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Action of d-Propranolol in Manic Psychoses

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Summary. Six manic patients were treated with high doses of d-propranolol or d- and dl-propranolol in a double-blind, placebo controlled study. The following variables were measured: propranolol dosage, propranolol serum concentration, pulse frequency, blood pressure, and psychotic behavior. In all cases an improvement was noticed. High dosages were necessary to obtain sufficient effect. The antimanic property of d-propranolol was approximately 50% smaller than the antimanic property of dl-propranolol. We conclude that at least some part of the antimanic action of beta-blockers is independent from the beta-blocking property.

Key words: Manic psychoses – Beta blockers.

Zusammenfassung. Im Rahmen einer doppelblind durchgeführten, placebokontrollierten Studie wurden sechs manische Patienten mit hohen Dosen d- oder d- und dl-Propranolol behandelt. Dabei wurden folgende Variablen gemessen: Propranolol-Dosis, Propranolol-Serumkonzentration, Pulsfrequenz, Blutdruck und Psychopathologie. In allen Fällen konnte eine klinische Besserung festgestellt werden, aber hohe Dosen waren erforderlich, um einen befriedigenden therapeutischen Effekt zu erreichen. Die antimanische Wirksamkeit von d-Propranolol erschien, verglichen mit der von dl-Propranolol, um etwa 50% geringer. Aus diesem Ergebnis kann geschlossen werden, daß wenigstens ein Teil der antimanischen Wirksamkeit von Beta-Blockern unabhängig ist von den beta-blockierenden Eigenschaften dieser Substanzen.

Schlüsselwörter: Manische Psychosen – Beta-Blocker.

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1. Introduction

The reports of Atsmon and his co-workers (Atsmon and Blum, 1970; Atsmon et al., 1971; Atsmon et al., 1972; Atsmon, 1976; Steiner et al., 1972) on a dramatic improvement of acute psychoses under very high dosages of propranolol stimulated the interest of some other research groups in the treatment of different types of psychoses by beta-blocking agents (Auriol et al., 1972; Volk et al., 1972; Volk et al., 1975; Gardos et al., 1973; Schwarz and Mertin, 1973; Yorkston et al., 1974; Yorkston et al., 1976; Yorkston et al., 1977; Yorkston et al., 1978; Rackensperger et al., 1974; Rackensperger et al., 1976; v. Zerssen, 1976). The differences of the results concerning the antischizophrenic effect can partly be explained by the differences of the research methods and the selection of patients. Some groups could not replicate an antipsychotic effect in a small number of schizophrenic patients; however, an antimanic action could be observed in some patients with schizoaffective psychoses and in all patients with purely affective psychoses of a manic type if a high dosage of propranolol or oxpranolol (0.5 g or more per day for at least one week) was administered (Rackensperger et al., 1974; Rackensperger et al., 1976; Volk et al., 1973; Volk et al., 1975; v. Zerssen, 1976). From these results the hypothesis was derived that—as far as acute endogenous psychoses are concerned—manic syndromes represent the main psychotic target disorders for β-blocking drugs (Rackensperger et al., 1976; v. Zerssen, 1976).

The demonstration of an antimanic action of propranolol, which is the racemic mixture of the β-sympathicolytic l-propranolol and the practically non-sympathicolytic d-propranolol, raised questions about the mechanism of this effect and about the pathogenesis of manic syndromes. Because of the β-adrenergic blocking property of l-propranolol, one is tempted to hypothesize central β-blockade as the pharmacodynamic basis of the antimanic effect. This explanation favors the catecholamine hypothesis (Schildkraut, 1965) of affective psychoses. On the other hand, other central effects, a local anesthetic membrane stabilizing effect or an effect on central transmitters other than catecholamines (for example, a GABA-mimetic action), could be responsible for the dl-propranolol induced decrease of manic symptoms. We intended to decide between these two hypotheses by means of a therapeutic study with d-propranolol, the stereoisomer of l-propranolol which has practically no β-blocking activity (Lefkowitz et al., 1976). The β-blocking effect of d-propranolol is 50—100 times smaller than the β-blocking effect of l-propranolol. We were interested in knowing if there was any antimanic effect with d-propranolol and, if it existed, how intense it was in comparison with the antimanic action of dl-propranolol. From the answer of this question one might expect some information on a possible specificity of β-adrenergic blockade in the pharmacotherapy of mania. The first observations in two cases did not render definite interpretation because of complications of treatment which made necessary a withdrawal of the medication and a change of the design (see v. Zerssen, 1976).

2. Methods

A number of precisely documented single case studies was performed. The trials were done in a double blind design with placebo control. Only patients with pure manic syndromes who had no

symptoms of an organic disease and who agreed to participate in the study were included. Informed consent was obtained in all cases from the patients themselves and from close relatives before the trial was started. Schizoaffective patients were excluded from the study to avoid complications of evaluation. The patients were free of neuroleptic medication for at least six days before the beginning of the trial. During the study sedative drugs (chloral hydrate or paraldehyde) were allowed only for control of extreme excitement and aggressiveness. The trial began with a placebo period of at least four days, during which an extensive physical and neurologic examination[1] of the patient was performed. After the placebo period the application of d-propranolol[2] medication was started. Because of the short half life of propranolol (2.5 h) the medication was given six times per day. The daily dosage was increased individually under control of pulse rate, blood pressure, ECG, and EEG. This was done until a distinct effect on manic symptoms was observed, but a daily dosage higher than 3.0 g d- or dl-propranolol was not allowed to reduce the probability of major side-effects on heart muscle, CNS, and other organs (see v. Zerssen, 1976). The dosage, which caused a distinct antimanic effect, was continued for four days. Then the propranolol dosage was decreased and replaced by placebos for four days. If a patient relapsed during this placebo period, a second trial with dex-propranolol or (in a later stage of the study) with dl-propranolol was performed. After this second trial and subsequent placebo medication for several days, the patient was treated with neuroleptics in the usual manner. If during the propranolol medication the blood pressure dropped below a value of 90/60 mm Hg and/or the heart rate to values below 60 per minute, the medication was reduced or discontinued. Deviations from the design, for example a shortening of the placebo period, were allowed if the patient's behavior was too disturbing for ward life.

