be observed as closely as the second group at St. Francis Hospital. Seven patients took 1 g. three times per day, nine patients took 0·5 g. five times per day, and two patients took 1 g. twice per day;

eight patients had to have phenobarbitone 1 to 2 gr. daily in addition, and six of those had phenytoin 0·1 g. two to three times as well before the maximum benefit was obtained. Three children had 0·5 g. Hibicon three times per day, and one of them had phenytoin 0·05 g. twice daily in addition.

Of the St. Francis group of patients, fifteen had to have 1·5 g. three times per day and eleven of those had phenobarbitone ½ to 1 gr. per day in addition; seven of these patients had epanutin 0·1 g. two to three times per day as well. Two patients had 1 g. of Hibicon four times per day, one patient had 1 g. three times per day and one had only 1 g. twice daily.

Several of the patients objected to the treatment because of the large size and dark colour of the capsules. It will also be noted that the number of capsules which make up the maximum dose is nine, and if other tablets have to be taken in addition the number of preparations which a patient has to take is rather formidable. In view of our remarks about the psychological aspects of the treatment of epilepsy this was a serious handicap.

Results

The results can perhaps be most aptly presented according to the response of the different type of seizures. In the Maudsley Hospital group the results were as follows:

The number of major seizures decreased in four patients, showed no change in four patients and increased in three patients. The psychomotor attacks responded very well. All four patients who suffered from that type of seizure improved. The number of Jacksonian attacks decreased in four patients and increased in three. Several of the patients reported that they felt generally better since treatment with Hibicon had started. It is perhaps noteworthy that all the children did well; not only was the number of attacks reduced; but they were reported by the parents to be more alert, and when the treatment had to be brought to an end these patients were very distressed.

The St. Francis Hospital group did not do so well as the Maudsley Hospital group. It must be borne in mind that this group consisted of particularly difficult cases. The number of major seizures decreased in six patients, showed no change in four, and increased in one. The temporal lobe seizures decreased in three patients, remained unchanged in two, and increased in two patients. The patient with cerebral arteriosclerosis who had atypical seizures improved. Six patients of those included in the improved group were completely free of seizures for several months. As far as the behaviour difficulties are concerned they improved markedly in at least one patient. But in most cases no change for the better was noted.

Table I shows the results taking both the Maudsley Hospital and St. Francis Hospital group together. This table illustrates that over half of the patients showed some degree of improvement. The table does not indicate such results as improvement in well-being and behaviour, which, although not always present, were nevertheless very striking in a small number of patients.

Table I

	Improved	No Change	Worse
Major seizures	10	8	4
Psychomotor seizures	7	2	2
Atypical seizures—Jacksonian	5*	—	3
Total	22	10	9

* This figure includes the patient who had Jacksonian attacks in addition to psychomotor seizures.

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Side Effects of the Treatment

The animal experiments showed a very low degree of toxicity and a wide margin of safety (Kaplan, 1952). The clinicians were struck by the relative absence of untoward effects of the treatment. Kaplan (1952) found no unpleasant side effects in his patients. The hypnotic effect, so troublesome with many other anticonvulsants, is absent with Hibicon. Hawkes (1952) found dizziness and slight gastrointestinal distress in some patients which he attributed to the treatment. These did not seem dangerous and did not persist.

These reports are borne out by our own experience. While under treatment with Hibicon all the patients had periodic blood counts and urine examinations carried out. Three patients showed a transitory leucopenia which disappeared even when treatment was continued. This reaction has been observed previously in relation to other drugs such as thiouracil (Young, 1949), tridione (Hoenig, 1951) and others. Young (1949), explains that this reaction is quite distinct from agranulocytosis, is transitory and not serious. Twelve patients complained of transitory dizziness, and one developed a tendency to fall to the right which lasted a few days without showing any other clinical signs referable to the nervous system. It is worth noting that the patients who had hypertrophy of the gums due to epanutin improved in that respect while on Hibicon. The only two serious complications which we encountered were (*a*) four patients lost weight while on the treatment, in the range from 8 to 12 pounds and (*b*) three patients developed status epilepticus in spite of the very gradual withdrawal of the previous medication. It is not very clear why this came about. It is not likely to have been merely a direct result of the withdrawal of previous anticonvulsant treatment, as it occurred in one patient several months after this withdrawal was completed. The patients were treated with Sodium Gardenal and recovered. Neither the loss of weight nor status epilepticus had been observed by previous workers.

