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Outcome and Risks of Ultra-Long-Term Treatment with an Oral Neuroleptic Drug

Relationship Between Perazine Serum Levels and Clinical Variables in Schizophrenic Outpatients

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Summary. In 33 schizophrenic patients treated continuously as outpatients with perazine over two decades, the rehospitalization rate decreased from 0.58 before treatment to 0.07 during treatment. The intensity of psychopathologic symptoms and the side effects were found to be remarkably low. The high intraindividual constancy of perazine plasma levels and the tight correlation between dose and plasma levels indicated satisfactory patient compliance. Plasma levels amounted to only 25% of those under acute treatment and correlated positively with the severity of the disease. Higher plasma levels coincided with more frequent side effects such as slightly pathologic liver function and moderate impairment of oral glucose tolerance. The results suggest that low-dose maintenance treatment of schizophrenic patients with oral neuroleptics is effective and relatively safe.

Key words: Long-term treatment – Schizophrenic outpatients – Perazine plasma level – Outcome – AMP system

Zusammenfassung. Bei 33 schizophrenen Patienten, die seit durchschnittlich 18 Jahren kontinuierlich ambulant mit Perazin behandelt wurden, sank die Rehospitalisierungsrate pro Jahr von 0,58 vor auf 0,07 während der Behandlung. Die Intensität der psychopathologischen Symptomatik sowie der Nebenwirkungen waren bemerkenswert gering. Die hohe intraindividuelle Konstanz der Perazin-Plasmaspiegels und die enge Korrelation zwischen Dosis und Plasmaspiegel sprach für eine befriedigende Compliance (Behandlungstreue) der Patienten. Die Höhe der Plasmaspiegel betrug nur etwa ein Viertel der

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Spiegel, die während einer Akutbehandlung gemessen werden, und sie korrelierte positiv mit der Schwere der Erkrankung. Je höher die Plasmaspiegel waren, desto häufiger waren Nebenwirkungen wie geringfügig pathologische Leberfunktion und eine mäßige Verschlechterung der oralen Glucosetoleranz.

Die Ergebnisse legen den Schluß nahe, daß eine niedrig dosierte Langzeitbehandlung schizophrener Patienten mit oralen Neuroleptika effektiv und relativ sicher ist.

Schlüsselwörter: Ambulante Langzeitbehandlung – Schizophrene Patienten – Perazin-Plasmaspiegel – Erfolgsstudie – AMP-System

1 Introduction

Double-blind controlled clinical trials provide the most reliable information about efficacy and risks of a particular drug treatment. As regards neuroleptic therapy of schizophrenic patients, such controlled studies, however, have been performed up to a maximal duration of three years (Davis 1975; Woggon et al. 1975; Pietzcker 1978). The performance of controlled studies over still longer time periods would raise nearly unsurmountable organizational and ethical difficulties. As a rule, patients receiving a placebo would be switched to an active medication after having suffered from a relapse, although in fact it would be necessary to continue the placebo treatment even after a relapse to allow a realistic comparison of clinical outcome under two different treatments. The same holds true for a controlled comparison of one neuroleptic drug with another, or of drug treatment with psychotherapy. As soon as a particular therapeutic procedure has proved to be more effective than another, it is hardly justifiable to withhold this therapy from the control group. On these grounds, we are depending on the evaluation of naturalistic therapeutic strategies when it comes to the critical assessment of the effects of very long-term neuroleptic therapy.

We had the opportunity to do such evaluations since in this department a comparative examination of the long-term effects of insulin coma versus neuroleptic maintenance treatment with perazine was performed during the early stages of the neuroleptic era (Hippius et al. 1961, 1967; Helmchen et al. 1967). A subgroup of the patient sample from that investigation has remained under our care up to the present. These patients have been treated now for nearly two decades within a special schizophrenic outpatient clinic attached to the hospital. There is no doubt that we are dealing here with a highly selected patient group. This hospital usually treats patients from the middle and upper classes (Bosch and Pietzcker 1975). In the meantime many patients have dropped (Gonçalves 1978), so that only the cooperative (compliant) patients can be examined. On the other hand, this is a positive factor in as much as the investigators have acquired an intimate knowledge of the course of the disease and its therapy in that patient group. Furthermore, all patients are treated with an oral neuroleptic of low potency (perazine) for which a reliable gas chromatographic determination method could be developed.

