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Perphenazine decanoate and *cis*(z)-flupentixol decanoate in maintenance treatment of schizophrenic outpatients

Serum levels at the minimum effective dose

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Abstract. Two groups of schizophrenic outpatients were treated with perphenazine decanoate ($N=20$) and *cis*(z)-flupentixol decanoate ($N=24$) respectively. Every 3 months the dose was gradually reduced until symptoms appeared that were suggestive of a prodromal phase of a psychotic episode. A slightly higher dose was then promptly reinstituted (the minimum effective dose). At each dose level, two blood samples were drawn for determination of serum concentration. The mean minimum effective dose of perphenazine decanoate was 99.3 mg/2 weeks (range 21.6–270.5), while the mean minimum effective dose of *cis*(z)-flupentixol decanoate was 60 mg/2 weeks (range 20–250). The corresponding mean serum level of perphenazine decanoate was 7.3 nmol/l (range 2.0–18.1) and of *cis*(z)-flupentixol decanoate 7.8 nmol/l (range 1.2–37.0). There was a significant correlation between the administered doses and the corresponding serum levels for both drugs ($r=0.87$, $P<0.01$). A weak positive correlation was found between serum levels at the minimum effective dose and symptom intensity (BPRS total score) ($r=0.53$, $P<0.02$) for perphenazine, but not *cis*(z)-flupentixol. No correlation was found between serum levels and side effects or length of neuroleptic treatment. It is concluded that the serum drug concentrations corresponding to the lowest effective dose are so variable that routine serum level monitoring may be of limited value in the long-term maintenance treatment of schizophrenia.

Key words: Schizophrenia – Perphenazine – Flupentixol – Pharmacokinetics – Therapeutic window

Perphenazine decanoate and *cis*(z)-flupentixol decanoate are intramuscular depot neuroleptics, widely used in maintenance treatment of schizophrenic outpatients. As for all neuroleptic medication it is essential to use the lowest possible dose in order to limit the occurrence of side effects. In this regard, monitoring of serum concentrations has been suggested as a useful tool, although the literature on the relationship between serum concentration and clinical response is controversial (Midha et al. 1987; Baldessarini et al. 1988). The question is to what extent serum concentration monitoring can improve treatment with perphenazine and flupentixol decanoate. Until now only a few studies of this subject have been performed with these drugs.

In two studies including 39 acute psychotic patients treated perorally with perphenazine, Bolvig Hansen et al. (1981, 1982) found 1) a good therapeutic outcome associated with plasma concentrations of perphenazine above 2 nmol/l, and 2) a low risk of extrapyramidal side effects associated with plasma concentrations below 3 nmol/l. All plasma concentrations were measured as trough values, immediately before tablet intake. In another study including 16 patients in continuous peroral perphenazine treatment, Bolvig Hansen and Larsen (1977) found a constant ratio (approximately 2.0) between the peak value (4 h after tablet intake) and the trough value within the same dose interval. Consequently, a concentration range between 2 and 6 nmol/l within the entire dose interval should give good therapeutic outcome with a low risk of provoking extrapyramidal side effects. In long-term treated patients with a duration of illness of more than 10 years, higher doses have been found necessary (Knudsen et al. 1985).

In a study of 23 schizophrenic patients treated with *cis*(z)-flupentixol decanoate, Saikia and Jørgensen (1983) found a significant correlation between dose and preinjection serum concentration ($r=0.79$, $P<0.01$). Kirk et al. (1984) observed a significant correlation ($r=0.93$, $P<0.001$) between the dose and serum concentration of *cis*(z)-flupentixol given intramuscularly as *cis*(z)-flupentixol decanoate and measured by a specific radioimmunoassay (Jørgensen 1978) and found a good antipsychotic effect with a serum concentration below 15 nmol/l. Balant-Gorgia et al. (1985), in a study of 23 acutely psychotic inpatients treated perorally with flupentixol, proposed a threshold concentration of 2 ng/ml

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Table 1. Patient data of the perphenazine group ($N=20$) including serum concentration, doses, total BPRS scores, extrapyramidal side effects (EPS) and anticholinergic medicine. The patients are arranged according to serum concentration

