THE PLACE OF PACATAL IN PSYCHIATRY

By J. T. HUTCHINSON, M.D., D.P.M.

and E. H. JACOBS, L.R.C.P.(Edin.), D.P.M.

Cane Hill Hospital, Coulsdon, Surrey

Tranquillizing drugs fall into two main categories. The first group consists of such drugs as meprobamate and suavitil, which are being used in the treatment of the neuroses and milder anxiety states. The second group consists of drugs which are, in the main, phenothiazine derivatives, such as chlorpromazine, pacatal, sparine, etc. and these drugs have been found to have a place in the treatment of the psychotic patient.

This review is concerned with the second group of drugs and with pacatal in particular. Pacatal is 10 (1-methyl-3-piperidylmethyl) phenothiazine. It was synthesized in 1953 and tested pharmacologically by Niescholz *et al.* (1954). In many ways it resembles chlorpromazine in its action, but it is not so powerful a sedative and its side effects are different. This will be discussed subsequently.

The chief clinical problem facing psychiatrists today is the treatment of the chronic population of the mental hospital. This group consists of patients who have missed the opportunity of having E.C.T., insulin coma therapy or pre-frontal leucotomy early in their illnesses, or else they have failed to respond to such measures. These patients have been subjected to numerous clinical trials of the new tranquillising drugs. It is impossible to review briefly the plethora of papers which have been written about such investigations, but the general impression gained is that there is some place for them in the treatment of the chronic psychotic patient.

As Sargent (1958) has pointed out, we are only now beginning to learn how to use chlorpromazine, although it has been available for over four years. Many of the controlled investigations carried out which have contrasted drugs of the phenothiazine group with amylobarbitone have concluded that such drugs are inferior to amylobarbitone in their effect on the patient (Raymond *et al.*, 1957). Such papers neglect to point out that amylobarbitone is quite a different type of drug and that although it has euphoriant properties it has failed to make a substantial contribution to the treatment

of the chronic mental hospital patient. One feels that it would be equally worthwhile to contrast the phenothiazine derivatives with the more palatable forms of ethyl alcohol. In spite of these adverse reports, there is no doubt that the tranquillizing drugs have come to stay. There is a general impression that there has been an improvement in the atmosphere of mental hospitals in the past four years. There are fewer locked wards, fewer patients are secluded, there is much less recourse to the padded room and to the wearing of strong clothing. The population of these hospitals has begun to decline. Of course such changes may be due to other factors which have not been defined so far, and one cannot make generalisations on such slender evidence.

In view of the bewildering variety of tranquillizing drugs now available, it is obviously the task of the clinical investigator to assess each one in an attempt to find out which variety of mental illness will respond best to a particular drug. It seems unlikely that a drug will appear which will be a panacea for all psychoses.

In the present state of knowledge, it would appear that chlorpromazine and reserpine (a rauwolfia derivative) have an established place in the treatment of the chronic schizophrenic patient (Leiberman and Vaughan, 1957). These patients become less violent and appear to show some evidence of improvement. A somewhat similar impression is gained from the literature on pacatal. Thorpe and Baker (1956) gave pacatal to a group of chronic schizophrenic in-patients. They found that its side effects were fewer than those of chlorpromazine and that it was equally effective in reducing tension. Mitchell *et al.* (1957), found the drug effective in reducing the number of aggressive actions in regressed psychotic patients, but considered the high incidence of side effects (43 per cent.) to be a detrimental factor. Leiberman and Vaughan (*idem*, 1957) thought that there might be a place for pacatal in the treatment of such chronic schizophrenic patients as had proved to be refractory to other forms of treatment. However,

they considered that the incidence of side effects was higher than those due to chlorpromazine. Simpson (1957) found it useful in the treatment of the chronic psychotic and noted it to be particularly effective where aggression, impulsiveness and overactivity were prominent. Gillie (1957) found the drug to be of limited value in the control of behaviour in a group of mental defective patients, but she considered that of 14 epileptics seven showed some improvement of note.

Pacatal has been in general use at Cane Hill since May 1956. Since our findings were quite different from those of the above writers it was thought that they were worthy of description. The first half of this investigation consisted of giving the drug to a fairly large number of chronic deteriorated female in-patients. This group had been given chlorpromazine previously and had shown some evidence of improvement, but no sign of complete recovery. The second half was taken up with evaluating the drug in the treatment of a variety of psychiatric disorders in the hope of defining accurate clinical indications.

