Controlled Trial of Penfluridol in Acute Psychosis

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Summary

A controlled study was made of penfluridol medication consisting of a single weekly oral dose of 30 mg in 30 patients with acute psychoses of varying type and origin. This medication was found to be effective. No significant side effects occurred.

Several long-acting neuroleptics for injection are now available. The development of an oral compound of this type is an asset because of the manageability of the oral drug in the hands of family doctors and social psychiatrists.

Introduction

Long-acting neuroleptics are those whose effect lasts at least one to two weeks after administration of a single dose. The first representative of this category was fluphenazine enanthate. Some recent additions are: fluphenazine decanoate, pipothiazine decanoate—both phenothiazine derivatives—and flupenthixol decanoate, a long-acting compound of the thioxanthine group. These long-acting compounds are esters of corresponding neuroleptics, dissolved in oil, which are administered by deep intramuscular injection. Their prolonged effect is based on two factors: (1) slow release of the ester from the oily solution, and (2) hydrolysis of the ester, which involves the formation of the free (active) base.

Finally, there are two long-acting compounds from the group of diphenylbutylpiperidines: fluspirilene (Janssen, 1971) and penfluridol (Janssen, 1970). These compounds are derived from and related to the butyrophenones, a group of which haloperidol (Serenace) is the prototype. Fluspirilene is administered by intramuscular injection and, within the muscle, forms a microcrystalline deposit which gradually releases the active principle in about one week. Penfluridol (see Formula) is

a compound for oral administration, and animal experiments indicate that its effect lasts about one week. The explanation of this remarkable paradox—oral administration and nevertheless prolonged effect—is that penfluridol enters the brain very slowly and leaves it with reluctance, but is not metabolized in the brain.

One controlled double-blind trial has been carried out with penfluridol in patients with chronic psychoses (Baro *et al.*, 1970),

and one uncontrolled trial in patients with acute psychoses has been reported (Bobon *et al.*, 1970). In both trials the compound was found to be effective.

The present paper reports on a controlled trial of penfluridol used in the treatment of patients with acute psychoses.

Patients and Methods

TEST SUBJECTS

The group studied consisted of 30 patients admitted to the Psychiatric University Clinic, Groningen, with acute psychotic manifestations of varying syndromal and aetiological type. Table I gives details of this group. If possible, medication was postponed until the beginning of the second week after admission

TABLE I—*Syndromal and Aetiological Typology of the Disease Pictures Treated*

Aetiology	Chiefly Paranoid, with Ideas of Reference		Chiefly Delusions (Excluding the Paranoid)		Chiefly Halluci- nations		Chiefly Disorders of Motility	
	P.	C.	P.	C.	P.	C.	P.	C.
Schizophrenic "process" ..	3	1	2	1	1	2	—	—
Demonstrable cere- bral process ..	—	—	1	—	—	—	—	—
Demonstrable extra- cerebral process ..	—	—	—	—	1	—	1	1
Psychogenic factors (including socio- genic and neurotic)	2	2	3	4	3	1	—	1

P = Penfluridol group. C = Control group.

in order to eliminate patients whose reintegration was effected by the mere fact of admission to hospital. The mean age was 42 (19-67) years in the penfluridol group and 39 (21-70) years in the control group. The former comprised 10 women and seven men, while the latter consisted of eight women and five men.

TEST ARRANGEMENT

The test subjects were divided at random into two groups. One group received weekly 30 mg of penfluridol and 0.5 mg of dextemide, an anti-Parkinsonian agent with sustained action (de Smedt *et al.*, 1970). The other group received identical placebo tablets according to the same schedule. Medication was continued for four weeks under double-blind conditions. Moreover, all patients of both groups were given one capsule thrice daily during the same period. In principle the capsules were filled with an inert substance; but they could be replaced by identical capsules containing 50, 100, or 150 mg of chlorpromazine. The same psychiatrist assessed daily, on the basis of the clinical condition, whether on that day the patient required chlorpromazine instead of placebo and, if so, how much. He aimed at the minimum effective dosage. The capsules were dispensed daily for specified patients by a research assistant to the head nurse of the research department.