Patient number	Sex/age (years)	Type of schizophrenia	Duration of illness (years)	Duration of neurological treatment (years)	Start dose (mg/2 weeks)	Number of dose reductions	Duration of minimum effective dose achievement (months)	Minimum effective dose (mg/2 weeks)	Serum concn (nmol/l)	Total BPRS score		EPS at minimum effective dose	Anticholinergic medicine
										Start dose	Min. eff. dose		
6	M/46	Par	11	11	54.1	2	7	21.6	2.0	2	2	–	–
4	M/52	Par	28	28	108.2	4	14	32.4	2.5	16	7	–	–
7	F/53	Par	6	6	54.1	2	7	27.0	2.5	8	8	–	Bip 6
15	F/36	Par	3	3	54.1	0	0	54.1	3.6	7	7	–	Bip 4
19	F/62	Par	29	29	32.4	0	0	32.4	3.7	11	11	–	–
1	M/34	Disorg	15	15	54.1	0	0	54.1	4.0	2	2	–	–
11	M/48	Disorg	16	16	108.2	0	0	108.2	4.2	10	10	–	Orph 400
2	M/32	Resid	12	10	81.2	0	0	81.2	4.7	13	13	–	Bip 4
13	F/58	Par	21	21	108.2	0	0	108.2	5.0	2	2	+	Bip 6
9	M/40	Disorg	14	9	54.1	0	0	54.1	5.6	13	13	–	–
12	F/60	Par	16	15	108.2	0	0	108.2	5.7	4	4	–	Orph 150
14	M/29	Resid	4	3	162.3	3	14	54.1	5.7	7	7	–	–
18	F/62	Par	16	16	54.1	2	7	32.4	7.9	6	4	–	Orph 150
16	F/59	Par	25	25	108.2	0	0	108.2	9.1	7	7	+	–
20	M/35	Disorg	7	7	162.3	2	7	81.2	10.1	9	12	–	–
5	M/35	Par	15	13	162.3	0	0	162.3	11.9	13	13	–	Bip 8
3	M/40	Cat	18	18	270.5	0	0	270.5	12.2	14	14	–	Bip 6
8	M/40	Disorg	19	19	162.3	0	0	162.3	12.5	21	21	+	Bip 2
17	M/53	Resid	43	10	216.4	0	0	216.4	15.4	10	10	–	–
10	F/42	Disorg	18	13	216.4	0	0	216.4	18.1	12	12	–	Bip 8
Mean	45.8		16.8	14.35	116.59	2.5	8.0	99.27	7.31	9.95	8.95		
Range	29–62		3–43	7–25	32.4–270.5	1–4	5–14	21.6–270.5	2.0–18.1	2–21	2–21		

Abbreviations: *Dur* duration; *Par* paranoid; *Disorg* disorganized; *Resid* residual; *Cat* catatonic; *Bip* biperiden; *Orph* orphenadine

Table 2. Patient data of the *cis*(Z)–flupentixol group ($N = 24$) including serum concentration, doses, total BPRS scores, extrapyramidal side effects (EPS) and anticholinergic medicine. The patients are arranged according to serum concentration

Patient number	Sex/age (years)	Type of schizophrenia	Duration of illness (years)	Duration of neurological treatment (years)	Start dose (mg/2 weeks)	Number of dose reductions	Duration of minimum effective dose achievement (months)	Minimum effective dose (mg/2 weeks)	Serum concn (nmol/l)	Total BPRS score		EPS at minimum effective dose	Anticholinergic medicine
										Start dose	Min. eff. dose		
5	M/30	Disorg	4	4	10	0	0	20	1.2	5	15	–	–
9	M/37	Par	8	8	20	1	3	20	1.3	2	2	–	–
7	M/44	Resid	15	12	30	1	3	20	2.3	10	10	+	Bip 4
23	M/49	Par	21	19	50	0	0	50	2.3	13	13	+	Bip 6
21	M/43	Par	5	5	30.0	1	3	20	2.4	5	5	–	–
15	F/38	Disorg	21	21	20	0	0	20	2.9	5	5	–	Bip 6
13	M/39	Cat	19	19	50	0	0	50	3.1	6	6	–	Bip 6
3	M/63	Disorg	35	35	20	0	0	20	3.7	15	15	–	Bip 8
24	F/60	Disorg	28	28	40	1	3	30	4.3	9	9	–	–
16	F/53	Par	12	12	60	2	6	20	4.4	12	12	–	–
14	F/48	Disorg	30	30	40	0	0	40	4.5	5	5	+	–
6	F/60	Disorg	21	16	40	2	9	20	4.7	8	6	–	–
4	M/35	Resid	5	3	100	0	0	100	4.8	19	19	+	–
11	F/46	Par	25	13	80	0	0	80	4.8	10	10	–	–
12	M/26	Resid	10	10	80	1	7	60	6.0	18	17	–	Bip 6
19	F/59	Par	21	21	30	0	0	30	6.4	5	5	–	–
10	F/58	Par	31	31	60	0	0	60	6.9	8	8	–	Orph 150
18	M/34	Schizaff	14	12	100	2	7	80	7.0	6	4	–	–
2	M/49	Par	16	9	100	0	0	100	10.5	15	15	+	–
17	F/39	Disorg	19	19	100	0	0	100	11.0	17	17	+	Bip 6
22	F/37	Par	9	7	100	0	0	100	15.6	8	8	–	Bip 6
8	M/30	Par	9	4	50	0	0	50	19.4	4	4	+	Bip 6
1	F/36	Disorg	8	6	100	0	0	100	20.0	11	11	+	–
20	F/46	Par	13	13	250	0	0	250	37.0	13	13	+	Orph 300
Mean	44.13		16.63	14.88	65.00	1.4	5.1	60.00	7.77	9.5	9.29		
Range	26–63		4–35	3–35	10–250	1–2	3–9	20–250	1.2–37	2–19	2–19		