The psychopathologic changes during the trial were precisely described in the medical record by the physician in charge of the patient. In addition, the patient was rated daily by a psychiatrist not informed about the patient's medication. The rating was based on the Inpatient Multidimensional Psychiatric Scale (IMPS according to Lorr et al., 1963). The nurses told about the patient's medication documented their daily observation using the Nurses' Observation Scale for Inpatient Evaluation (NOSIE according to Honigfeld and Klett, 1965)[3]. The propranolol serum concentration was analyzed during the trial by one of us (E.R.) as a control of drug intake and for an estimation of pharmacokinetic data.

For evaluation of psychopathology the scores of five factors of the IMPS globally reflecting the manic symptomatology (Excitement, Hostile Belligerence, Grandious Expansiveness, Motor Disturbances and Conceptual Disorganization (see v. Zerssen and Cording, 1978) were averaged. This IMPS score and the score of the NOSIE were correlated with the daily dosage and serum concentration of propranolol and with the pulse rate. For an evaluation of the dose-effect relationship, we calculated the correlation coefficients according to Pearson's and Spearman's method. Further details of evaluation are given elsewhere (Emrich et al., 1979).

3. Results

It proved very difficult to find patients who fulfilled the criteria for the study and to complete the trials without deviations from our design. There are several reasons for these difficulties: the rarity of incidence of manic psychoses, the uncooperativeness of manic patients, the duration of the trial, and interference with spontaneous remission of the disease. As a result of investigation during three years we can communicate only the data of six cases treated with d-propranolol alone or in alternation with dl-propranolol.

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Case 1

Mr. B., a 51-year-old office worker, was suffering from a bipolar manic-depressive psychosis (ICD-No. 296.3). His mental disorder was first diagnosed three years ago. He had experienced one depressive and two manic episodes, during which he was treated in a psychiatric hospital.

Three weeks before admission to our hospital he presented symptoms of euphoric mood, extreme irritability, aggressive behavior, a feeling of superiority, increased activity, logorrhea, restlessness, squandermania, and sleep disturbances. After three days of clinical observation under placebo medication during which he exhibited the reported symptoms, he received d-propranolol in daily increasing dosages up to 2760 mg per day. Three days after the beginning of medication the higher dosages of d-propranolol led to a distinct decrease of manic symptoms. While the patient received the highest dosage, he showed practically no signs of mania. During decreasing propranolol dosage the manic symptoms gradually recurred, and on the first placebo day the same clinical picture reappeared as had been observed on admission. The patient was

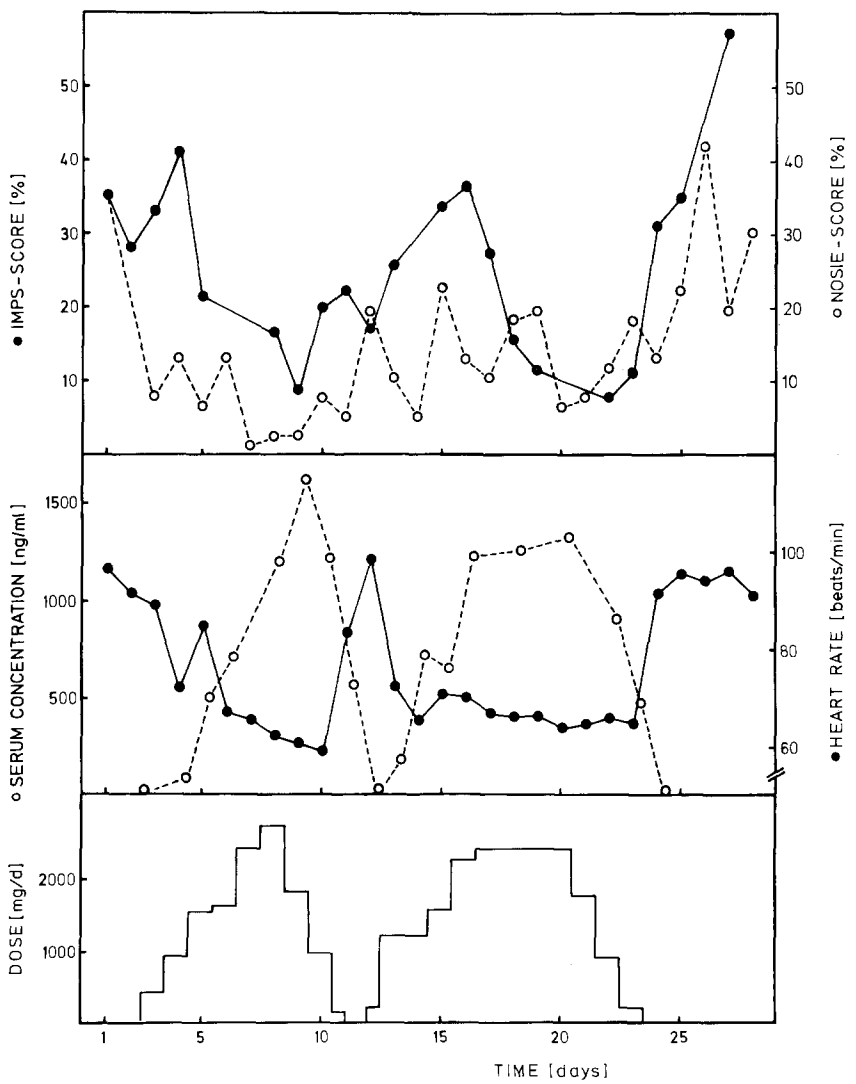

Fig. 1. Treatment of a 51-year-old manic patient with d-propranolol

very irritable, aggressive, and extremely disturbing in his behavior so that after one day of placebo medication, he had to be put again on active medication. During the second treatment period with d-propranolol the manic symptoms diminished once again. While the patient received a dose of 2400 mg per day, he was almost inconspicuous, cooperative, and well integrated in ward activities. After four days the d-propranolol dosage was gradually reduced, and the patient again became increasingly inadequate in his behavior. During the third placebo period he relapsed completely: He was restless, irritable, hyperactive, logorrhoic, could not sleep and wrote official notes during the whole night. Neuroleptic treatment (24 mg haloperidol) gradually induced a disappearance of symptoms.