Discussion and Conclusions

Hibicon therapy has produced better results in the out-patient group treated at the Maudsley Hospital than in the in-patient group at St. Francis Hospital. This is to be expected in view of the type of case treated at St. Francis, i.e. the sort of patient who is so severely afflicted that he has to be confined to hospital for many years. Furthermore, out of a whole group of mental hospital patients suffering from epilepsy, only those were chosen who had not responded satisfactorily to other types of medication. Considering this fact, we came to the conclusion that Hibicon does at least as well as hydantoinates. As is usual when different types of anticonvulsant drugs are compared, some patients who have not done well on one, do better on the other; or else some seem to get slightly worse when changed over to the new medication. This trend is also apparent in the present trial. We find that over half of the patients showed some improvement, not only in regard to the number of seizures, but in a few cases also in regard to general well-being and behaviour. But on the other hand, a quarter of the patients seemed to get worse. These results bear out previous reports by Kaplan (1952) who reports in 50 per cent. of the patients marked improvement and in 25 per cent. slight improvement or no change, and Hawkes (1952) who finds 39 per cent. of his patients improved, and 28 per cent. worse, and finally Gotton *et al.* (1951) who achieved in 17·5 per cent. excellent control; in 30·5 per cent. some improvement and in 52 per cent. no satisfactory control. As most of these trials only refer to small numbers of patients, the slight fluctuations in results are probably not significant. Hawkes (1952) was treating

a control group, adequately matched, with hydantoinates. The results in his two groups were fairly equal.

As regards the response of the different types of fit to the treatment, our figures would indicate that psychomotor attacks associated with focal lesions in the temporal lobe do particularly well. Our figures, however, are too small to allow definite conclusions in this respect. In view of the fact that this type of epilepsy has proved to be the most intractable so far to non-surgical methods of treatment, this finding is certainly worth further investigation. Should the psychomotor seizures be proved to respond at least as well as the major seizures the result would be very encouraging. Previous workers have also reported favourable results with psychomotor seizures, but their groups did not contain many patients suffering from that type of attack. Kaplan (1952) had one patient in whom the number of seizures were reduced by over 50 per cent., and Hawkes (1952) states that psychomotor attacks showed some response although not as good as major seizures. As regards petit mal seizures Hawkes (1952) reports that they do not seem to be affected by Hibicon. None of the patients in our group had petit mal type of attack, and the present trial cannot add anything with regard to the response of this type of epilepsy to Hibicon.

The most remarkable finding is the absence of toxic or unpleasant side effects. In so far as any did appear, namely giddiness and mild nausea, they were transitory and did not prove an obstacle to treatment. The three cases of status epilepticus are of course extremely serious. None of the previous workers has reported status epilepticus occurring during treatment. In fact we are not clear about the aetiology of the status. As we pointed out above, it is unlikely that it was precipitated by too rapid a withdrawal of previous medication. It is possible, although we have no evidence to offer in support of this view, that the entirely different chemical structure of Hibicon from other anticonvulsants may invoke a change of electro-physiological balance in the central nervous system, leading to a transitory instability during the change over which, in turn, increases the liability to serial fits. It would seem that, until we know more about it, the utmost caution is indicated when patients are changed to treatment with Hibicon.

As regards the loss of weight observed in some patients the connection between this and Hibicon is even more difficult to understand. It may easily have been coincidental. Some of the patients who showed the loss in weight did generally poorly, but two improved in other respects.

Another difficulty is the fact that in order to achieve an adequate dosage a large number of capsules has to be taken by the patient. This should not be taken lightly in view of the importance of the psychological aspects of epilepsy and its treatment. In the case of Hibicon this difficulty was particularly noticeable as the capsules are of a large size and an unpleasant dark brown colour. These are factors which are probably quite easy to remedy.

We would finally conclude that Hibicon does not seem particularly superior to hydantoinates. It does produce better results in some cases but not in all. It is certainly worth adding to the list of anticonvulsants to be tried in resistant cases. Furthermore, the absence of side-effects makes it a safer drug than most other anticonvulsants, and in patients where hydantoinates have produced such side effects as acne or hypertrophy of the gums, Hibicon will prove a useful alternative treatment, possibly for long periods or perhaps only as a temporary standby until the toxic effects of the previous medication have subsided.

SUMMARY

Forty patients suffering from various types of epilepsy were treated for six months with Hibicon. The results are on the whole at least as good as with hydantoinates. Psychomotor

attacks in particular show an encouraging response. The drug is particularly innocuous and produced only very minor and transitory side effects. Hibicon is a valuable addition to the anticonvulsant armamentarium.

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