The present investigation was focused on (i) the clinical outcome and risks of a very long-term treatment, (ii) the constancy of the perazine serum levels, and (iii) the relationship between serum levels and clinical symptoms or side effects.

2 Patient Sample and Methodology

2.1 Selection Criteria

All patients who have been treated continuously with perazine during at least the last ten years were included in this study[1].

2.2 Description of the Patient Sample

Of the 33 schizophrenic patients examined, 29 were female and 4 male. The mean age was 55 ± 11 years, ranging from 33 to 79. All patients had been treated previously as inpatients of this hospital before they were transferred to the outpatient clinic for maintenance treatment. The average duration of treatment within the outpatient clinic was 18 ± 2.1 years. The aim and organizational structure of the schizophrenic outpatient clinic is described elsewhere (Gonçalves 1978).

2.3 Clinical Assessment

The retrospective longitudinal assessment of the course of the disease, including calculation of the number of relapses and the total cumulated perazine dose, was based on the patients' files.

The perazine serum concentration was determined two times within an interval of two weeks by a gas chromatographic method developed in this laboratory (Müller-Oerlinghausen et al. 1977; Schley et al. 1978). Information on the time and amount of medication during the last 24 h was given by the patient. Compliance of the subjects was not controlled. As we did not want to influence the usual medication pattern of the patients, they were not informed beforehand about the reason for the blood sample and the background of this study altogether. Blood samples were drawn on average 15 ± 7 h after the last tablet was taken.

As suitable liver function tests, the enzyme activities of GPT[2], GOT[2], and γ-GT[2] were determined. Pathologic liver function was assumed if at least one transaminase activity was increased by more than 50% of the normal value, or if GPT and GOT activity were both beyond normal values.

An oral glucose tolerance test was performed once as described previously (Müller-Oerlinghausen et al. 1979). The evaluation criterion of the European Diabetes Epidemiology Study Group (EDESG 1970) served to identify pathologic tolerance curves. The Köbberling-Creutzfeldt criterion[3] (1970) was also calculated.

The psychopathologic and neurologic assessment was performed and documented at the time of the first blood sample by a psychiatrist on forms 3 and 4 of the AMP-system (Scharfetter 1971). Deriving from the individual symptom ratings, factor scores were calculated according to Baumann and Angst (1975)[4]. A global morbidity rating was made by means of the Clinical Global Impression Scale (CGI), filled in independently by a psychiatrist and a research nurse.

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1 Perazine (Taxilan®), manufactured by PROMONTA, Hamburg, FRG, is a short-acting phenothiazine with a piperazinyl side chain; its antipsychotic potency is approximately equivalent to chlorpromazine (Breyer et al. 1977).

2 GOT = glutamic oxalacetic transaminase (aspartate aminotransferase), GPT = glutamic pyruvic transaminase (alanine aminotransferase), γ-GT = glutamyl transferase

3 oGTT pathologic, if the sum of blood glucose concentrations 1 and 2 h after glucose load is > 300 mg%

4 It should be mentioned, however, that the factor scores presented in this study did not undergo *t*-transformation

3 Results

3.1 Retrospective Longitudinal Evaluation (Course of the Disease, Rehospitalizations)

The mirror method, i.e., an intraindividual comparison of relapse frequency within identical periods before and after onset of the maintenance treatment, is the only way to evaluate retrospectively the efficacy of the treatment in this patient group.

It is not possible to cover reliably the number of patient relapses in the period before entering long-term outpatient treatment. Therefore, we compared the number of rehospitalizations before and after onset of treatment. The number of rehospitalizations allows a rough estimation of the true relapse rate, as it is known that in big cities two-thirds to three-fourths of schizophrenic relapses result in admission to a psychiatric hospital (Serban 1974; Hogarty 1974; Bosch and Pietzcker 1975).