Figure 1 shows the scores of IMPS factors, the NOSIE scores, pulse rate, propranolol serum concentration, and oral dosage as a function of time. The data are well in accordance with our clinical impression. The IMPS scores and the NOSIE scores are closely correlated with each other. The reductions of the IMPS scores and the NOSIE scores run parallel to the reduction of pulse rate and are in inverse proportion to propranolol dosage and propranolol serum concentration.

Case 2

Mrs. E., a 35-year-old housewife, was suffering from a bipolar manic-depressive psychosis (ICD-No. 296.3). The patient had already experienced several depressive and manic episodes of short duration during the last year which required clinic admission. The change from one phase to another occurred very rapidly. During periods of pronounced depression she repeatedly made serious attempts to commit suicide.

Several days before the admission to our hospital the patient was unable to sleep and suffered from increasing restlessness. She was very generous in spending money and began countless activities. Her elevated mood could easily change into one of irritation or even rage and anger, especially when she was criticized. She showed dominating and sometimes verbally aggressive behavior. During nine days of clinical observation and examination, at first without medication, later with placebo, there was little change in symptoms. Then the patient received d-propranolol in daily increasing dosages up to a peak of 2900 mg per day, which had to be reduced to a plateau dosage of 2400 mg because of repeated reduction of pulse rate below 60/min. From a clinican's point of view improvement was only modest. Under the highest dosages the patient seemed to be somewhat less dysphoric. The verbal aggressiveness, irritability, loudness, and restlessness were not so noticeable. Clinical appearance fluctuated greatly. The therapeutic effect was not satisfactory, but the patient was slightly more cooperative and tolerable on the ward. During the decrease of d-propranolol and especially during the two days of placebo medication, there was a remarkable aggravation of the clinical features. Therefore, a daily medication of chloral hydrate (up to about 1.5 g) was necessary. The placebo period had to be finished after two days because the patient was not tolerable on the ward at this time.

The treatment with d-propranolol was started again; however, the dosage could be increased only up to about 2900 mg because of heart rate reduction. Nonetheless, the improvement was somewhat better than during the first treatment episode. During decreasing of d-propranolol and after termination of d-propranolol medication, the patient's manic behavior showed a marked increase. She was constantly on the go, never seemed to tire, and she was in a dysphoric mood and reacted with anger and aggression whenever her wishes were not immediately fulfilled. Because of her disturbing behavior it was necessary to isolate her at times. Haloperidol in combination with lithium quickly led to a full remission of the manic dysphoric syndrome.

Figure 2 shows the variables measured. The ratings of the physician and of the nurses are well correlated and in concordance with the reported global clinical impression. The psychopathologic improvement is parallel with the reduction of pulse rate and in inverse proportion to the propranolol dosage and the propranolol serum concentration.

Case 3

Mrs. G., a 26-year-old student, was suffering from the sixth episode of an endogenous mania (ICD-No. 296.1). For the last five years the patient had had yearly a manic episode. One year before this admission she had been treated with dl-propranolol in two trials (compare Case 6 of

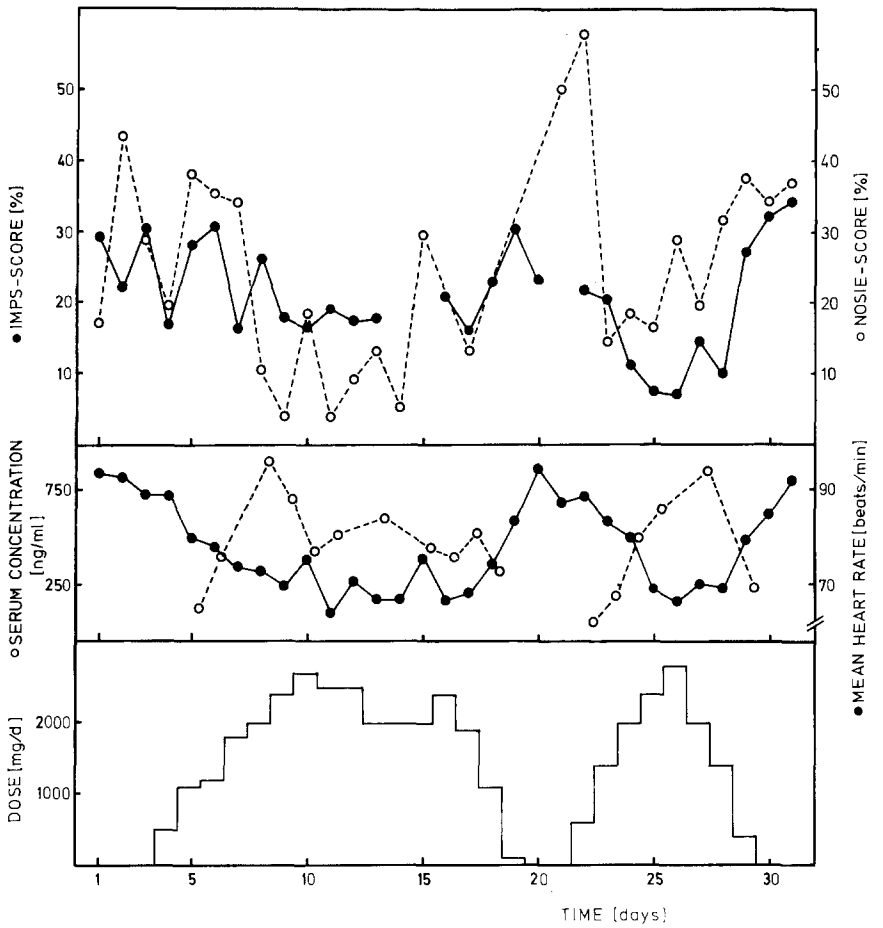

Fig. 2. Treatment of a 35-year-old manic patient with d-propranolol

Rackensperger et al., 1976). In the first trial there was a remarkable decrease in manic symptoms, especially of excitability and conceptual disorganization, by a dosage of 760 mg; in the second trial, by a dosage of 2300 mg.

