PRELIMINARY COMMUNICATIONS

Propranolol in the Control of Schizophrenic Symptoms

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Summary

All schizophrenic symptoms remitted completely in six out of 14 adults who had not responded to phenothiazine drugs and who were then given propranolol. Another patient improved markedly and four improved moderately. Two had minimal or transient improvement, and one left hospital unchanged after a short, severe, toxic reaction. The six with complete remissions all began to improve within a few days of starting propranolol and the florid symptoms remitted completely after three to 26 days. They were stabilized on a daily dose of 500-3,500 mg of propranolol and at the time of writing had remained well for up to six months. Two patients who stopped propranolol after their symptoms remitted relapsed severely within a few days. Toxic effects (ataxia, visual hallucinations, and confusional states) were related to the rate of increase rather than to the absolute dose of propranolol. After the procedure was modified unwanted effects were usually mild or absent.

Introduction

Psychotic symptoms remitted completely in a patient with acute porphyria with psychosis who was treated with large doses of propranolol (Atsmon, 1972) and similar remissions were seen in psychiatric patients with psychoses (Atsmon *et al.*, 1971; Atsmon *et al.*, 1972). Propranolol in lower dosage and practolol were reported as being ineffective (Gardos *et al.*, 1973; Rackensperger *et al.*, 1974).

A pilot study was therefore undertaken, with the permission of the medicines division of the Department of Health and Social Security, in patients with psychotic illnesses, particularly those with schizophrenia. We planned to replicate the earlier method of using propranolol for psychosis and if remissions occurred to modify the method to reduce the toxic effects.

Patients and Methods

Fourteen patients, nine men and five women aged 20-48, were selected on the basis of having overt psychotic illnesses with clear-cut symptoms by which to assess change (table I). There were 11 patients with hebephrenic schizophrenia, one (case 3) with a puerperal psychosis, one (case 10) with paranoid schizophrenia, and one (case 11) with schizoaffective psychosis. The schizophrenic symptoms had not responded to large doses of phenothiazine drugs, often given for months or years. The duration of the illness and of the episode studied here and the maximum dose of chlorpromazine previously used in their treatment—on average 450 mg/day—are shown in table II. Patients were excluded if they had heart disease, bronchial asthma, liver disease, diabetes mellitus, or other severe systemic illness.

Questions about "first-rank" symptoms of schizophrenia were asked in a structured interview and were rated as not present if there was any doubt. Ten items were considered: audible thoughts, somatic passivity, thought insertion, thought withdrawal, thought broadcast, passivity of feelings or impulses, passivity of volition, auditory hallucinations that described actions as they took place, hallucinatory voices discussing the patient, and primary delusions.

Two psychiatrists rated each patient on the brief psychiatric rating scale (B.P.R.S.) (Overall and Gorham, 1962; Turner, 1963), and the two ratings were averaged. The B.P.R.S. was modified by changing the scoring from 1-7 to 0-6. Three scales were added: excitement, disorientation, and pressure of speech. The scales were placed into three groups (table I): the "thought disorder" scales were conceptual disorganisation, hallucinatory behaviour, and unusual thought content; the "other schizophrenic" scales were blunted affect, grandiosity, suspiciousness, emotional withdrawal, motor retardation, and mannerisms and posturing; the "remaining" scales are self-evident.

At first Atsmon's (1972) regimen of propranolol administration was followed: this reached 1 g/day on day 2 and increased by 400-800 mg/day until remission or toxic effects occurred. Our earlier patients nearly all developed toxic effects and so this system was modified. The drug was given twice daily, the daily total was raised much more gradually, and propranolol was often combined with phenothiazine drugs. Propranolol was withheld if there were toxic symptoms or if the pulse was below 60/min or the blood pressure below 90/60 mm Hg.

All the patients were seen in a survey at the beginning of August 1974. Two psychiatrists made B.P.R.S. ratings and overall ratings of any toxic effects. They also rated the clinical state on a scale from −1 to 4: −1 = worse, 0 = unchanged, 1 = minimal improvement, 2 = moderate improvement, 3 = marked improvement, 4 = complete remission.