Table 1 shows that the first psychotic episode occurred on average 3.9 years before admission to the outpatient clinic. The rehospitalization rate per patient and year was reduced from 0.58 (before treatment) to only 0.07 within the 18 years of maintenance therapy. Of 33 patients 16 were not rehospitalized during maintenance treatment. However, comparison of periods of unequal length may lead to erroneous results. Therefore, a comparison of rehospitalization rate during identical periods before and after admisssion is shown in Fig. 1. If all 33 patients are compared, taking into account one year before and after admission, respectively, the rehospitalization rate fell from 1.3 to 0.12. If three corresponding years are mirrored, the original rehospitalization rate is reduced from 0.72 to 0.05. The effect of maintenance treatment seems to diminish the longer the patients were ill before onset of treatment. However, in the group of seven patients where 10 years can be mirrored, the original risk of 0.25 is still reduced to 0.06. The methodologic implications of such evaluations are discussed further below.

Table 1. Hospitalization rate before and after admission to the outpatient clinic

	Total sample ($N=33$)
Before admission to the outpatient clinic	
Duration of disease (years)	3.9 ± 4.7
Number of hospitalizations	74
Hospitalizations per patient and year (hospitalization rate)	0.58
After admission to the outpatient clinic	
Duration of treatment (years)	18.0 ± 2.1
Number of rehospitalizations	41
Rehospitalizations per patients and year (rehospitalization rate)	0.07

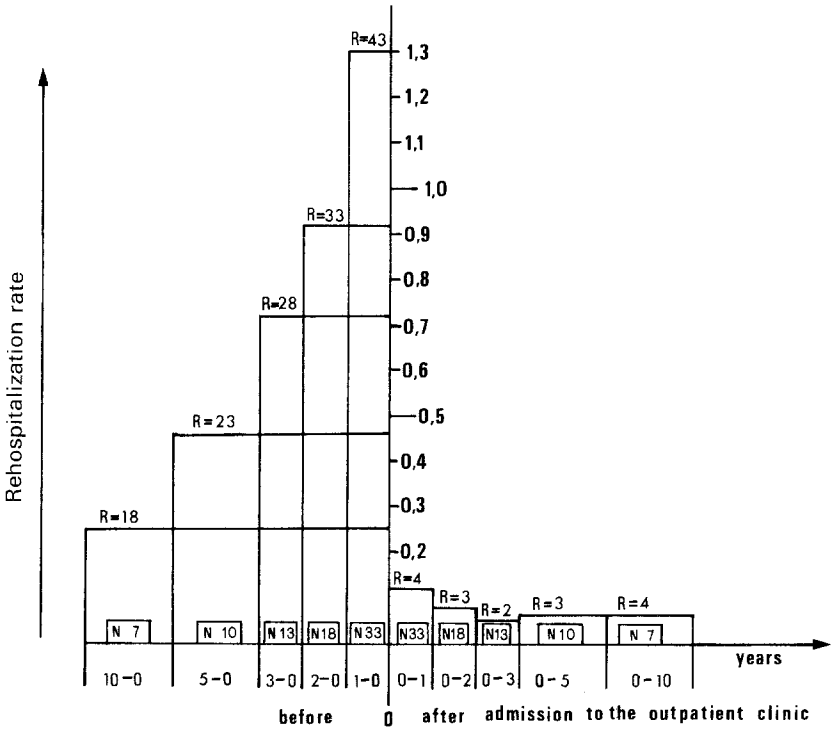

Fig. 1. Long-term neuroleptic treatment with perazine. Rehospitalization rates in 33 patients before and after admission to the outpatient clinic (mirror method). Rehospitalization rate (ordinate) = rehospitalizations per year (mean values/subgroup). N = number of patients per subgroup, R = total number of rehospitalizations per subgroup within the mirrored period

3.2 Cross-Sectional Examination

3.2.1 Psychopathologic Assessment

The general severity of the disease at the time of this investigation was rated by the psychiatrists as 2.9 (CGI), on the average, a score of 3 corresponding to 'slightly ill.' For assessing the productive-psychotic symptomatology at the time of this investigation, we used the sum of the scores[5] of the AMP syndromes 'hallucinatory-desintegrative' (HALL), and 'paranoid' (PARA). This results in a mean score of 2.67, which is rather low. The median value is 0, as 50% of the patients do not score at all on these two syndromes. For assessing depression in these patients, the sum of the scores[5] of three AMP factors 'apathy' (APA), 'somatic-depressive' (SODEP), and 'retarded-depressive' (REDEP) were used, the mean value being 4.42.