The psychiatrist and research assistant mentioned were not involved in scoring and did not know in which group the patients were. The physicians and the nurse who scored the rating scales did not know whether the patients received

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TABLE II—Results of a Test for Increasing or Decreasing Trend (one-tailed) of Scores Summated per Patient and per Item before and during Medication

		Nurse		Physician 1*		Physician 2†	
		Penfluridol	Control	Penfluridol	Control	Penfluridol	Control
Summated score per patient		T = 5.40 P<0.01	T = 4.90 P<0.01	T = 7.33 P<0.01	T = 5.94 P<0.01	T = 7.76 P<0.01	T = 5.96 P<0.01
Summated score per item		T = 6.58 P<0.01	T = 5.18 P<0.01	T = 7.05 P<0.01	T = 6.95 P<0.01	T = 7.22 P<0.01	T = 7.53 P<0.01

*Attending physician.

†Physician not involved in the treatment.

penfluridol or placebo tablets and were unaware of the contents of the capsules.

During the test period no other medication was given apart from an incidental soporific of the barbiturate type.

The hypothesis tested was the following: if penfluridol is therapeutically effective, then (1) the number of patients who require supplementary medication and (2) the amount of supplementary medication per patient should be larger in the control group than in the penfluridol group.

SCORING

Two rating scales were used. *Scale A* is a Wing (1961) scale which we modified. It is a three-point rating scale aimed at visually observable variables of behaviour. Its interrater reliability was established to be high (van Praag *et al.*, 1970). The scale was scored by the head nurse of the department. *Scale B* is a three-point rating scale of our own design; scoring requires verbal communication with the patient. This was done by the attending physician and, independently, by a physician not involved in the treatment of the patient. Both scales were scored before medication and twice weekly during medication, always on the same day of the week at the same time.

Final Score.—At the end of the fourth week of medication, moreover, each of the three raters gave a final score on a five-point scale ranging from marked improvement via no improvement to deterioration as compared with the condition at institution of treatment.

Side effects were recorded twice weekly by the attending physician on a check-list of motor items and some other items. He also indicated their severity (0 = absent, + = mild, ++ = moderate, +++ = severe).

Blood picture, liver function (SGOT, SGPT, and alkaline phosphatase), and urine (protein, urobilin, and sediment) were checked weekly.

Results

The degree of agreement between the pretherapeutic scores of the two physicians varied from $r = 0.49$ for the item "affect" to $r = 0.79$ for the item "mood" (Bravais-Pearson correlation coefficient). All correlation coefficients differed significantly from 0 ($P < 0.01$), but in our opinion were too low to warrant combination of the two scores. The scores of the two physicians were therefore separately analysed. For the scale used by the nurse a high interrater reliability had been established in a previous study ($r = 0.85$); this is why scale A scoring was done by only one nurse in this study.

The scores of scales A and B were analysed in two different ways, by calculating: (1) the scores on all items summated per patient, and (2) the scores for all patients summated per item. Application of the test for increasing or decreasing trend in rankings (one-tailed test) showed that in the course of four weeks of medication significant improvement had been noted by all raters in both groups (Table II). The final scores assigned by all raters, too, indicated improvement of the clinical condition in both groups at the end of the period of medication.

According to the nurse and attending physician no difference in degree of improvement was demonstrable between the two

groups. According to the independent physician, improvement in the control group—as measured by the difference between the last and the first summated score per patient and per item—was more pronounced than that in the test group (Mann-Whitney test $\Sigma R = 250.5$; $P < 0.05$. Wilcoxon test $\Sigma R = 8$; $N = 10$; $P < 0.05$). As measured by the final scores, the two groups showed an identical degree of improvement according to all raters. In both groups the mean improvement was between slight and marked.

