THE USE OF PROCHLORPERAZINE (STEMETIL) IN CHRONIC PSYCHOTIC DISORDERS

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PROCHLORPERAZINE, 1–[3–(3–chloro–10–phenothiazinyl)propyl]–4–methyl–piperazine dimaleate, a phenothiazine derivative related to chlorpromazine, was discovered in the Rhône Poulenc laboratories, and studied pharmacologically in 1956, by Ducrot and Koetschet, for its anti-emetic properties. Clinical trials, following this experimental evidence, suggested that, as well as possessing powerful anti-emetic properties, the drug was of considerable therapeutic value in migraine, Ménière's syndrome, and vertigo of other origins.

Owing to an impression that the sedative effect of the drug was considerably below that of chlorpromazine, prochlorperazine was not employed, in its early stages, for psychiatric conditions in this country. Reports from abroad, however, indicated that it was proving of great value in mental hospital patients and might even replace chlorpromazine: at the same time, disturbing side-effects were observed when the dosage was increased to a level that was considered necessary for the treatment of psychiatric patients. In order to examine these claims, the trial reported in this communication was undertaken.

METHOD

Prochlorperazine, in the form of 25 mg. tablets, was administered in doses of 1 tablet t.d.s. (75 mg. orally), in most cases until it became plain whether the drug was proving effective or not, or until side-effects necessitated withdrawal, reduction, or alteration of medication.

Patients who had been ill for a considerable time were selected so that they could act as their own controls for the trial. All these patients had received various forms of treatment, including insulin coma therapy, electroplexy, tranquillizers of the phenothiazine and Rauwolfia groups; and some had undergone prefrontal leucotomy, whilst others had been subjected to cardiazol convulsions many years before. No benefit had been obtained from any of these forms of therapy. (Later, when results from treatment of the chronic group became evident, a further small group of acutely ill patients was added to the trial.)

The group consisted of 13 male patients, with an average duration of illness of 13·4 years, and 46 females with an average duration of illness of 8·3 years.

Of the 13 male patients, 9 were hebephrenic, 1 was catatonic, 1 paranoid, and 2 were simple schizophrenics. Ten of these suffered from auditory hallucinations and delusions which dictated their behaviour and caused them to act in a violent, aggressive, impulsive way at times. The remaining 3 were the subjects of hypochondriacal delusions which inhibited any form of normal response or activity.

TABLE

	Number of Patients Previously Treated but Failed to respond								Average Duration of illness	Average Age of Patient	Number of Patients Treated	Results			
	Leucotomy	Cardiazol	Insulin S.T.	E.C.T.	Tranquillizers	Average Daily Dose	Not Improved	Improved in Hospital	Improved Home on Maintenance Dose	Recovered Home without Maintenance Dose					
						(mg.)									
Schizophrenics:															
Simple	—	—	4	5	5	75	3	2	—	—	5				
Catatonic	—	—	2	2	2	75	—	1	—	1	2				
Hebephrenic	—	4	25	27	27	75	6	12	3	6	27				
Paranoid	1	1	4	8	8	75	2	2	2	3	9				
Affective States:															
Agitated depression	1	—	3	8	8	75	4	2	1	1	8				
Mania	—	—	—	2	2	150	1	2	—	2	5				
Reactive with neurotic depression ..	—	—	3	3	3	75	2	1	—	—	3				

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Thirty of the female patients were schizophrenics, made up of 18 hebephrenics, 3 simple, 1 catatonic, and 8 paranoids, all presenting the same problems as were encountered with the males. The remaining 16 females were suffering from severe agitation of long standing or manic depressive psychoses, the average duration of their illnesses being 5½ years.