At the time of admission to our hospital most patients had been severely psychotic as could readily be seen from the patient files. However, the AMP system was only introduced in 1968 as routine documentation for all patients admitted. Therefore, no direct comparison is possible between the AMP scores at present and

5 The procedure of summing up the paranoid-hallucinatory and the depressive syndromes seems to be justified by the fact that these syndromes are highly intercorrelated (Baumann and Angst 1975)

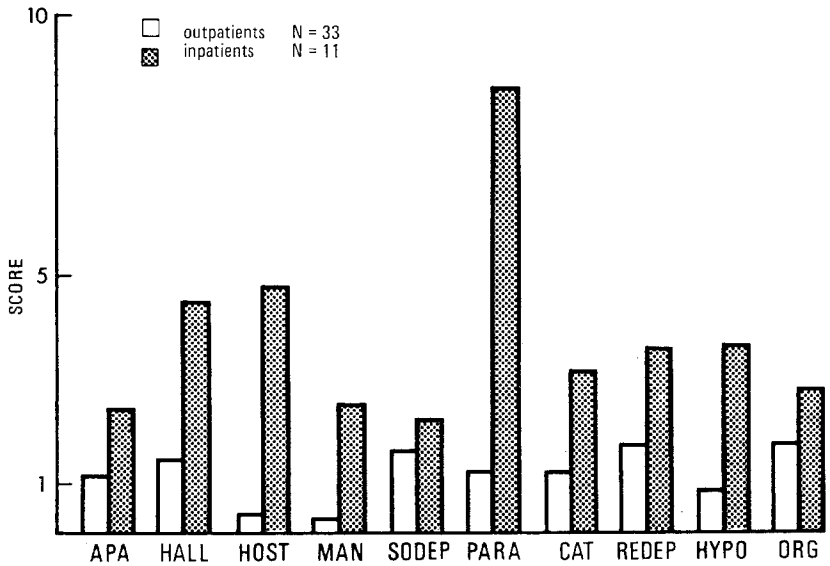

Fig. 2. AMP syndrome-profiles of the total outpatient sample and of 11 newly admitted schizophrenic inpatients. AMP syndromes: apathy (APA); hallucinatory syndrome (HALL); hostility (HOST); manic syndrome (MAN); somatic-depressive syndrome (SODEP); paranoid syndrome (PARA); catatonic syndrome (CAT); retarded-depressive syndrome (REDEP); hypochondriasis (HYPO); psycho-organic syndrome (ORG)

at the time of the index hospitalization. To illustrate for readers not familiar with the AMP system the relevance of the AMP scores obtained in the study group, a comparison with average AMP factor scores taken from 11 newly admitted schizophrenic inpatients is presented in Fig. 2 (Pietzcker et al. 1977). The outpatient group differs particularly in regard to the much lower scores for acute psychotic syndromes, whereas depressive symptomatology, though obviously lower, is more similar to that of the inpatient group.

3.2.2 Side Effects

3.2.2.1 Extrapyramidal Symptoms. Symptoms of hypokinesia (in 12%) and tardive dyskinesia (in 9% of the patients) occurred rarely and were always of low intensity. Among tardive dyskinetic symptoms, merely buccolingual movements could be observed.

3.2.2.2 Liver Function. 'Patholoigic' liver function tests occurred in 30% of the patients. Enzyme activities, however, were increased only slightly and never caused discontinuation of the perazine treatment. GOT and GPT did not exceed 33 and 63 U/l respectively, whereas γ-GT showed a somewhat greater variance of 5–121 U/l. In two patients with the highest values, there was evidence of chronic alcoholism.