For an unknown period of time before this admission the patient showed augmented activity, excess speech, was fond of traveling, performed a striptease in front of strangers, could not sleep, and rioted throughout the night in her apartment. After admission, in addition to these symptoms the patient was extremely irritable, exhibiting flight of ideas and feelings of superiority. She tried to provoke the doctor to sexual acts by doing the striptease. She cried for several hours and went to the toilet on the floor. She was so excited that during the first days after admission, therapy with neuroleptics was necessary in order to make clinical examination possible. As a result of the medication with 10 mg haloperidol and 25 mg periciazine, a distinct improvement was induced. Some days later neuroleptics were intermitted to start the first d-propranolol trial. The same clinical features as seen on admission recurred during the placebo treatment. Under higher dosages of about 2000 mg d-propranolol we observed a distinct improvement: The patient was less excited and hyperactive, more orderly and adequate, and showed no disturbances of thinking. After we stopped giving d-propranolol, the symptoms returned. The patient showed nearly the same clinical features as on admission.

After six days the second trial began. Through a misunderstanding the patient was treated with dl-propranolol instead of d-propranolol. Although the symptoms did not decrease as much as during the first trial with d-propranolol, the dosage could not be increased beyond 1200 mg

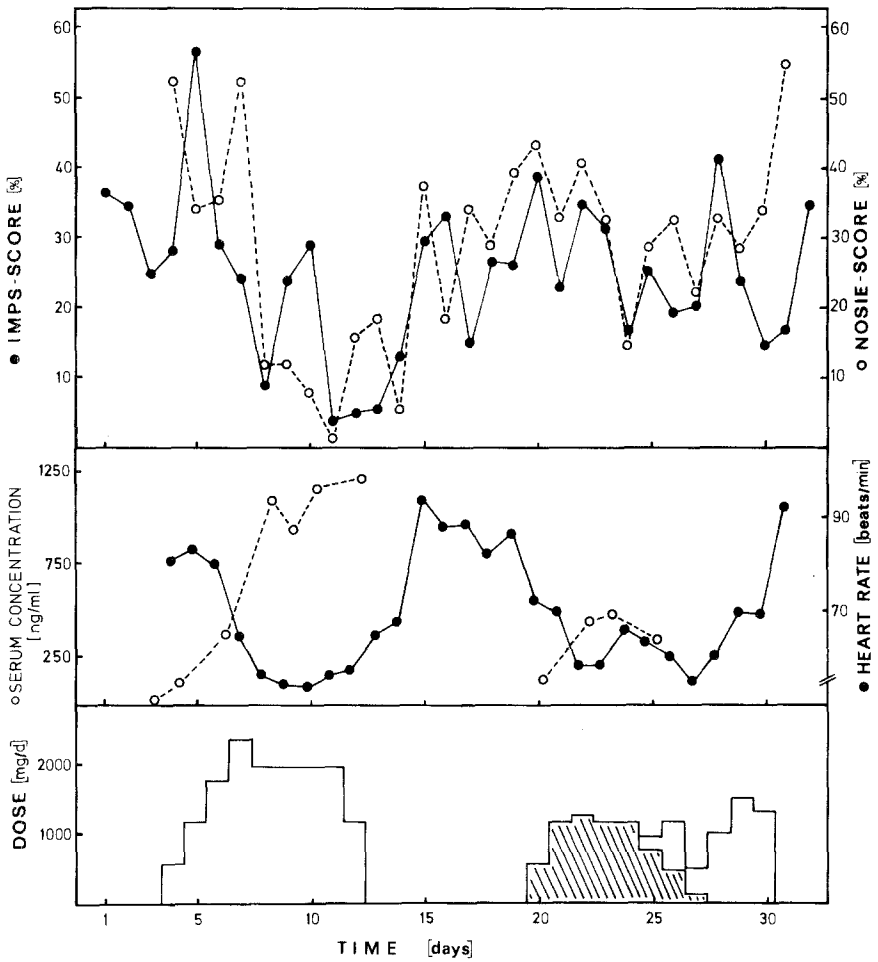

Fig. 3. Treatment of a 26-year-old manic patient with d-propranolol (□) and dl-propranolol (▨)

because of a pronounced reduction of heart rate. Dl-propranolol was then replaced by 1600 mg d-propranolol. This dosage could not be raised because of the low heart rate. There was no impressive difference between the effect of this dosage of d-propranolol compared to 1200 mg dl-propranolol. After stopping medication the patient again developed a full manic syndrome. Her behavior was so disturbing that it was necessary sometimes to isolate her from other patients. Two days later we began a neuroleptic medication (150 mg chlorprothixene, 60 mg periciazine). With this therapy a remission was gradually obtained.

IMPS and NOSIE scores (Fig. 3) are in accordance with the reported clinical impression. As far as we can judge from the short treatment period, there is no marked difference between the antimanic effect of d- and dl-propranolol. Oral dosage and serum concentration of propranolol are in inverse proportion to the antimanic effect and the reduction of pulse rate.

Case 4

Mrs. K., a 32-year-old secretary with a manic syndrome, was interpreted as a reactive psychosis based on an irritable personality with low intelligence (ICD-No. 298.1, 301.3, 310). At first we considered the diagnosis of an endogenous mania (ICD-No. 296.1). The differential diagnosis was not absolutely clear.