Method

The design of the experiment has been as follows. In view of the fact that there was no ward in the hospital where tranquillizers had not been used, no fresh population was available to us for the trial of pacatal. Therefore the plan was made of taking two identical wards where chlorpromazine was already in use. In one ward pacatal was to be substituted for chlorpromazine and the behaviour of the patients in that ward was to be contrasted with the behaviour of the patients in the other ward where chlorpromazine was in use. The plan of the experiment was kept secret from the nursing staff who were told simply that this was a drug, similar to chlorpromazine, which was not expected to be any better than chlorpromazine. In all 50 patients were changed from chlorpromazine to pacatal in doses varying from 150 to 300 mg. daily. Most of the patients are chronic schizophrenics. They showed a clinical picture which varied from stupor to aggressive excitement. They complained that they were persecuted and they also experienced auditory hallucinations. Their habits were filthy and they behaved in a destructive way. Food had little interest for them and they appeared to be quite lost and cut off from normal human intercourse. The average age of these patients is 50 years and their length of stay in hospital varied from two to 40 years.

Results

The changeover from chlorpromazine to pacatal was effected without incident about two years ago.

A recent survey of these 50 patients showed the following results: 42 (84 per cent.) showed evidence of improvement and only 8 (16 per cent.) showed no change. It should be emphasized that the phrase 'no change' meant that they were as well sedated by pacatal as they had been previously by chlorpromazine. The form the improvement took was that the patient became more animated. The ward staff noted that the patients were much more responsive and communicative. They would dress and wash themselves and would come to the meal table when called to do so. This spontaneity of speech and action was really quite striking. One patient who had been mute and uncommunicative for many years rediscovered her powers of speech and was able to tell the ward doctor that she was suffering from depression. She was then given a course of E.C.T. with further improvement. Another patient described how her mind felt much clearer and she was able to plan and think much more easily. The most striking change in these patients was the degree of emotional improvement. They showed cheerfulness, emotional warmth and responsiveness to a much greater extent than that encountered commonly in schizophrenics.

Further Findings

In view of the fact that this group of patients tolerated pacatal well and showed some signs of improvement, it was decided to extend its use to approximately 50 other female patients of various diagnostic categories. Again the dosage given varied between 150 and 300 mg. daily. On the whole the smaller dosage was preferred.

Paranoid Schizophrenics (including Paraphrenics)

This group consisted of 21 patients whose average age was 59.5 years. It is essentially an illness of later life, characterized by well-maintained delusions of persecution without much deterioration of personality. Eighteen of these patients showed marked improvement. This improvement was characterized by the disappearance of delusions of persecution and hallucinations and also by a marked increase in clarity of thought. A typical example of this is as follows:

E.J. Age 41. She was admitted seven years ago suffering from the belief that her brain was occupied by a man who controlled her thoughts in an unpleasant way. She was noisy and aggressive, requiring seclusion in a single room from time to time. She had E.C.T. and insulin coma therapy, without benefit. Chlorpromazine was given in a dosage of 200 to 450 mg. daily from January to November 1956, when it was discontinued because she had developed a dry eczema of the skin of her right hand and forearm.

This treatment had made her less aggressive, but her delusion remained unchanged. For three months she was given pacatal 300 mg. daily. Within one month she lost her paranoid beliefs, she felt much more clear in her thoughts and is now a useful hospital worker, since she has no proper home to go to.

Mixed Organic States

This is a miscellaneous group of 14 patients whose average age is 67 years. They suffered from a variety of physical disorders—chiefly of a vascular nature, e.g., arteriosclerosis, hypertension and diabetes. Their mental state was frequently one of depression, but paranoid ideas were not unknown. On the whole they did best on a fairly small dose of pacatal, e.g., 75 to 150 mg. daily. A typical example of this is as follows:

J.H. Age 66. She suffered from arteriosclerosis and diabetes. She believed she was being persecuted by the C.I.D. and was extremely suspicious in her manner. She had been a patient here for seven years. In August 1956, she began a course of pacatal 150 mg. daily, which was later reduced to 75 mg. daily. On this regime she improved remarkably. She lost her suspicions, her hallucinations and her paranoid beliefs, and she was discharged from hospital in January 1957. She has remained well on this drug ever since.

E.S. Age 33. This patient suffering from congenital G.P.I. was of marked interest. She showed evidence of epilepsy and suffered from kleptomania. Her memory for recent events was poor and it was considered that her prognosis was bad in spite of the fact that she had had full courses of anti-luetic treatment. Previously she had had chlorpromazine without success. Her most disabling symptom was urinary incontinence. Treatment with pacatal 100 mg. t.d.s. was begun on June 18, 1956. Since then there has been a complete absence of urinary incontinence, and she has ceased to pilfer. Her behaviour has been quite exemplary and she has been discharged from hospital.

Nine of this group of 14 patients have already left hospital and are maintaining a satisfactory progress outside, without any evidence of relapse.