Therapeutic results can be influenced by the severity of the disease symptoms. This is why pretherapeutic scores in the penfluridol and control groups were compared. Nurse and attending physician differed significantly in their initial scores for test group and control group: the nurse found the control group more disturbed, whereas the attending physician found the control group less disturbed than the penfluridol group. The independent physician noted no difference. The differences considered in this respect were only just significant at the 5% level. Moreover, they pointed in different directions and seemed to have no unequivocal influence on differences in therapeutic effect between the two groups. We believe ourselves justified, therefore, in concluding that the therapeutic results were not influenced by a difference in severity of disease symptoms between the two groups.

Chlorpromazine was required by 7 of the 17 patients in the penfluridol group and by 11 of the 13 in the control group. The number of patients requiring chlorpromazine was significantly larger in the control group than in the test group ($P < 0.05$, Fisher test).

The seven patients in the penfluridol group who required supplementary medication totalled a mean requirement of 4,200 mg of chlorpromazine per patient per four weeks of medication. Six of these patients received less than 4,000 mg per four weeks. The 11 patients requiring chlorpromazine in the control group averaged a total of 10,600 mg per patient per four weeks. The total dose exceeded 4,000 mg in nine of these patients. The number of patients who required only a small dose of chlorpromazine ($< 4,000$ mg per four weeks) was significantly larger in the penfluridol than in the placebo group ($P < 0.02$, Fisher test).

The seven patients in the penfluridol group who required chlorpromazine received about half the total dose given during the four-week period of medication within the first week of treatment (Table III). Of the total dose required within the first week, about half was given during the first two days of medication. In the control group chlorpromazine medication was more evenly distributed over the four weeks of medication (Table III).

Four patients (three in the penfluridol and one in the control group) had to be excluded, always within the earlier half of

TABLE III—Amount of Supplementary Chlorpromazine Medication Required in the Penfluridol and Control Groups

Group		Patients		Mean Amount of Chlorpromazine per Patient per Week (in mg)*			
		Total No.	No. Requiring Chlorpromazine	1st week	2nd week	3rd week	4th week
Penfluridol	..	17	7	2,000	1,200	600	400
Control	..	13	11	3,100	2,600	2,800	2,100

*Rounded up in hundreds.

TABLE IV—Sum of the Number of Plus Signs Scored for Items Hypokinesia and Rigidity before Medication and at the End of the Four Weeks of Medication

Case No.	Penfluridol Alone (Weeks of Medication)					Chlorpromazine Alone (Weeks of Medication)					Penfluridol + Chlorpromazine (Weeks of Medication)				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	0	0	0	0	0	0	1	2	1	1	0	0	1	1	1
2	0	2	1	0	0	0	1	1	0	0	0	0	0	0	0
3	1	1	2	0	0	1	1	0	0	0	0	1	2	2	2
4	0	0	1	1	0	0	0	0	0	0	1	2	1	0	1
5	0	0	0	0	0	0	0	0	0	0	0	2	1	1	1
6	1	2	1	0	0	0	2	1	0	0	0	1	1	0	0
7	0	0	1	1	1	1	1	1	1	0	0	2	1	1	0
8	0	0	0	0	0	0	1	2	1	1	0	0	0	0	0
9	1	1	2	1	1	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	1	2	1	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Sum	3	6	8	3	2	3	9	9	3	3	1	8	7	5	5
Corrected sum ..						2.7	8.2	8.2	2.7	2.7	1.4	11.4	10	7.1	7.1

the first test week. This means that, in order to form a group of 30 patients, 34 patients were studied. The reason for exclusion was not to be found in side effects, but invariably in a fulminating course of the psychosis which called for more intensive therapy (parenteral neuroleptic medication or electric convulsion therapy).

No significant side effects occurred either in the penfluridol group or in the control group. In no case was medication discontinued because of side effects. Table IV lists the number of plus signs scored per patient for the items "hypokinesia" and "rigidity" before treatment and at the end of four weeks of medication. It shows that penfluridol can provoke mild motor symptoms comparable with those sometimes seen in response to relatively modest doses of chlorpromazine. The combination of the two drugs seems to make this effect more pronounced. Blood picture, renal function, and liver function showed no systematic abnormalities.