Results

THERAPEUTIC EFFECTS

Six of the 14 patients lost all their schizophrenic symptoms completely (table II). They felt and looked well. They were not euphoric; indeed, their affective reactions were appropriately modulated and were indistinguishable from normal. Several found the change hard to believe. The first evidence of improvement in these six patients was within a week of starting propranolol and at a dose which varied from 120-1,000 mg/day. The daily dose of propranolol at the time the symptoms remitted completely varied from 240 to 3,000 mg; the maintenance dose was 500-3,000 mg/day. The use of accompanying phenothiazine drugs is summarized in table II.

Of the remaining eight patients, improvement was "marked" in one, "moderate" in four, "minimal or transient" in two, and absent in one patient who left hospital after a short, severe, toxic reaction.

Propranolol was continued except in the patient in case 2, who left hospital, and the patient in case 10, who was transferred for

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TABLE I—*"First Rank" Symptoms of Schizophrenia and Scores on Brief Psychiatric Rating Scale (A) before Propranolol and (B) at Survey*

Case No.	Sex	Age (Years)	No. of "First Rank" Symptoms Present	Brief Psychiatric Rating Scale Scores							
				"Thought Disorder" Scales		"Other Schizophrenic" Scales		"Remaining" Scales		Total	
				A	B	A	B	A	B	A	B
1	M.	24	5	13	0	13	0	13	0	39	0
2	M.	30	4	10	8	15	2	25	11	50	21
3	F.	26	0	13	0	25	0	27	1	65	1
4	M.	38	5	16	0	15	0	31	1	62	1
5	F.	42	8	17	6	26	9	38	5	81	20
6	M.	24	2	13	0	22	0	29	0	64	0
7	M.	30	7	13	9	25	13	33	17	71	39
8	F.	36	6	14	5	24	5	22	1	60	11
9	F.	20	8	5	5	11	2	29	6	45	13
10	M.	48		8		11		9		28	
11	M.	33	0	8	0	13	0	25	0	46	0
12	F.	34	3	13	7	19	7	37	10	69	24
13	M.	27	4	9	0	0	0	9	0	18	0
14	M.	21	7	14	7	4	0	19	3	37	10

TABLE II—*Time Intervals to Improvement and Remission, Drugs Used, Toxic Effects, and Stateat Survey in 14 Patients. Figures in Parentheses apply to Earlier Courses of Propranolol*

Case No.	Duration of:		Propranolol Treatment					Previous Dose of Chlorpromazine (mg/day)	Concomitant Drugs (mg/day)		Toxic Effects					Survey		
			First Improvement		Remission		Maintenance Dose (mg/day)		Initial Dose	Maintenence Dose	Ataxia	Visual Hallucinations	Acute Confusional State	Pallor	Severity*	Discharged	State†	Time Since Remission (Months)
	Illness (years)	Episode (years)	Day	Dose (mg/day)	Day	Dose (mg/day)												
1	1	1	8	875	8	875	2000	800	Trifluoperazine (30)		− (+)	− (+)	−(+)	− (+)	0 (3)	+	4	<1
2	7	8 months	0					300			+	+	+	−	3	+	0	0
3	5 weeks	5 weeks	3	1000	15	3000	3000	400			+	+	+	−	3	+	4	5
4	3½	6 weeks (3½)	2	240	26	1500	1000	800	Chlopromazine (300)	Chlorpromazine (300)	− (+)	−(+)	−	− (+)	0 (3)	−	4	<1
5	17	6	90	2000			1500	800	Chlorpromazine (300)	Chlorpromazine (300)	+	−	−	−	2	−	2	0
6	6	8	3	750	3	750	750	450			−	−	−	−	0	+	4	6
7	13	11	42	2500			1500	150	Chlorpromazine (200)		+	+	+	+	2	−	2	0
8	10	5	42	720			1500	100	Chlorpromazine (100)	Trifluoperazine (15)	+	+	−	−	2	−	2	0
9	7	7	14	820			160	300			+	+	−	−	2	−	2	0
10	21	19	30	1000				400	Chlorpromazine (200)	Chlorpromazine (80)	−	−	−	−	0	−	1	0
11	2 months	2 months	4	120	10	240	500	550	Chlorpromazine (300)		−	−	−	−	0	+	4	2
12	9	6	6	120	(13)	(360)	1500	900	Promazine (300)	Promazine (300)	−	−	−	−	0	−	1	0
13	2½	2½	2	160	10	360	1250	250	Chlorpromazine (300)	Chlorpromazine (150)	−	−	−	−	0	+	4	1
14	7	7	3	240			1000	150			−	−	−	−	0	−	3	0