Over the last 17 years the patient had repeatedly developed attacks of psychomotor excitation and/or hysteriform behavior. Therefore, she was treated in various hospitals under different diagnoses ranging from oligophrenia, brain damage, epilepsy, and personality disorder to endogenous psychosis.

The patient was admitted to our hospital because she was in a euphoric mood and infantile in behavior. She showed a tendency to quick changes of mood from euphoria to dysphoria and depression depending on the situation. Logorrhea, flight of ideas, feeling of superiority, ideas of divine mission, and augmented drive could also be noted. During clinical examination and observation, psychopathology showed great fluctuation, but no spontaneous remission occurred. During treatment with higher dosages of d-propranolol up to 2400 mg, a pronounced improvement could be observed. The patient became almost well-balanced, cooperative, kind, less impulsive and less disturbed in thinking, and could integrate herself in the ward. She gained more distance from her ideas of divine mission, although she still showed slight manic symptoms. During the decrease of medication the patient relapsed and showed the same maniform features as on admission.

Because the patient's behavior became too disturbing, a placebo interval was not possible. We had to begin the next treatment period immediately, this time with dl-propranolol. The dl-propranolol dosage could only be increased up to 850 mg because of pronounced reduction of heart rate. With this dosage the same antimanic effect as in the d-propranolol treatment period was obtained. While medication was being decreased and during the subsequent placebo

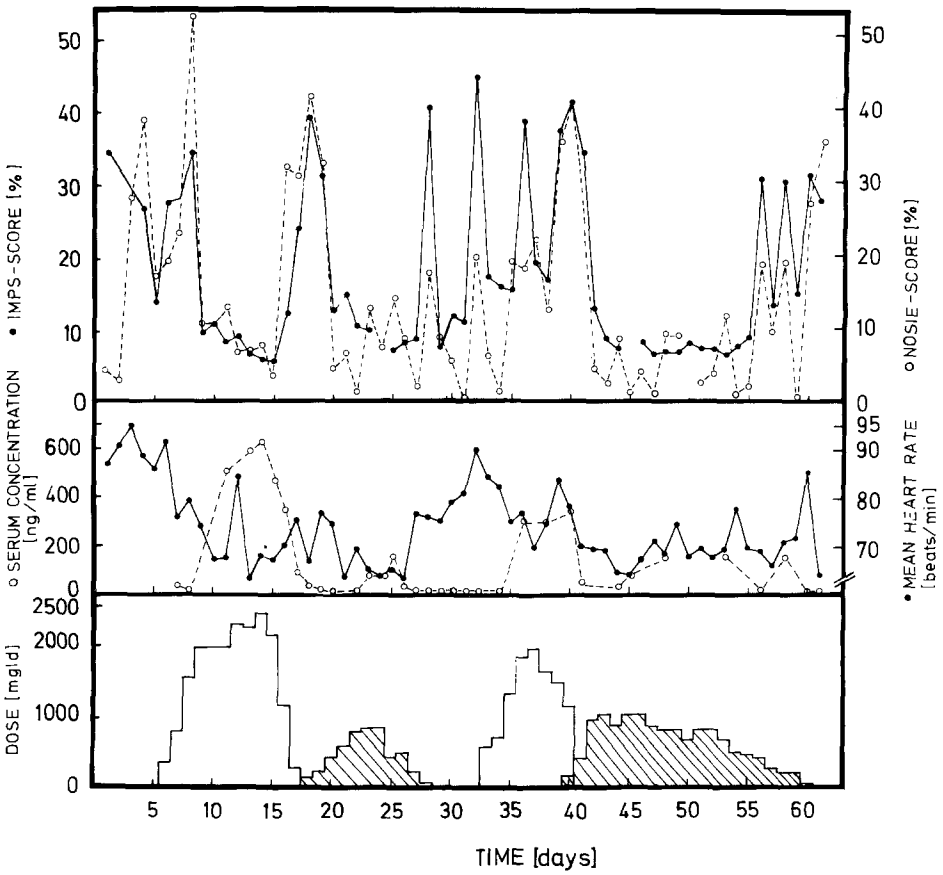

Fig. 4. Treatment of a 32-year-old manic patient with d-propranolol (▭) and dl-propranolol (▨)

period, the patient again developed her maniform behavior. We tried to eliminate this symptomatology using the same dosage of d-propranolol as of dl-propranolol in the last treatment period, e.g., 840 mg. The effect was not satisfactory, however, and an increase of dosage was necessary. With higher dosages up to 2400 mg the antimanic effect was also only modest in comparison with the first d-propranolol treatment period. In contrast to this, a treatment with about 1000 mg dl-propranolol during the following few days had a pronounced effect comparable to that of the first dl-medication. To find out a therapeutically satisfying combination of a relatively low dl-propranolol dosage and a neuroleptic, we added 25 mg periciazine to the 1000 mg dl-propranolol and then reduced the dosage of propranolol to evaluate the minimal necessary dosage. In spite of the combination with periciazine, the patient relapsed gradually into her maniform behavior during the decrease of propranolol. During the following few days she refused to take neuroleptics; therefore, we accepted her demand to take only 2 tablets of oxazepam per day. This medication had a slight tranquilizing effect, but the patient was always disturbed by hyperactivity, elevated mood, unrealistic ideas, and irritability. Three weeks later she was discharged, only slightly improved.

IMPS and NOSIE scores (Fig. 4) are well correlated with each other and with the clinical impression. The fluctuation of symptomatology is particularly remarkable in this case. Dl-propranolol seems to be three times more effective than d-propranolol. The reduction of pulse rate during the second d-propranolol treatment period is not so pronounced as in the first d-propranolol treatment period. This correlates with the less distinct change of manic symptomatology.