Discussion

Significant improvement occurred during the four weeks of medication in the control group as well as in the penfluridol group. Both groups showed an identical degree of improvement according to all rating methods used and according to all raters using them. The only exception was the scale B score of the independent physician, which indicated more pronounced improvement in the control group than in the penfluridol group.

The penfluridol group contained fewer patients who required supplementary chlorpromazine medication than did the control group. The penfluridol patients requiring chlorpromazine received a smaller mean amount of chlorpromazine than those who required the chlorpromazine in the control group. This warrants the conclusion that penfluridol, given once weekly, is therapeutically superior to a placebo in patients with acute psychoses. The side effects of penfluridol were insignificant, and never called for discontinuation of medication.

As we noted in the Introduction, penfluridol is as slow in leaving the brain (hence the prolonged effect) as it is in entering. A priori it is therefore likely that a therapeutic effect, if any, will not become manifest immediately but only gradually. It was consistent with this expectation that those who required supplementary medication received most of this within the first two days of treatment. This is why penfluridol seems less suitable for the treatment of states of acute agitation in which immediate intensive sedation is a necessity.

TEST ARRANGEMENT

Our reasons for preferring a test arrangement which was rather demanding in terms of work and staff involved to the classical placebo experiment were the following: (1) To begin with,

infrequent administration of a drug in the case of acute psychosis exerts a negative suggestive influence on the patients and their relatives. This is the more true when other patients in the same ward who are not involved in the trial usually receive medication several times daily. This situation can lead to underevaluation of the test drug. (2) Moreover, an orthodox double-blind placebo experiment, when carried out on patients with acute psychoses, often meets resistance on the part of medical and nursing staff which is expressed in therapeutic impatience. There is a strong inclination in favour of supplementary medication in this situation, even in cases in which a more expectant attitude still seems justifiable.

In the past these factors have often been found to lead to early exclusion of patients from the trial. This is why we considered it important to incorporate arrangements for the possibility of supplementary medication in this trial.

The test arrangement we chose also has its disadvantages. To begin with, it is not to be ruled out that the therapeutic effect observed is based, not on penfluridol per se but on penfluridol plus a handful of (placebo) capsules. In many cases, however, a long-acting drug is likely to be prescribed, not in the first instance but in maintenance therapy after a period of daily medication. One can then explain why the maintenance medication is given infrequently, and this may reduce its negative suggestive influence. Another disadvantage is that the arrangement chosen permits of only a rather gross evaluation. The rating scale makes no distinction between the effect of penfluridol and that of chlorpromazine (if given). This forced us to measure the penfluridol effect indirectly, by the need for supplementary medication, rather than directly on the basis of the scores on the rating scales.

BENEFITS OF LONG-ACTING NEUROLEPTICS

The importance of long-acting neuroleptic drugs is evident, particularly in the treatment of chronic or frequently relapsing psychoses. For, on the one hand, a correlation has been shown between strictness in using the maintenance medication and the relapse rate (Prien *et al.*, 1969) and, on the other hand, it is certain that over 50% of chronic (schizophrenic) patients are bound to neglect maintenance medication (Renton *et al.*, 1963). The reasons for this negligence can be widely diverse, including poor disease insight, side effects, resentment against the drug as "embodiment" of the illness, and the inconvenience of having to take drugs every day. It has been shown that the relapse rate of chronic schizophrenia can indeed be reduced with the aid of the depot principle (Lowther, 1969; *British Medical Journal*, 1971). However, the importance of long-acting neuroleptics is not confined to the chronic psychoses alone. Patients with acute psychoses can likewise benefit from these agents, specifically if admission to hospital is either impossible or undesirable. The latter situation may prevail, for example, with psychoses chiefly

provoked by social stress. In these cases quick sociotherapeutic and psychotherapeutic intervention can sometimes obviate the need for admission to hospital, provided this intervention is supported by medication. In such circumstances it is imperative that the patient does in fact receive the drug prescribed.