*Severity of toxic effects was rated as follows: 0 = none; 1 = mild, not interfering significantly with patient; 2 = moderate, significantly interfering with patient; 3 = severe
†see text for ratings.

surgery. All the clinical improvements were sustained in the individuals who continued to take propranolol. One patient (case 4), however, twice relapsed severely within days of stopping propranolol on his own initiative, but the symptoms remitted for the second and third time when propranolol was again introduced. The patient in case 12, who experienced temporary complete remission of symptoms, relapsed within two days after stopping her own tablets shortly before the survey.

Once the dose was stabilized no side effects were found.

TOXIC EFFECTS

The main toxic effects were ataxia, confusional states, and visual hallucinations. The frequency and severity of toxic effects are summarized in table II, which shows that the toxic effects were more common and severe with the earlier courses of treatment. Most of the unwanted reactions seemed related to raising the dose of propranolol rapidly rather than to the total daily dose. Toxic symptoms tended to occur when the dose exceeded 750 mg/day (though two patients who had shown evidence of toxicity while the dose was being increased were stabilized on 2 g and 3 g/day), but toxic reactions were fewer and milder when propranolol was given less often, when the dose was raised more slowly, and sometimes when it was combined with phenothiazine drugs which were later reduced or stopped.

Occasionally when large doses of propranolol were reached rapidly, ataxia began suddenly, seemed to be cerebellar in character, was occasionally gross, and subsided in minutes or hours. Sometimes ataxia was preceded by slightly slurred speech, or by "hysterical" incoordinated movements or emotional behaviour. Transient drop attacks, not associated with hypotension or loss of consciousness, were observed. Ataxia is not a well-known toxic effect of propranolol but it has been reported with large doses (Atsmon *et al.*, 1972).

Visual hallucinations sometimes occurred by day without any clouding of consciousness, and these have been noted before (Stephen, 1966). Visual and tactile hallucinations were also associated with a confusional state with disorientation and restless ataxic movements.

Case Reports

To illustrate these findings we describe two patients whose schizophrenic symptoms remitted completely. The first patient (case 1) had many toxic symptoms at first when propranolol was increased rapidly to a high dosage, but later with a modified regimen the schizophrenic symptoms remitted completely with no untoward effects. The patient in case 6 had a complete, rapid remission with no side effects.

CASE 1

One year after a depressed fracture of the right parietal bone a man of 24 began to feel strange. He heard voices "like multi-channel telecommunications," and believed that a girl's voice was seducing him by telepathy. Voices made brief comments on his behaviour, discussed him, and gave him messages and commands. He had thought insertion and somatic passivity, his thoughts were broadcast, he walked with his hands placed symmetrically on his thighs to keep his mental balance, and he was unkempt and uncommunicative. His speech was hesitant and slow, and he often lost track of a conversation and stared. "I have an unbalanced mind. Mind moves across the spectrum. Mind is bouncing. Mind moves from homosexual to lesbian and it's bouncing between them." The electroencephalogram showed a generalized abnormality which was maximal in the right parietal region.

He was given four courses of propranolol. The first two were stopped because of toxic effects and the third for an orchidopexy. Remission occurred on the eighth day of his fourth course.

In the first course propranolol was increased rapidly to 3 g/day over three days with the daily total divided into 10 doses. The voices began to say, "Concentrate on your heartbeat." By the fifth day he seemed a little more relaxed and cheerful (3·5 g/day). On day 7 (4 g/day) he had an episode of rapid breathing in which he clutched his abdomen, seemed agitated, felt weak, and was ataxic. He had some poorly defined left-sided chest pain which was not accompanied by any abnormal cardiovascular signs or electrocardiographical changes. On day 14 (4·1 g/day) he had an acute confusional state with marked incoordinate restlessness associated with striking pallor and transient hypertension (the blood pressure rose from 120/70 to 160/110 mm Hg; pulse 70/min). Within an hour he returned to his previous state. Propranolol was discontinued.