Abbreviations: *Dur* duration; *Par* paranoid; *Disorg* disorganized; *Resid* residual; *Cat* catatonic; *Bip* biperiden; *Orph* orphenadine

(4.6 nmol/l) for antipsychotic effect. A therapeutic serum level of *cis*(z)-flupentixol was not found in these studies.

The aim of the present study was to find the minimum effective dose and the corresponding steady state serum concentrations of two different neuroleptics (perphenazine decanoate and *cis*(z)-flupentixol decanoate) in the maintenance treatment of chronic schizophrenic outpatients. Such an approach has never been applied in the search for optimal serum neuroleptic levels and may cast new light on the usefulness of serum concentration monitoring in the treatment of schizophrenia.

Materials and methods

Patients. The patients were selected from the population of psychotic patients already treated with perphenazine decanoate or *cis*(z)-flupentixol decanoate at Sct. Hans Hospital outpatient clinic. Inclusion criteria were: age between 18 and 65 years, a diagnosis of schizophrenia according to DSM–III–R (chart review), a duration of illness of 2 or more years and treatment with the decanoate at a constant dose and dose interval (14 days) for a period of at least 6 months. The patients were all stabilized on the current neuroleptic dose, had responded to the antipsychotic therapy and had been discharged from the hospital. No other psychotropic drugs and no antiepileptics or somatic medicine were allowed. Unstable or criminal patients and patients with known organic disorders, drug or alcohol abuse, were not included in the study. Informed consent was obtained from all patients.

A total of 101 patients were treated with perphenazine decanoate. Twenty-six were excluded as they did not fulfil the DSM–III–R criteria of schizophrenia. Seven patients were older than 65 years. Eight patients could not be treated with one neuroleptic only. Fifteen patients were unstable or criminal; 11 patients abused drugs or alcohol and 12 patients simply did not want to participate. One patient had to be excluded after the termination of the study, because of one missing blood sample. One patient (a 55-year-old schizophrenic female of disorganized type treated with 81 mg perphenazine decanoate/2 weeks) was excluded after she remained well without medicine for more than 1 year. The remaining 20 patients completed the study. Demographic data are given in Table 1.

A total of 112 patients were treated with *cis*(z)-flupentixol decanoate. Twenty-eight patients did not fulfil the DSM–III–R criteria of schizophrenia; 5 were older than 65 years and 11 could not be treated by monotherapy. Nineteen patients were unstable or criminal; 11 abused drugs or alcohol and 12 did not want to participate. One patient was excluded because she had been lobotomized. A 47-year-old schizophrenic female of disorganized type chronically treated with 10 mg *cis*(z)-flupentixol decanoate/2 weeks was excluded after she remained well without medicine for more than 1 year. The remaining 24 patients completed the study. Demographic data are given in Table 2.

The design of this study (gradual dose reduction until deterioration, see below) necessitated a close contact between the psychiatrist, the nursing staff, the patient and his/her family in order to detect and treat a psychotic exacerbation as quickly as possible. Therefore before dose reductions the psychiatrist discussed the nature of the illness with the patient and the family, with special emphasis on characteristic signs and prodromal symptoms which might precede a psychotic episode (Carpenter and Heinrichs 1983; Lieberman and Kane 1986).