Case 5

Mrs. Sc., a 22-year-old office assistant, was suffering from a manic syndrome of a circular psychosis (ICD-No. 296.3). The patient had gone through several hypomanic and depressive episodes which had not required hospitalization.

Six weeks before admission to our hospital she showed euphoric and sometimes dysphoric moods, rambling and excessive speech, augmented activity and irritability, unrealistic planning, and reduced need of sleep. During four days of clinical examination and observation great fluctuation of symptoms became obvious. We started drug treatment with d-propranolol and noticed a remarkable improvement with dosages of 2000 to 3000 mg per day. Apart from modest dysphoria and irritability, the patient reacted adequately and cooperatively on the ward. Two days after withdrawal of medication the symptoms recurred, but did not reach the same degree as on clinical admission. In contrast to this clinical impression of physicians and nurses, the IMPS rater did not notice the change in psychopathology until the third day. The reasons for the discrepancy between IMPS and NOSIE raters will be discussed in the following case report.

In the second treatment period dl-propranolol was given up to a dosage of 2000 mg per day. Because of the pronounced reduction of heart rate, a greater increase of the dosage was not possible. During this period we saw a distinct improvement comparable with the change during the first treatment period. Since there was no relapse after the end of the dl-propranolol treatment, interference with spontaneous remission seems probable. Because of spontaneous remission during the second period of the study the evaluation of the drug effect can only be based on the first trial.

Figure 5 shows a reduction of IMPS and NOSIE scores and the pulse rate during d-propranolol treatment. As mentioned above, there is a discrepancy between NOSIE and IMPS during the placebo interval after the first treatment period. After the end of the second treatment period, pulse frequency increases but the scores of IMPS and NOSIE do not.

Case 6

Mrs. L., a 48-year-old housewife, was suffering from an endogenous mania (ICD-No. 296.1). The patient had been hospitalized during her first manic episodes six years ago.

A few days before admission to our clinic the patient became again increasingly euphoric, but unstable in mood. She was hyperactive and moved quickly from one activity to another, never finishing what she started to do. She was hypersociable and intimate with strangers; at times she misidentified people and took strangers for friends of hers. She spoke without inter-

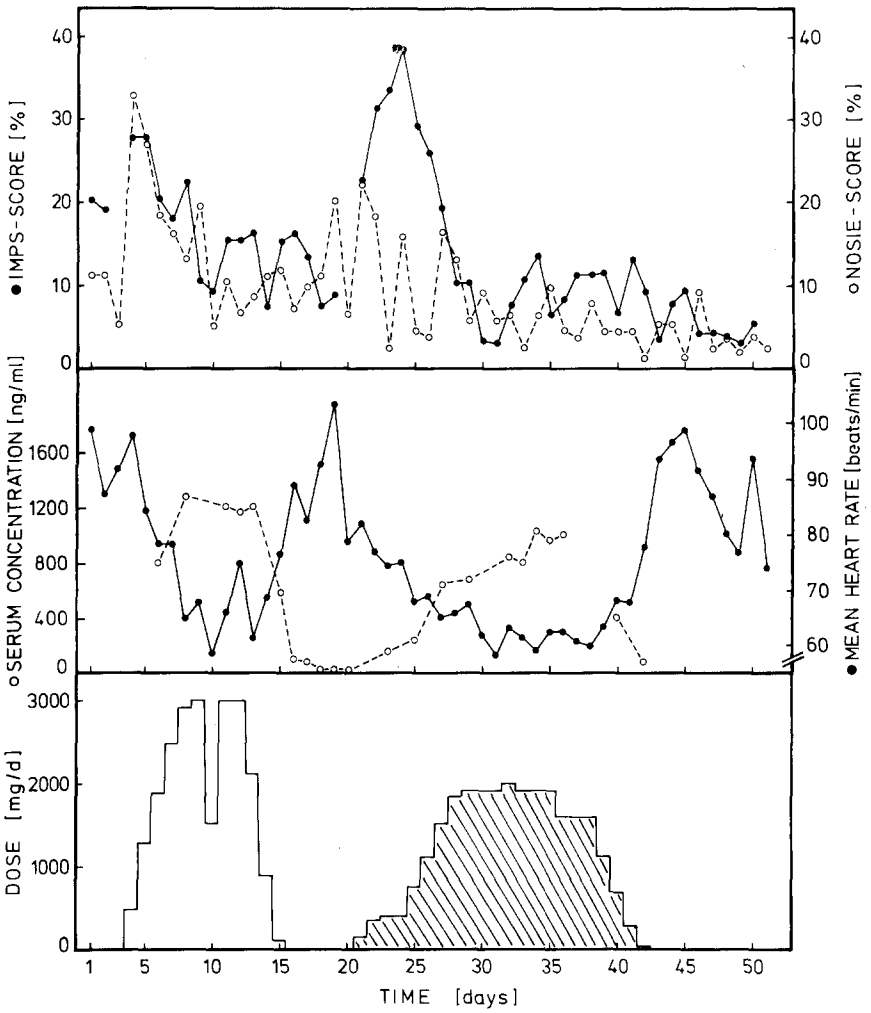

Fig. 5. Treatment of a 22-year-old manic patient with d-propranolol (□) and dl-propranolol (▨)

ruption and was unable to adhere to a line of thought and pursue it to a logical conclusion. She disregarded the needs of others and reacted aggressively if criticized. During the first trial we used dl-propranolol in a dosage of only 240 mg per day (because of the intensive reduction of heart rate). This dosage was not sufficient to attain the desired effect. However, the patient nevertheless showed a slight decrease of activity and less restlessness. After withdrawal of dl-propranolol, a worsening of symptoms was observed clinically. After the end of the placebo period the patient received d-propranolol. It was not possible to increase the dosage beyond 1200 mg per day because of the reduction of heart rate. According to our clinical impression a slight improvement occurred. The patient's behavior showed great fluctuation; sometimes she was euphoric or dysphoric, logorrhoic, loud and hyperactive, sometimes more depressive and inclined to weep. After withdrawal of medication, an increase of symptoms occurred. The patient was often in a wildly euphoric mood, logorrhoic, rambling, singing, and reciting poems. Three days after the end of the d-propranolol treatment, we started a treatment with haloperidol (24 mg/day) and lithium. As a result of this medication, the symptoms gradually disappeared.