After this he was free of hallucinatory voices though he retained his delusions. Ten days later the hallucinations returned and propranolol was resumed. On day 12 of the second course (4·0 g/day), however, he developed a marked cerebellar type of ataxia with unsteady gait, mild incoordination of all four limbs, and bilateral horizontal nystagmus. Within two and a half hours he was walking quite normally again. Further attempts to increase the dose led to gross temporary ataxia: he could not sit upright, rise from a chair, or walk without the help of two people. Propranolol was continued in a dose of 3·5 g/day until it was stopped on day 21. Trifluoperazine (to 30 mg/day) with chlorpromazine (to 800 mg/day) was associated with little change. The third course of propranolol six months later was introduced more gradually with trifluoperazine 30 mg/day. The voices decreased, but the course was stopped for an orchidopexy.

In the fourth course propranolol was added to trifluoperazine (30 mg/day) to reach 0·5, 1 and 2 g/day by days 2, 18, and 32 respectively. On day 8 (875 mg/day) he looked better, and he felt "great" and "unusually relaxed." He heard no voices that day; he thought that the telepathy had all been his imagination. He continued to improve both in insight and behaviour as propranolol was gradually increased to 2,000 mg/day, and trifluoperazine was stopped. Instead of being occupied with seduction by telepathy he conversed and made plans to return home and to his old job. He looked back on the illness as a trance in which he used to imagine a girl whom he had seen only once. He was discharged on propranolol, free of symptoms.

CASE 6

A man of 24 requested urgent admission because he was burning up from the effects of the sun from which he would either die or go mad. He said that he had learned psychiatry but would like to stay indefinitely to study psychiatry, ceramics, and art. He was dishevelled; he walked up and down aimlessly; when spoken to he stared and looked away; he chuckled to himself, and talked in a hesitant, jerky, and often vague way. "It's a question of two things —the cup and the saucer—they're related—can't you see the two?" Odd mannerisms included suddenly putting the backs of his hands together "to shut myself up." He heard his own thoughts, knew that his thoughts were being broadcast, and had auditory hallucinations. He fluctuated between being agitated, afraid, sad, and perplexed; he did not seem elated or depressed. He had been ill intermittently for six years and the episode we treated had lasted for eight months. Previous treatment included chlorpromazine 450 mg/day.

Three days after starting propranolol (when on a dose of 750 mg/day and no other drugs) the "voices stopped and I became calm and reasonable." He went home that day and continued to take propranolol.

At follow-up interviews he remained calm and symptom free. He felt that he had matured. He obtained a place in college, worked steadily, and had remained well for six months at the time of writing.

Discussion

The initial schedule of giving propranolol every two or three hours was based on the fact that the half-life of propranolol in the plasma is about two and a half hours (Paterson *et al.*, 1970), and, furthermore, this method was reported to be effective (Atsmon, 1972). In our series, however, toxic effects commonly occurred in the afternoon or evening, which suggested a cumulative effect. It is now realized that the pharmacological half-life of propranolol is longer than the plasma half life, and in higher doses increasing the amount of propranolol tends to prolong its effects rather than increase the magnitude of the response (Carruthers *et al.*, 1973). Recent work with propranolol in hypertension has shown that it is just as effective when given twice a day as when given four times daily (Hansson *et al.*, 1971; Wilkinson *et al.*, 1974). We therefore raised the daily total more slowly, reduced the number of doses a day from 10 to two, and often added propranolol to an existing dosage of a phenothiazine drug, which was later reduced or stopped. To avoid the danger of toxic effects all patients were treated in hospital while the dose of propranolol was being increased and they were individually reassessed before each dose. An advantage of propranolol was the absence of any parkinsonian effects.

The mechanism of propranolol's action in florid schizophrenia and other psychoses is not known. The mode of action may not be so much by peripheral β-blockade as by stabilizing functions of the central nervous system. Animal experiments have shown that propranolol is concentrated in the grey matter of the brain (Masuoka and Hansson, 1967).

This preliminary report has many obvious limitations—for example, the study was not controlled, the follow-up was short, and sometimes phenothiazine drugs were also used. To confirm the place of propranolol in psychotic illnesses double-blind controlled studies will be needed to compare the effects of propranolol and phenothiazine drugs. Nevertheless, these early results suggest that a modified regimen may reduce the risk of the toxic effects of propranolol and yet retain its beneficial effects. If the findings of this study are extended and our results are confirmed in controlled trials propranolol may prove to be useful in the study and treatment of schizophrenia and other psychotic illnesses.

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