Drug administration and blood sampling. Perphenazine decanoate in sesame oil (108 mg/ml) (Trilafon Decanoate) and *cis*(z)-flupentixol decanoate in Viscoleo (20 mg/ml or 100 mg/ml) (Fluanxol Depot) were given intramuscularly every 2 weeks. The patients were dosed individually. According to the design of the study (Fig. 1) the dose was gradually reduced by one fourth every 12 weeks until the minimum effective dose was found. [Studies on the metabolism and pharmacokinetics of perphenazine decanoate (Knudsen et al. 1985) and *cis*(z)-flupenthixol decanoate (Jørgensen et al. 1980) indicate that steady state is reached within 12 weeks].

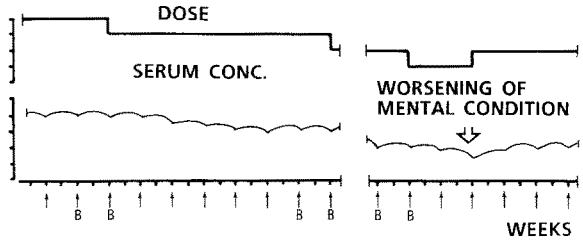

Fig. 1. Study design. The dose was gradually reduced by one fourth every 12 weeks. This reduction was continued until worsening of the mental condition (prodromal symptoms and signs). Then the dose was increased one step to the minimum effective dose. *B* = preinjection blood sample. ↑ = intramuscular injection of depot neuroleptic

Any additional neuroleptics given before the study were withdrawn before inclusion. Only small doses of nitrazepam as a night sedative and biperiden/orphenadrine as antiparkinson drugs were allowed. No other medication was allowed. Biperiden and orphenadrine were not systematically reduced.

Before dose reduction two blood samples were drawn at a 2-week interval on the day of depot injection, immediately before injection (Fig. 1). Blood was allowed to coagulate and serum was separated by centrifugation and deep frozen. The analysis was performed after termination of the study.

Clinical assessment. The psychotic condition and side effects were evaluated on the days when the blood samples were taken, using the Brief Psychiatric Rating Scale (BPRS, 18 items) (Overall et al. 1962) and the UKU Side Effect Scale, a comprehensive rating scale for side effects induced by psychotropic drugs, composed by 48 items scored operationally from a semi-structured, directive interview (Lingjærde et al. 1987). All evaluations were performed by the same investigator (KK).

Drug analyses and statistics. The serum concentrations of perphenazine and *cis*(z)-flupentixol were determined in the serum samples by means of high-performance liquid chromatographic methods (Aaes-Jørgensen 1980; Larsen et al. 1985).

Correlation-regression analysis was performed using Spearman's rho-test.

Results

Dose reduction strategy

The study showed that the design utilizing gradual dose reduction in chronic schizophrenic patients in maintenance treatment was feasible and did not result in any marked increase in the number of readmissions. Only in one case (no. 8, Table 2) was a short admission necessary because of an acute exacerbation of symptoms. In all other cases it was possible to stabilize the condition by a return to the dose given before the last dose reduction.

Six patients from the perphenazine group (see Table 1) and eight patients from the *cis*(z)-flupentixol group (Table 2) benefited from the systematic dose reduction. In these cases the dose was reduced by 21.7–108.2 mg perphenazine decanoate/2 weeks (49%) and 10–20 mg flupentixol decanoate/2 weeks (34%). As seen from the

tables, the six perphenazine patients had two to four dose reductions over 7–14 months before deterioration, while the eight flupentixol patients had one to two dose reductions over 3–9 months. The tables also show that it is not possible to differentiate (e.g. with respect to age, total BPRS score or serum levels) .between those patients tolerating and those not tolerating a dose reduction.

Fourteen patients from the perphenazine group and 16 from the *cis*(z)-flupentixol group could not be treated with a lower dose without presenting prodromal signs of an impending relapse. In one patient (no. 5, Table 2), dose of *cis*(z)-flupentixol decanoate had to be increased from 10 mg/2 weeks to 20 mg/2 weeks. In the group as a whole, the dose was reduced by about 10%; 14.86% in the perphenazine group and 7.7% in the *cis*(z)-flupentixol group.