3.2.2.3 Oral Glucose Tolerance. Oral glucose tolerance tests (oGTT) were performed in 30 patients. One patient was known to have had manifest diabetes mellitus for many years.

Table 2. Cross-sectional examination: oral glucose tolerance (oGTT)

Sample (*N*)	31 (27♀, 4♂)	
Relative overweight (Δ%; $\bar{x}$)	7%	
Diabetes (*N*)	1	
Observed pathologic oGTT (EDESG-criterion)	8 (26.7%)	$P<0.01$*
Expected pathologic oGTT (ref. Studer et al. 1969)	8.6%	

* Significance is calculated according to the exact confidential limits of the binomial distribution (Geigy Scientific Tables, 7th edn.)

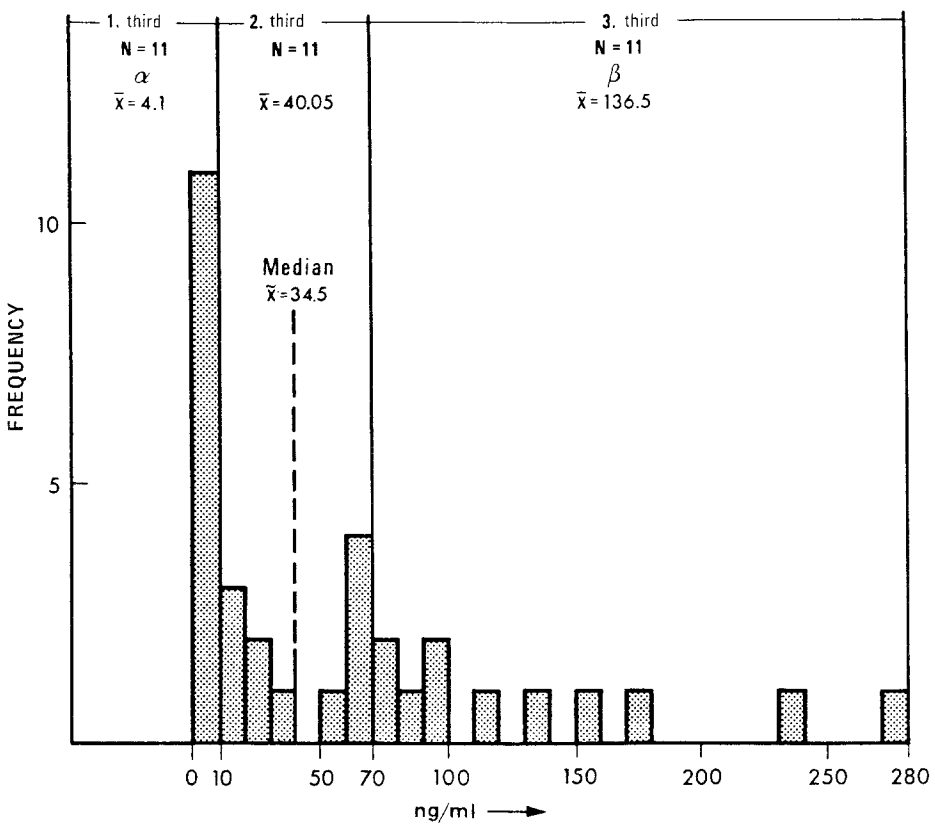

Fig. 3. Distribution of perazine plasma level (class width 10 ng/ml)

The percentage of pathologic blood glucose curves observed (see Methods) is three times higher than would be expected by the comparable reference study by Studer et al. (1969). Impaired glucose tolerance appeared not to be related to the relative overweight, the latter being defined as the ratio $(\frac{\text{obs. body wt}}{\text{av. body wt}^6} - 1) \times 100$ (Table 2).