RESULTS

Improvement in the patients, if improvement there was to be, became apparent within the first 48 hours of treatment. The beneficial effect of the drug showed itself in the form of cessation of aggressive and violent behaviour, the patients no longer acting at the command of their delusions or hallucinations. They were enabled to react adequately to their surroundings and to behave amiably towards their fellow patients, relatives, and the nursing staff. This was in complete contradiction to their previous attitude of absolute hostility of many years standing, often carried to the length of violent assaults. Hallucinatory experiences were no longer reported by the patients and independent observation did not reveal any evidence of their presence. Delusions were no longer voiced and enquiry of the patients concerning such manifestations was dismissed or shrugged off as being of no consequence. Concurrently with these improvements, the patients became able and willing to take part in ward activities, attend occupational therapy, and visit their homes for the first time in many years. Furthermore, those patients who previously had been faulty or neglectful in their habits were now able and anxious to attend to their own needs, with the result that their appearance and physical state improved markedly.

Five patients, who had been very disordered in every respect, improved to such an extent that they developed actual insight into the psychogenic origin of their illnesses. This was the more remarkable because these five had been ill for well over 10 years and had, during the whole period of their illnesses, been quite unable to discuss their problems with any suggestion of insight.

The change in patients who responded appeared gradually, and it was impossible to predict at what stage, both as regards dosage and period of administration, maximum improvement might be expected in individual cases; so, as an empirical measure after a period varying between 30 and 150 days of treatment, dosage was halved. A small number of patients soon relapsed and only regained their improvement after dosage was restored to a single dose of 75 mg. daily, but the majority maintained or continued their improvement on half this dosage.

All improvements mentioned took place in patients in whom delusions and hallucinations were prominent features. Those patients whose symptoms were less spectacular, and whose behaviour was only mildly disturbed, exhibited little or no benefit from the administration of prochlorperazine. Furthermore, agitated depressives showed no response, although they were helped by chlorpromazine. Manic-depressives, in the manical phase, were also disappointing. A dosage of up to 200 mg. per day was necessary to control their excitement, but, even at that level improvement was not maintained, and remissions could only be obtained by employing other forms of physical treatment.

Of the responsive group, however, a number (21) continued to improve after prochlorperazine was withdrawn, and were able to return to their homes and to make the necessary social adjustments incumbent upon such a change in environment and responsibility.

Illustrative Cases

N.T., single female, aet 37, who had been suffering from schizophrenia for 4 years. Her condition fluctuated between catatonic stupor with flexibilitas cerea and cyanotic extremities, and periods of psychotic excitement during which she frequently smashed windows and crockery. She had previously been treated with insulin coma therapy on 2 occasions, had received repeated courses of electroplexy, and had been given tranquillizers or sodium amytal without any signs of improvement.

When she started on prochlorperazine she was in a catatonic stupor. Within a remarkably short time she improved, became active, co-operative and pleasant, joined in the ward activities, and was soon able to go home for weekends. Her physical state improved and the cyanosis of her extremities disappeared. After 3 months on 75 mg. prochlorperazine daily, she became tearful, developed a tic affecting her arms and shoulders. At her request the tablets were discontinued. The tic was regarded as being of psychogenic origin rather than a side-effect of the drug, and soon afterwards she developed insight into the origin of her illness when her tic was regarded as "throwing up her arms in despair" at the hopelessness of ever achieving satisfactory relationships in the face of emotional blackmail from her stepmother. She is now well able to cope with these emotional difficulties.

A.P.D., a single male, aet 34, had suffered from hebephrenic schizophrenia for 10 years. His behaviour was frequently disturbed as the result of insulting auditory hallucinations and persecutory delusions. He made frequent attacks on other patients and the nursing staff; smashed many windows, neglected himself, and was never accessible to ordinary reasoning.

After the failure of insulin coma therapy, electroplexy, and a prolonged course of chlorpromazine, prochlorperazine was started at a daily dosage of 75 mg. and within a short time, his violent, unco-operative, disturbed behaviour disappeared. No longer did he respond to auditory hallucinations, nor did he feel persecuted. He became tidy, clean and helpful, rational conversation became possible, and he was able to enjoy every freedom within the hospital. The improvement continued after the dose of prochlorperazine was halved and he is soon to attend the rehabilitation centre.

