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NEUROLEPTIC CONCENTRATIONS AND CLINICAL RESPONSE

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INTRODUCTION

The clinical effectiveness of antipsychotic chemotherapy has been proven worldwide, yet a multitude of problems remain concerning that significant percent of the target population who do not benefit from such chemotherapy. Since the introduction of chlorpromazine in the early 1950s, other phenothiazines, the butyrophenones, the thioxanthenes, the dihydroindolones, and the dibenzoxazepines have been introduced and have proven therapeutically effective with varying degrees of potency and side effects(1). Non-responders to chlorpromazine have responded to some of the newer drugs, but the parameters of safe and effective dosage remain to be set. In the many uncontrolled and controlled clinical trials and anecdotal case reports, drug dosing has been mainly empirical, based on pushing doses to toxic levels or on a trial-and-error titration of dose and clinical effect. The lack of therapeutic guidelines in the clinical use of the antipsychotic drugs has moved interested groups to attack the problem of wide variability in drug dosage and clinical response among psychiatric patients.

The introduction of sensitive antipsychotic drug assays in biologic fluids (2) revolutionized pharmacokinetic and pharmacodynamic knowledge about the various antipsychotic drugs used in different types of clinical disorders. It

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became evident that the pharmacokinetics of antipsychotics vary considerably with age, duration of illness, duration of previous drug therapy, and interactions with drugs prescribed with the antipsychotics (3). These facts, together with indistinct and nonspecific clinical end points, rating scales of varying sensitivity, and technical problems in the chemical assay of antipsychotic drugs, have contributed to the failure of studies in different laboratories to establish a correlation between the plasma concentration of antipsychotic drugs and clinical improvement or side effects (4–12).

This review will summarize recent studies on therapeutic monitoring of plasma concentration of neuroleptics in psychiatric patients and emphasize data that are of significance in establishing guidelines in the clinical use of these drugs.

CHLORPROMAZINE

Correlation of Biologic Fluid Concentrations and Clinical Effect

The value of plasma chlorpromazine (CPZ) monitoring in the therapeutic management of psychiatric patients depends on the existence of a positive correlation between plasma CPZ concentration and clinical response. Several studies using sophisticated assay techniques have measured CPZ and its metabolites in various biologic fluids other than plasma, such as RBC (13), CSF (9, 14), urine (15), saliva (16), and whole blood (17), in an attempt to establish a therapeutic concentration range. Whereas data from a number of studies (18–21) suggest that plasma concentrations of CPZ greater than 30 ng/ml are required for clinical effectiveness and that concentrations higher than 200–300 ng/ml may be associated with signs of toxicity, there is much disagreement about a "therapeutic window" based on these studies. Several critical reviews in the last decade (22–25) have expressed concern about the validity of the conclusions claimed by the various studies aimed at establishing a correlation between plasma concentration and clinical response. Deficiencies involving assay methodology, study design, study population, and statistical data analysis were pointed out in both positive and negative studies. Studying the correlation of plasma concentration with clinical responses requires a specific, sensitive, and accurate assay method for the compound, a controlled randomized double-blind design, and a sensitive and reliable clinical assessment scale for specific target clinical signs or symptoms.

Unfortunately, strictly randomized controlled studies are often unachievable for several reasons. First, population homogeneity may be compromised by (*a*) "good-prognosis" patients with self-limited types of schizophrenia who do well with or without drugs; (*b*) "treatment-resistant" patients with "organic-type"

schizophrenia who do not or will never respond to any dose of any antipsychotic drug; (*c*) the use of the word *acute* to describe either a de novo acute episode, a relapse in a first episode, or a chronic relapsing schizophrenia; and (*d*) the use of the word *chronic* to include patients, previously treated or untreated, who are either drug responsive or drug resistant. Second, fixed doses, which are highly desirable in most controlled trials, may be inappropriate for antipsychotic drugs, where plasma concentrations are consistently shown not to correlate with dose. Since antipsychotic therapeutic trials often run for 6–8 weeks, it is ethically inappropriate to fix a dose that obviously does not work or that induces significant toxicity in a particular patient. Third, placebo use involves ethical and legal risks in the acute schizophrenic, who needs treatment and whose drug response is readily measured compared to the chronic population. And, finally, a wide spectrum of target manifestations in different types of schizophrenia, including delusions, withdrawal, retardation, depression, and thought disorders, respond differentially to neuroleptics.