6 Documenta Geigy, Scientific Tables, 7th Edition

Table 3. Relation between dosage and plasma level of perazine in the total sample ($N = 33$)

	1st assessment	2nd assessment	Linear correlation
	M SD	M SD	
Daily dosage (mg/kg)	2.5 ± 2.1	2.8 ± 2.6	
Perazine plasma level (ng/ml)	61.2 ± 68.5	74.5 ± 101.4	$r = 0.89$
Perazine plasma level (ng/ml) of patients with unchanged dosage	60.8 ± 71.3	68.1 ± 93.7	$r = 0.91$

3.2.3 Perazine Dose and Serum Levels

The individual perazine serum levels vary from patient to patient by a factor of approximately 30 (Fig. 3 and Table 3), whereas total daily doses (mg/kg) vary by approximately 15. At the time of the second blood sample the daily dose prescribed was increased by 12%, whereas the mean serum level increased by 21%. In those patients where the dose was kept constant within the two weeks before first and second sampling, the mean serum level only increased by 12%. It seems very likely that the experimental situation had improved patient compliance. Nevertheless, the perazine serum levels at the two sampling days show a high correlation (Spearman's r_s): $r_s = 0.89$ for all patients; $r_s = 0.91$ for patients with constant dose. The correlation between serum levels and daily dose was also still high with $r_s = 0.76$.

3.2.4 Cumulative Perazine Dose

During maintenance treatment the patients received a mean total dose of 1170 ± 625 g (400–3300 g for 18–19 years). The average dose per year amounted to 64.7 ± 32.3 g. This annual total dose shows a significant though rather low correlation to the perazine serum level ($r_s = 0.45$; $P < 0.01$).

3.2.5 Distribution of Perazine Serum Levels

The individual serum levels are distributed as follows: In 11 patients they are 0–10 ng/ml; another 11 patients show values of 10–70 ng/ml; in the last third of the sample we find a large variation of 70–280 ng/ml (Fig. 3). To make the relationship between serum levels and clinical effects more evident, we shall consider only the 11 patients with the lowest (α-group) and the other 11 patients with the highest values (β-group).

It should be emphasized that all significant correlations described below can be demonstrated also when the total sample is taken into account. However, this dichotomization possesses the additional advantage that both the α- and β-group consist of patients having received only perazine and no other drugs, whereas the middle group comprises seven patients who had temporarily received other neuroleptics. None of the investigated subjects received anti-parkinsonian medication during the last ten years of maintenance treatment.

3.2.6 Relationship between Perazine Serum Levels and Clinical Data

With regard to sex, age, and duration of treatment, α-and β-group are comparable. After admission to the outpatient clinic, the hospitalization rate was similar in both groups (Table 4).

However, significant differences between both groups existed in the cross-sectional psychopathologic values. The global rating (CGI) led to 80% higher values in the β- than in the α-group. As regards the AMP factor scores for paranoid-hallucinatory and depressive symptomatology, significantly higher values were obtained in the β-group, i.e., the patients with higher serum levels (Table 5).

Hypokinetic syndromes were equally distributed (Table 6); all three patients with tardive dyskinesia belonged to the middle group and had also temporarily received other high potency neuroleptic drugs.

Table 4. Hospitalization rate before and after admission to the outpatient clinic in patients with low versus high plasma levels

	α-group (low plasma levels) $N=11$	β-group (high plasma levels) $N=11$
Before admission to the outpatient clinic		
Duration of disease (years)	4.8 ± 5.5	3.5 ± 5.6
Number of hospitalizations	25	21
Hospitalization per patient and year (hospitalization rate)	0.47	0.55
After admission to the outpatient clinic		
Duration of treatment (years)	18.5 ± 0.8	18.5 ± 1.3
Number of rehospitalizations	9	10
Rehospitalization per patient and year (rehospitalization rate)	0.04	0.05

Table 5. Relation between clinical data and perazine plasma level

	α-group (low plasma levels) $N=11$		β-group (high plasma levels) $N=11$		P^*
	M	SD	M	SD	
Severity of illness (CGI)	1.8 ± 1.0		3.3 ± 1.8		<0.05
Paranoid-hallucinatory syndrome (AMP)	0.3 ± 0.9		3.8 ± 8.0		<0.1
Depressive syndrome (AMP)	2.3 ± 2.5		5.1 ± 3.5		<0.05

* Mann-Whitney Test (2-tailed)