There is a discrepancy (Fig. 6) between the IMPS ratings, the clinical impression of the

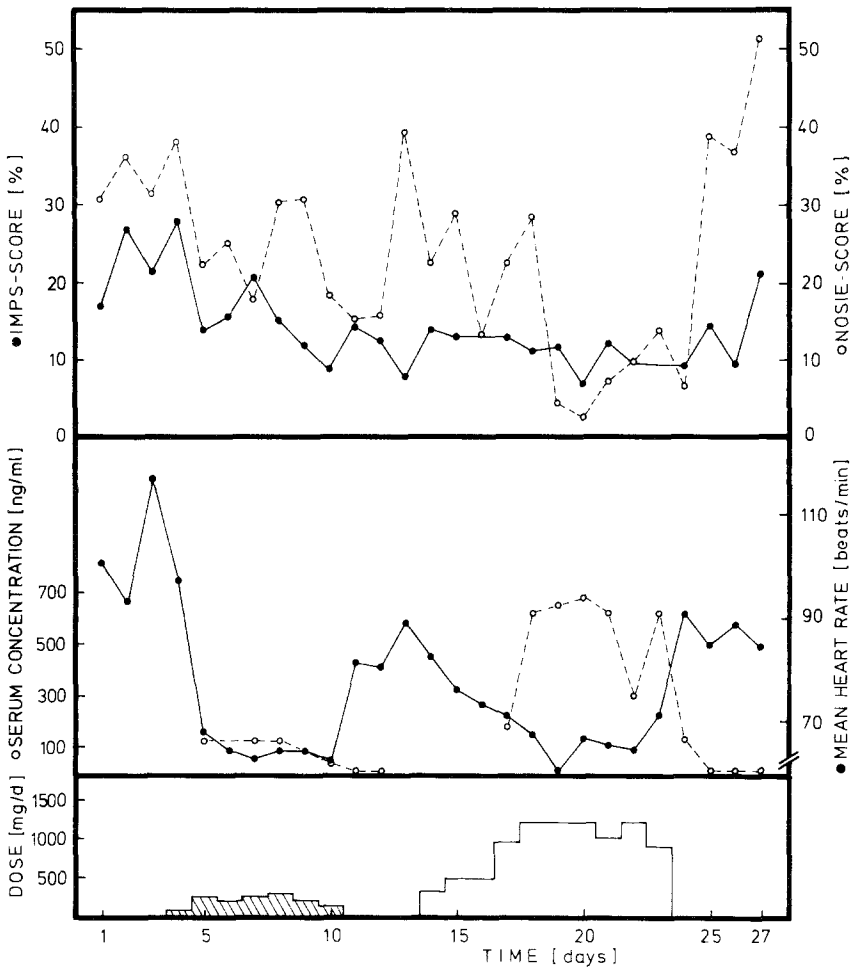

Fig. 6. Treatment of a 48-year-old manic patient with dl-propranolol (▨) and d-propranolol (□)

physician in charge of the patients, and the nurses rating (NOSIE). NOSIE scores are slightly better correlated with the oral dosages and the serum concentration of d-propranolol and still better correlated (in inverse proportion) to the reduction of pulse rate. The discrepancies between the ratings of the IMPS rater and the nurses can be explained by the fact that the nurses were able to observe the patients during the whole day, whereas the IMPS rater could observe the patient only for short periods of time. On the other hand, this result may reflect a bias on the part of the nurses who were aware of the stages of treatment in contrast to the IMPS rater who was not informed about the actual medication. For quantitative evaluation of dose-effect relationship we used only the data of the d-propranolol period because, according to our experiences, the dl-propranolol dosage was too low to be clinically effective.

We made the observation that the manic symptoms of six patients were reduced during treatment with d-propranolol. The intensity of all manic symptoms decreased, not only disturbances of affect and activity, but also disturbances of thinking. The antimanic action depended on the dosage, became observable a few days after the beginning of d-propranolol medication, and disappeared after

Table 1. Results of d- or dl-propranolol treatment

Patient	ICD-number	Sex	Age	Propranolol	Plateau dose (mg) per 24 hours	Maximal propranolol plasma level	Success	Spearman's rank correlation coefficient IMPS/propranolol	Rank correlation coefficient NOSIE/propranolol
1	296.3	m	51	d	2760	1600 ng/ml	++	−0.61	−0.55
				d	2400	1400 ng/ml	++		
2	296.3	f	35	d	2400	900 ng/ml	+	−0.60	−0.60
				d	2700	900 ng/ml	+		
3	296.1	f	26	d	2000	1250 ng/ml	+	−0.30	−0.42
				dl	1200	450 ng/ml	(+)	−0.13	−0.19
4	298.1	f	32	d	2400	600 ng/ml	++	−0.42	−0.06
				dl	840	200 ng/ml	++	−0.63	−0.43
5	296.3	f	22	d	3000	1200 ng/ml	+	−0.27	−0.22
				dl	2000	1100 ng/ml	spontaneous remission		
6	296.1	f	48	dl	240	100 ng/ml	no evaluation, dosage too low		
				d	1200	700 ng/ml	(+)	−0.43	−0.71

++ recovery or marked improvement; + moderate improvement; (+) slight improvement

the discontinuation of the active medication. The antimanic effect was not the same in all patients. Two patients showed marked improvement; two, moderate; and two, slight improvement (Table 1). In most cases the correlation of psychopathologic changes and the dosage of propranolol from the previous day lies between 0.4 and 0.6 (Table 1). High dosages were necessary to induce a sufficient therapeutic effect. Generally the daily dosage lay between 2000 and 3000 mg d-propranolol.