Side Effects

Parkinsonism. The most alarming side-effect experienced during the administration of prochlorperazine was a Parkinsonism-like state. This was heralded by muscle twitchings, pallor, lethargy, and complaints of tightness in the chest, and progressed towards complete muscular rigidity with excessive tonus, tremor, and painful muscular distortions. The time of onset varied between 3 and 90 days. The condition disappeared soon after withdrawal of the drug, and it was observed that mental improvement was maintained during and after such an episode. So soon as the condition had disappeared, it was found that there was no recurrence when prochlorperazine was re-started, at the same dose, if administered together with 25 mg. promethazine, dose for dose, and, if anything, with enhanced benefit to the mental condition.

Skin. One patient developed a skin reaction, similar to that seen with chlorpromazine, which disappeared two days after withdrawal of the drug.

Vasomotor symptoms. Four patients displayed vasomotor symptoms resembling peripheral vascular collapse. Prochlorperazine was withdrawn immediately and the patients quickly recovered. All 4 patients were re-started on the drug, at a lower dosage, 12½ mg. t.d.s., which was gradually increased without the appearance of further symptoms.

Drowsiness. Three patients became drowsy after 2 days on 75 mg. per day. Dosage was halved and there was no further complaint.

Excitement. One patient felt that prochlorperazine increased excitement and asked for the drug to be stopped. The drug was withdrawn and the excitement subsided.

Three schizophrenics, who had shown partial remissions through the administration of prochlorperazine, asked for the drug to be stopped as they believed that it was the cause of their disease. When the drug was withdrawn they continued to improve and soon became symptom free.

Discussion

Prochlorperazine is one of many phenothiazine derivatives and, as such, shares pharmacological properties to a varying degree with other compounds. Because of this, a trial and a report concerning it would be of little value unless one of these properties was so outstanding as to render prochlorperazine more efficacious than other compounds in any particular disorder.

This trial confirmed that prochlorperazine was more effective than chlorpromazine in the control of certain severe psychotic symptoms. Its main benefit was found to be in patients whose behaviour was severely disturbed as the result of persistent hallucinations and delusions.

Patients with excessive psychomotor activity, who were usually overactive, hostile, and aggressive, obtained maximum benefit from the drug. Those who showed only thought disorder, without abnormal psychomotor behaviour, did less well or failed to benefit at all.

It is of interest that the nature of the side-effects suggested that the toxic action of the drug was exerted on those parts of the brain which are concerned with motor activity; the symptoms being those commonly associated with irritative lesions of the basal ganglia as found in Parkinsonism. From this it might be tentatively deduced that prochlorperazine acts on the brain stem, the basal ganglia in particular. If the argument be continued further, it may be suggested that the beneficial effect of the drug, in patients with abnormal psychomotor activity, is primarily due to its action on the primitive motor ganglia.

Many clinicians are, however, directly opposed to the assumption that abnormal psychomotor activity is the primary disorder. The latter is usually regarded as an expression of a disorder of thinking and abnormal perspective, and, that so long as disordered thoughts exist, disorder of motor activity results. On this premise, disorder of thinking is the primary symptom, and disorder of behaviour the secondary, in which case, as the action of prochlorperazine is primarily on the secondary symptoms, it remains to be explained how and why those primary symptoms remit during administration of the drug.

The results of this trial indicate that prochlorperazine is mainly effective in severely disturbed, chronic patients; and, therefore, has its main place in mental hospitals: little or no indications for its use in psychiatric out-patients or in general practice could be found. The side-effects are of a nature to cause alarm to the patient and his relatives and they provide additional reasons why the drug should be restricted to selected patients undergoing hospital treatment, and those for whom the necessary maintenance dose has been determined in hospital.

Summary

The effect of prochlorperazine on psychiatric patients has been investigated and found to be of value in the treatment of severely disturbed schizophrenics. It was found to be of little use in other psychiatric conditions.

The main side-effect was a type of Parkinsonism which provoked alarm in the patient and those around him. This disappeared on withdrawal of the drug or when promethazine was administered concurrently.

Prochlorperazine in doses effective for psychiatric conditions should be employed mainly in mental hospitals.

(Prochlorperazine, under the trade mark of "Stemetil", was provided by May & Baker, Dagenham.)

Reference

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