The total BPRS scores before entering the study and at minimum effective dose were almost the same: for the perphenazine group 9.95 and 8.95 (mean values) and for the *cis*(z)-flupentixol-group 9.54 and 9.29 (mean values).

Perphenazine decanoate

The mean minimum effective dose of perphenazine decanoate was 99.3 mg/2 weeks (range 21.6–270.5). The corresponding mean perphenazine serum level (for each patient the average of two blood samples) was 7.3 nmol/l (2.0–18.1). Twelve of the 20 patients (60%) had serum concentrations within a range of 2–6 nmol/l (Table 1 and Fig. 2) (which has been recommended for short-term treated patients, see Introduction). A significant positive correlation was found between the minimum effective dose and the corresponding serum concentration ($r=0.87$, $P<0.01$, Fig. 2).

A weak positive correlation was found between the serum concentration at minimum effective dose and the BPRS score ($r=0.53$, $P<0.02$). No correlation was found between the serum level and side effects, duration of neuroleptic treatment, age, gender (Table 1). weight or body surface.

Eleven of the patients treated with perphenazine decanoate used antiparkinson drugs (see Table 1). Of these,

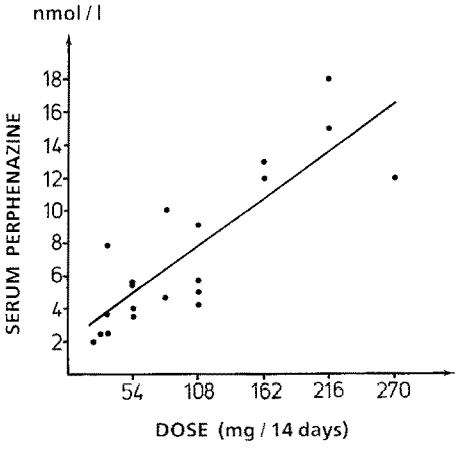

Fig. 2. Relationship between perphenazine serum concentration and minimum effective dose. r = 0.87; N = 20; $P<0.01$

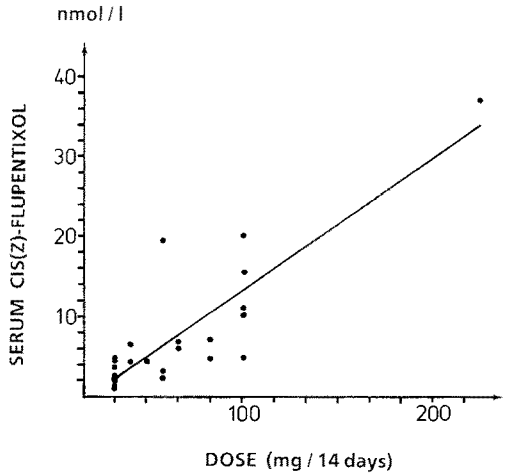

Fig. 3. Relationship between *cis*(Z)-flupenthixol serum concentration and minimum effective dose. r = 0.87; N = 24; $P<0.01$

one patient (no. 8) scored 1 point on the item rigidity, and another patient (no. 13) 1 point on motor akathisia. One patient, who did not use an anticholinergic (no. 16), also scored 1 point on motor akathisia. Otherwise, none of the patients had extrapyramidal side effects at the minimum effective dose.

Other side effects were: sedation in one patient, astenia in 1, weight increase in four and sexual disturbances in two. Nitrazepam 5–15 mg/day was used by six patients, mainly as a night sedative.

Cis(z)-flupentixol decanoate

The mean minimum effective dose of *cis*(z)-flupentixol decanoate was 60.0 mg/2 weeks (range 20.0–250.0). The corresponding mean *cis*(z)-flupentixol serum level was 7.8 nmol/l (1.2–37.0). Eighteen of the 24 patients (75 %) had serum concentration within a range of 1–8 nmol/l (Table 2 and Fig. 3). A significant correlation was found between the minimum effective dose and the corresponding serum concentration ($r=0.87$, $P<0.01$, Fig. 3). No correlation was found between the serum level and corresponding BPRS score, side effects, length of neuroleptic treatment, age, gender (Table 2), weight or body surface.

Eleven of the patients used antiparkinson drugs (Table 2). Of these, one patient (no. 8) scored 1 point each on rigidity and tremor and four patients (nos 7, 17, 20 and 23) 1 point on motor akathisia. Four patients (nos 1, 2, 4 and 14), who did not use anticholinergic drugs, suffered slight extrapyramidal side effects.