In addition to the six cases reported here in detail, two other young female patients suffering from endogenous mania were treated with d-propranolol. The first of them was only hypomanic, however, and her symptoms during the first placebo period were not marked enough to evaluate an improvement quantitatively with sufficient reliability. The other patient exhibited such an extreme degree of manic behavior that it was necessary to apply injections of haloperidol during the first few days of the d-propranolol treatment period. The clinical improvement was almost complete during a treatment period of 12 days. As the patient did not relapse during the subsequent placebo period, there was no indication for another drug period.

Apart from the expected reduction of pulse rate and signs of hypotensive dysregulation, no other side effects of therapy with dosages of d-propranolol up to 3.0 g/day were observed. In our former study with still higher and more rapidly increasing dosages of d- and dl-propranolol, more serious side effects were recorded (Rackensperger et al., 1974, 1976; v. Zerssen, 1976). They led to a change of the dose schedule in our design.

We performed two interindividual comparisons of d- and dl-propranolol treatment. In the first case (case 3) d-propranolol proved to be more effective than dl-propranolol. In the second case (case 4) dl-propranolol was nearly three times more effective than d-propranolol. Including the results of our dl-propranolol study (Rackensperger et al., 1976), we had the global impression that generally the antimanic effect of d-propranolol was smaller than that of dl-propranolol: Higher dosages were necessary to induce the same effect. To come to a decision about the intensity of the antimanic effect of d- and dl-propranolol, we performed a quantitative comparison of all our trials with d- and dl-propranolol in mania (Emrich et al., 1979). This comparison has led to the conclusion that the antimanic effect of dl-propranolol is on the average about twice that of d-propranolol.

4. Discussion

According to our findings an antimanic action is exerted not only by dl-propranolol but also by d-propranolol. Compared with the neuroleptic therapy of manic syndromes, the essential advantage of propranolol is that the patients have no extrapyramidal side effects and have not the feeling of being restrained. Apart from bradycardia and signs of hypotensive dysregulation, other side effects are rare and usually not serious if the dosage is not increased too rapidly. The antimanic action of propranolol resembles most the antimanic effect of lithium (see Schou, 1974). Considering the fact that the antimanic action of propranolol

is only modest and that the propranolol treatment of mania must be controlled very intensively, it is not recommended that the neuroleptics in the treating of mania be replaced by either d- or dl-propranolol.

The antimanic effect of propranolol seems to be somewhat different from mere sedation, since the patient did not feel tired during medication and the EEG curves did not exhibit changes similar to these induced by typical sedatives (Coulin et al., in preparation). On the other hand, there is some evidence that the antimanic effect of propranolol is a central effect: Apparently the antimanic effect of propranolol is not caused by a peripheral mechanism (peripheral β-adrenergic receptor blockade or peripheral membrane stabilization). The patients do not feel exhausted; therefore, the reduction of psychomotor excitation cannot be explained by somatic exhaustion. Not only motor excitation and affective disorders change, but also disturbances in thinking disappeared. The latter effect can hardly be explained by a peripheral effect. In animal experiments only beta-blockers which are able to pass the blood brain barrier showed a marked effect on excitation (Engel and Liljequist, 1976; Delini-Stula and Meier, 1976). There are some animal experiments which indicate a central effect of propranolol (Goldman et al., 1971; Leibowitz, 1970; Margules, 1970, 1971; Greenblatt and Shader, 1972; see Jefferson, 1974; Koella, 1977; Schwarz, 1975).

The quantitative comparison of all our trials with d- and dl-propranolol in mania (Emrich et al., 1979) has led to the conclusion that the antimanic effect of d-propranolol is on the average about twice that of d-propranolol. However, this conclusion is based on only a small number of patients. Nonetheless, the antimanic effect of d-propranolol observed in our investigation cannot be explained exclusively through the contamination of the tablets with 2%–3% beta-blocking l-propranolol (see Emrich et al., 1979; Riedel et al., in press) or by a minimal beta-blocking activity of d-propranolol. In 3000 mg d-propranolol there can exist maximally a beta-blocking activity equivalent with about 200 mg dl-propranolol. We have observed that a satisfying antimanic effect usually is only to be expected from much higher doses of dl-propranolol (500–3000 mg/day). Therefore, we conclude that at least some part of the antimanic action of dl-propranolol must be caused by a mechanism which is independent of the beta-blocking property of propranolol. On the other hand, we conclude from the observed data—the antimanic effect of dl-propranolol is more pronounced—that the beta-blocking property seems to be one of the mechanisms of antimanic action of propranolol.

The fact that d-propranolol is less effective in maniform excitation than dl-propranolol is supported by findings from animal experiments. Using an animal model of manic excitement (pargyline-reserpine induced locomotor excitation in mice), Delini-Stula and Meier (1976) found that d-propranolol was less effective than l-propranolol by the factor of 10. Treating locomotory activity in mice Engel and Liljequist (1976), observed that d-propranolol was less effective than dl-propranolol by the factor of 80. Whereas the results of Engel and Liljequist give evidence for a pure beta-blocking effect, we conclude from the results of Delini-Stula and Meier that the effect is caused not by beta blockade alone. The model of Delini-Stula and Meier seems to be the most adequate animal model of mania, and their findings are in basic accordance with the results of our clinical investigations.

On the basis of our experimental findings we conclude that d-propranolol has an antimanic property approximately 50% less than the beta-blocking property of dl-propranolol. At least part of the antimanic action of d-propranolol is caused by a mechanism which is independent of the beta-blocking property of propranolol. This hypothesis raises many questions concerning the possible molecular mechanism of the non beta-blocking antimanic property (see Emrich et al., 1979). One possibility is the well-known anesthetic (membrane stabilizing) effect in which d- and dl-propranolol are equipotent. On the other hand, some other central effects of propranolol have to be discussed—for example, a GABA-mimetic effect or an effect on other central transmitters.

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