Table 6. Relation between clinical data and perazine plasma level

	α-group (low plasma levels)	β-group (high plasma levels)	P
	$N=11$	$N=11$	
Hypokinetic syndrome	2 = 18%	1 = 9%	n.s.*
Pathologic function of the liver	1 = 9%	7 = 64%	<0.05*
	$N=9$	$N=10$	
Pathologic oGTT (EDESG criterion)	2 = 22%	5 = 50%	n.s.*
Sum of glucose concentrations 1 and 2 h after glucose load	264.6 ± 92.6	322.3 ± 60.4	<0.1**

* Fisher-Yates test
** Mann-Whitney test (2-tailed)

Pathologic liver function tests occurred with significantly higher frequency in the β-group (Table 6). In patients with elevated transaminase activity the total perazine dose was higher than in those with normal values (1505 ± 812 g vs. 1037 ± 512 g perazine; $P < 0.1$, Mann-Whitney-Test 2-tailed). Pathologic glucose tolerance curves (EDESG criterion) were more frequent in the β-group, though the difference is not significant. The sum of the blood sugar concentrations after 1 and 2 h (Köbberling-Creutzfeldt criterion) was slightly higher in the β-group (Table 6).

4 Discussion

4.1 Prevention of Rehospitalizations

The efficacy of a long-term maintenance treatment with low oral doses of a low potency neuroleptic drug is demonstrated clearly in the present study by the fact that the annual rehospitalization rate fell from 0.58 before treatment to 0.07 after admission to the outpatient clinic. Half of the patients were not rehospitalized. The rehospitalization rate observed before admission is similar to the reported rehospitalization rates of placebo-treated patients in controlled studies (Davis 1975). The rehospitalization rate after onset of the maintenance treatment in our patients is as low as the best results of controlled studies (Davis 1975; Rifkin et al. 1977; Müller et al. 1977). These studies, however, did not extend over more than approximately two years. When the results of the present investigation are compared with those of other truly long-term studies, the extremely low rehospitalization rate becomes evident. Thus, Beard et al. (1978) studying patients 9 years after admission to an open rehabilitation program, found a cumulated relapse rate of 68%, which is higher than our figure observed during a period of 18 years.

It might be argued that due to a special selection process the results reported here could not be compared to other studies and should possibly not be generalized. Against the background of common prognostic criteria, i.e., number of previous hospitalizations, duration of the disease, and age of first manifestation, the subjects reported on here belong to the group of patients with moderate or even poor prognosis (Bland et al. 1976, 1978; Stephens et al. 1963, 1978; Strauss et al. 1974, 1977). Also those patients who did not relapse at any time did not differ from relapsing patients with regard to these prognostic criteria. Nevertheless, two factors leading eventually to a more favorable outcome should be considered:

(i) it might be that a selection of patients with rather good prognosis according to other criteria had occurred before admission to the outpatient clinic.

(ii) There is no doubt that the long-term maintenance treatment results in a selection of the compliant patients, and it might be speculated that this kind of compliance (Linden, in press) is related to a good prognosis. The fact that females are clearly overrepresented in this patient group, whereas this was not so at the time of admission (Goncalves 1978) would support this argument since it has been demonstrated that a better long-term prognosis exists for female schizophrenic patients (Affleck 1976).

Difficulties also arise when it comes to the interpretation of rehospitalization figures obtained by the mirror method over very long periods. According to Bleuler (1972) the course of schizophrenic psychoses usually becomes stabilized after approximately 10 years, and thus, the decrease of the rehospitalization rate might not be due to treatment, but to spontaneous remission. This hypothesis is partially supported by our data which demonstrate that the rehospitalization rate of patients who had been ill for longer periods is lower than of those in whom the disease became manifest only recently.

However, this could never fully explain the very low rehospitalization rate. Even in patients having been ill 10 years before admission to the clinic, the risk of rehospitalization was reduced to approximately 25% of the previous figure, the latter being probably underestimated as the documentation of rehospitalizations over such long periods tends to be unreliable. Furthermore, 21% of the patients were rehospitalized once or several times between the 10th and the 20th year of treatment.

In conclusion, it must be emphasized that on methodologic grounds the results obtained cannot be generalized. On the other hand, the positive psychiatric effect of the maintenance treatment appears to be unambiguous for the investigated patients.