Other side effects were: sedation in three patients, astenia in six, weight increase in four and sexual disturbances in four. Nitrazepam 5–15 mg/day was used by eight patients, mainly as a night sedative.

Discussion

In the present investigation the minimum effective dose was found by means of a gradual, systematic dose reduc-

tion, whereafter the corresponding serum concentration was measured. This method proved feasible. Only 1 out of 44 schizophrenic patients had to be temporarily admitted to the hospital during the course of the investigation. Consequently, it can be concluded that this procedure is useful not only for investigational purposes, but also in the daily clinical routine, under the condition that close contact between the therapist and patient/relative is maintained.

Other strategies of neuroleptic dose reduction are continuous low-dose treatment and targeted or intermittent treatment (for review, see Kane and Liebermann 1987). An evaluation of the low-dose strategy suggests that relatively low doses (e.g. fluphenazine 5 mg/2 weeks) can diminish adverse effects and improve measures of well-being, but the incidence of psychotic exacerbation does increase (Kane et al. 1985; Marder et al. 1987). Similarly, intermittant medication in schizophrenia (Carpenter and Heinrichs 1983) can reduce the consumption of drugs and the incidence of side effects, but the percentage of relapses increases significantly (Herz et al. 1990). Consequently, the minimum effective dose principle used in the present study appears to be the dose strategy to be recommended.

In the present study about one third of the patients in each group tolerated dose reduction by 55% and 34%, respectively, whereas two thirds could not tolerate dose reduction. On the basis of clinical parameters it was not possible to predict which patients could sustain a dose reduction. The only way to clarify this question is to use the gradual dose reduction principle. In this study about two thirds of the patients were already treated with the minimum effective dose.

The study showed that there was a significant correlation between the dose and serum concentration for both perphenazine and flupentixol ($P < 0.01$ in both cases). A similar correlation has been found in earlier studies with flupentixol (Saikia 1983; Kirk et al. 1984), while perphenazine has not been studied in this respect.

The serum concentration corresponding to the minimum effective dose showed such a large range (perphenazine 2.0–18.1 nmol/l and flupentixol 1.2–37 nmol/l) that it is difficult to use it as a guideline in the maintenance treatment of chronic schizophrenic patients, although 60–75% of the patients had serum concentrations within a relatively narrow lower level. It must be concluded that among chronic schizophrenic patients, there are those who require a relatively high serum concentration and in whom a dose reduction would cause a worsening of the psychic condition. This is in accordance with the findings of preliminary investigations regarding flupentixol (see Introduction). For perphenazine, a serum concentration between 2 and 6 nmol/l may produce an optimum therapeutic effect with a minimum of side effects in acutely ill patients (see Introduction) while a more chronic population may require higher concentrations (Knudsen et al. 1985).

In the case of perphenazine a slight positive correlation was found between the serum concentration and BPRS score. Severe symptoms required a higher serum concentration. This would indicate that more severe conditions may, not unexpectedly, require more intensive treatment than less severe conditions (see also Bjørndal and Aaes-Jørgensen 1984; Browne et al. 1988).

About half of the patients in both groups received anticholinergic drugs. However, because there was no systematic attempt to reduce or withdraw anticholinergic medication, no conclusion can be drawn regarding the need for anticholinergic medication. Only few and mild side effects were seen. The low level of side effects in general explains the lack of correlation between the serum concentration and side effects. These observations suggest that schizophrenic patients in long-term neuroleptic treatment present relatively few, if any side effects when treated at the lowest effective dose.

In conclusion, among chronic schizophrenic patients in maintenance neuroleptic treatment, it was found that the dose of perphenazine decanoate/flupentixol decanoate could be reduced in one third of the patients (by 34–49%), while two thirds were already treated with the minimum effective dose. For both drugs a significant positive correlation was found between the administered dose and serum concentration. The serum concentration varied considerably, making routine serum level monitoring of limited value in the long-term maintenance treatment of schizophrenia. A strategy aimed at continually seeking the lowest effective dose appears more appropriate. On the other hand, there are still a number of situations (e.g. therapeutic inefficacy, troublesome side effects, suspicion of non-compliance and special pharmacokinetic conditions such as hepatic or renal disease, old age or drug interactions) where measurement of serum concentrations is important in the treatment of the individual patient.

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