Intramuscular injection of long-acting neuroleptics has the advantage of being the only mode of administration which gives absolute certainty that the drug does reach its proper place. Moreover, the magic "charge" of the syringe exceeds that of a tablet. But oral medication has the advantage over parenteral administration of being much more manageable for "field workers" (social psychiatrists and general practitioners). It is therefore of importance that a long-acting oral compound is now available besides the long-acting neuroleptics for injection.

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Exchange Transfusion with Dextran 40 in Polycythaemia Secondary to Hypoxic Lung Disease

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Summary

In eight patients with polycythaemia secondary to hypoxic lung disease 10 elective exchange transfusions were performed to reduce red cell mass, packed cell volume (P.C.V.), and whole blood viscosity. The rationale for reducing P.C.V. is discussed. It is concluded that patients with P.C.V. of 60% or over will benefit from exchange transfusion and that most patients with P.C.V. over 50% and true polycythaemia will also benefit. We also confirm that the technique of exchange transfusion is a rapid, safe, and effective method of achieving large venesections and reducing red cell mass.

Introduction

In the past various methods have been used to treat polycythaemia which is secondary to lung disease in an attempt to lessen its harmful effects. Venesection occasionally gives some relief (Auchincloss and Duggan, 1957) but leads to a temporary increase in clotting tendency with an added risk of thrombosis and embolism. Continuous oxygen therapy has been successful in reducing red cell mass and packed cell volume (P.C.V.) with symptomatic benefit but ordinarily necessitates a hospital stay of about six weeks (Chamberlain and Millard, 1963). Pyrimethamine with dapsone or phenylhydrazine has also been used and produced symptomatic improvement, but these drugs carry the risk of thrombocytopenia and overcorrection of the polycythaemia (Pengelly, 1966, 1969).

A method of rapidly lowering red cell volume by using an isovolaemic exchange transfusion technique has recently been described (Gregory, 1971a) and initial results in patients with

secondary polycythaemia were very encouraging (Gregory, 1971b). Further experience with the method is now reported.

Patients and Methods

Ten elective isovolaemic exchange transfusions were performed in eight patients with polycythaemia secondary to hypoxic lung disease. The technique (Gregory, 1971a) consists in the simultaneous intravenous infusion of dextran 40 in 5% dextrose into one arm and venesection from the other arm. The total volume of dextran infused is equal to the volume of blood venesected, but only half is given during the period of the venesection, because low-molecular-weight dextran attracts an additional volume of fluid equal to its own volume from the extravascular space into the circulation. The remaining dextran is given over the next 8 to 16 hours.

The reason for using dextran 40 is primarily because it is an effective plasma expander, and with this technique 2 litres of blood can be safely removed in about 45 minutes. It also has the theoretical advantages of reducing red cell aggregation and, because it is hypertonic and draws fluid into the vascular space from the interstitial space, of improving tissue capillary blood flow.

All eight patients had a long history of respiratory illness with several previous admissions to hospital; all except one (Case 5) had a history of ankle swelling and raised jugular venous pressure. Their clinical and other data are given in Table I. Chronic bronchitis was defined according to the Medical Research Council (1965) classification, and emphysema was diagnosed on posteroanterior and lateral chest radiographs, the criteria of Laws and Heard (1962) being used. In none had there been any change in the symptoms or signs of their pulmonary or cardiac condition in the week preceding the study, and the weight of each patient measured daily had remained steady during that week. Two patients (Cases 4 and 6) were admitted on two occasions for exchange transfusion.

Red cell volume was measured with chromium-51-labelled red cells and whole blood, and plasma volumes were either estimated indirectly from this (Cases 1-5) or measured directly with iodine-125-labelled albumin (Cases 6-8). The results are expressed in millilitres per kilogramme of body weight. Whole blood viscosity was estimated on heparinized venous blood in vitro with a capillary viscometer and the results are expressed in centipoise. Arterial blood was obtained by brachial artery

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