4.2 Serum Levels and Compliance

Compared with controlled studies where 200 mg perazine t.i.d. was administered to acute psychotic patients, the serum levels observed in the present investigation are remarkably lower, i.e., they amount to approximately 25% of the concentrations measured during the first 4 weeks of acute treatment (Dimroth et al. 1980). The constancy of serum levels within two weeks is certainly noteworthy and is contrary to what has been reported by Hansen and Larsen (1977) or Muusze and Vanderheeren (1977) with regard to perphenazine or thioridazine plasma

levels, respectively. Also the correlation between multiple daily doses and serum levels appears to be higher than in other studies which might be due to the fact that rather low doses were used so that saturation kinetics would not be involved (March et al. 1972; Axelsson 1975; Wiles et al. 1976). Both observations demonstrate that a stable steady state is reached, and that patient compliance is very satisfying. Enzyme induction, which may lead to marked reduction of serum levels within the first weeks and months of neuroleptic treatment (for review Müller-Oerlinghausen 1980a) does not influence steady state serum levels after years of treatment. The *cumulated* total amount of perazine ingested showed a significant, though only weak correlation with the actual serum level indicating that the dose was not fixed over the whole treatment period but varied according to the patients' clinical state.

4.3 Psychopathologic Symptoms

After an average treatment period of 18 years the frequency and intensity of psychopathologic symptoms were very low as compared to acutely ill patients. The higher the present severity of the disease, the higher were the perazine serum levels. It can thus be concluded that all patients had been titrated down to the minimal dose required according to their actual psychopathologic state.

4.4 Side Effects

Side effects, particularly extrapyramidal disturbances, were rare and of low intensity. Much higher frequencies of tardive dyskinesia have been reported in other studies where either higher oral doses or depot neuroleptics were used for maintenance therapy. The high incidence of impaired glucose tolerance agrees with previous findings in patients of the outpatient clinic and in hospitalized patients (Gonçalves and Grüneberg 1975; Schwalb et al. 1974; Müller-Oerlinghausen et al. 1978, 1980b). Since pathologic glucose tolerance was not correlated with overweight but was more frequent in patients with higher perazine serum levels it seems plausible that the slight disturbance of carbohydrate metabolism is due to the inhibition of insulin release induced by phenothiazines and not just to obesity[7].

The disturbance of liver function in some patients, though more marked in those with higher perazine serum levels, has to be considered as mild. Degkwitz (1976) found disturbed liver function in 80% of patients under long-term neuroleptic medication.

4.5 The results of this study provide strong evidence that a long-term maintenance treatment with low oral doses of a short-acting neuroleptic drug is highly effective. Recent control studies seem to support this finding (Rifkin et al. 1977; Hogarty et al. 1976; Levine et al. 1979). Estimating the risk-benefit ratio, we believe

7 The question whether the patients examined in the present study are really more obese than the normal German population cannot be answered from our data but would require a comparison with figures from a representative sample (Müller-Oerlinghausen and Poser, manuscript in preparation)

that the relapse preventing efficacy of the treatment far outweighs the low risk of side effects. The increased incidence of side effects in those patients with a clinically required higher perazine dosage seems also justified on the ground that even in this group the frequency of rehospitalizations could be reduced to 10% of the corresponding figure before onset of treatment. The existence of a certain risk of side effect leads to three indispensable demands:

(i) The indication for a long-term neuroleptic treatment and its risk-benefit ratio must be examined very carefully on the ground of prognostic criteria (Helmchen 1978; Pietzcker 1978; Levine et al. 1979).

(ii) The minimally required dose should always be sought (Hogarty et al. 1976; Rifkin et al. 1977; Lonowski et al. 1978; Pietzcker 1978).

(iii) To minimize the risk of side effects regular neurologic and laboratory controls are imperative with particular regard to tardive dyskinesia, hematology, body weight, and glucose tolerance. It should be remembered that the mortality due to cardiovascular disease is markedly overrepresented in schizophrenic patients under long-term neuroleptic treatment (Schwalb et al. 1974; Giel et al. 1978).

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