Side-Effects

These consisted commonly of dry mouth, dilation of pupils and leucopenia. Dry mouth occurred in about 5 per cent. of this series. Dilation of pupils occurred in 10 per cent., but this group was chiefly under the age of 50 and an even smaller proportion complained of inability to read. Leucopenia was seen in 4 per cent. of the patients, all of whom had routine white cell counts.

The lowest cell count noted was 3,000 W.B.C. This improved when the drug was omitted. In one patient the white cell count was found to be 4,000 c.mm. Pacatal was continued in a dosage of 300 mg. daily and serial blood counts were made. It was noted that the white cell count returned to a level of 8,000 c.mm. in the course of seven days.

Discussion

From the above results it is apparent that the best results were obtained with patients in the older age groups. Although a great many patients suffering from schizophrenia simplex showed signs of improvement, none was discharged. It seems likely that pacatal is not so effective as chlorpromazine in the treatment of the young schizophrenics suffering from schizophrenia simplex, but the older patients did show some evidence of benefit. Better results were obtained in the group of patients suffering from paranoid states, including paraphrenia, but these illnesses occur most commonly in later life. By far the best results were obtained in the group of mixed organic states. It should be emphasised that the organic conditions seen were those of later life, e.g., arteriosclerosis, hypertension and diabetes. Depression which does not respond to E.C.T. is often seen in these patients. It is difficult to understand why pacatal should help this type of depression to lift. It could be argued that depression is an illness of cyclical type and tends to remit spontaneously, hence the high incidence of recoveries in this group, but there seemed to be no doubt that these patients felt much better as soon as this form of treatment was begun.

In this series no alarming falls in blood pressure were noted, but these had been frequent and upsetting when such elderly patients had been given chlorpromazine. Complaints of visual disturbance were not noted to any appreciable degree, but as Bowes (1956) has pointed out these are much commoner in young patients. It is a paradoxical fact that pupillary dilation was hardly seen at all in the older patients in whom glaucoma would have been a serious risk. The chances of a patient developing leucopenia and a fatal agranulocytosis are inherent in many of the remedies used today.

A recent editorial in the *Lancet* (1957) drew attention to this fact and listed no less than nine fatal cases of agranulocytosis due to chlorpromazine. The writer emphasised the importance of paying attention to the early signs of agranulocytosis and of instituting prompt action. In this hospital both chlorpromazine and pacatal have been used extensively for some time, but no fatal case of agranulocytosis has occurred, although some rather low white cell counts have been found.

No other side-effects were noted other than those listed above. Jaundice was not seen and the postural defects described by Kline and Jacob (1955) and by Mitchell *et al.* (1957) were not encountered. This could be due to the fact that high doses of the drug were not given and that the patients were very carefully selected for the treatment. It is at this point that the present writers would like to state their belief that it is a mistake to give large quantities of new drugs to groups of psychiatric patients in the hope of producing some improvement. These patients are individuals and have individual differences, and although they are chronic psychiatric patients there are definite points of difference between their various complaints. No cardiologist would give digitalis in a standard dose to all patients with heart disease. Such a procedure would be contrary to the best medical teaching, and the results would be disastrous. It is important therefore to assess each patient carefully, in a clinical trial, and to decide early in the trial which type of patient is likely to be helped best by a particular drug, and then to concentrate one's resources on treating this group.

Summary and Conclusion

Pacatal (a new phenothiazine derivative) has been used on 85 psychiatric patients. These consisted of a large group of chronic schizophrenics, a smaller group suffering from paranoid states, and another small group of patients who had a physical organic illness as well as a psychiatric disorder. The physical illness was usually of the type associated with old age, e.g., arteriosclerosis, hypertension and diabetes. The best results were obtained in the small group of organic patients, and nine of the 14 patients seen were discharged from hospital. Patients suffering from paranoid states showed a great improvement.

The chronic schizophrenics were helped to some extent, but none was discharged from hospital. The improvement noted in all patients consisted of an increased clarity of thought, fading of delusions and hallucinations, and improvement in social behaviour.

Side effects were few and consisted of dry mouth (5 per cent.) pupillary changes (10 per cent.) and leucopenia (4 per cent.). No fatal case of agranulocytosis developed, and in one patient the white cell count returned to normal levels in spite of the fact that the drug was not discontinued. Dosage levels varied from 75 to 300 mg. daily but on the whole the commonest dose was 150 mg. daily.

In the main the patients helped most were in the older age groups. It is among these patients that pacatal appears to be more useful than any of the tranquillizing drugs in current use. However, it is important to select one's patients carefully, and to review their progress frequently.

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