In the cited studies on plasma CPZ and clinical response, Wode-Helgodt (21) was the first investigator to support the earlier claims of Rivera-Calimlim et al (18–20) of a positive correlation between plasma concentration of CPZ and clinical response by doing a randomized, placebo-controlled, double-blind clinical trial in 48 acute schizophrenics. This study attempted to obtain a fairly homogenous group of patients with acute schizophrenic psychosis, focusing on thought disorders, delusions, and hallucinations as inclusion criteria. By *random assignment* patients received one of the three doses tested (200, 400, and 600 mg daily) after a placebo period. Plasma and cerebrospinal fluid (CSF) CPZ concentrations were measured by a mass fragmentographic method. Clinical improvement and side effects were rated according to the comprehensive psychopathological rating scale (CPRS) of Asberg et al (26) and side effects by a scale introduced by Simpson & Agnus (27). They showed a positive correlation between CPZ concentrations in CSF and plasma, and both CSF and plasma concentrations were correlated with clinical response, with CSF concentrations showing a better correlation. There was more interindividual variation in plasma CPZ concentrations than in CSF concentrations; this may be explained by individual variations in plasma protein binding. Rank correlation coefficients with clinical measures for psychotic morbidity were highest for CPZ concentration in CSF, followed by CPZ concentration in plasma, dose per kg body weight, and total dose.

Wode-Helgodt's study suggested that for the achievement of a more than 50% reduction in the morbidity score, CSF concentrations of CPZ should be above 1 ng/ml and plasma concentrations of CPZ above 40 ng/ml. These findings are in agreement with previous studies (9, 19, 20) that showed a correlation of CSF and plasma concentrations of CPZ with clinical effects. Data from our prospective studies of acute psychiatric inpatients treated with

CPZ in a naturalistic design suggested that the various symptoms of schizophrenia respond differentially to CPZ (19–20). Stratification of symptoms to form the major categories of thought disorder, paranoid delusions, withdrawal retardation, and depression facilitated assessment of the correlation of plasma CPZ with clinical improvement. Our study suggested that the correlation was best with thought disorder, less good with the total brief psychiatric rating scale (BPRS) score and paranoid delusion, and least good with depression and withdrawal retardation. In 1978 (20), data from 46 acute psychiatric patients studied following the protocol utilized in 1976 (19) were analyzed by multiple-regression analysis to correlate CPZ plasma concentration with clinical improvement. Scores for the total BPRS, thought disorder, paranoid delusion, depression, and withdrawal and retardation, corrected for initial clinical status, were examined as dependent variables at the end of the third week of treatment with CPZ. The mean CPZ plasma concentration, hospital, year of illness, CPZ dose, and preadmission BPRS were used as independent variables. The analysis supported the early suggestions that thought disorder, paranoid delusion, and total BPRS scores correlated significantly ($p=0.007$, 0.04, and 0.02 respectively) with plasma CPZ levels. As in the Wode-Helgodt study, the percent variation explained (r^2) by the plasma concentration was about 26–53%.

Garver et al (13) suggested that erythrocyte (RBC) concentration is a better predictor of brain concentrations and reported that dystonic patients have higher RBC levels of butaperazine than do non-dystonic patients. Whether butaperazine and chlorpromazine kinetics are similar is not known. Others have suggested that saliva is a more logical fluid to measure, as it would reflect the free neuroleptic, which is the form that distributes to the brain (16), but methodological problems in saliva assays have been reported (28). CSF concentration unquestionably should relate best to brain concentration, as has recently been shown (9, 14), but for routine clinical application such measurements are impractical. Since both Axelsson (9) and Wode-Helgodt (21) have established a positive correlation between CSF and plasma concentrations of CPZ in psychiatric patients, studies using plasma concentrations measured by reliable, specific, accurate, and sensitive methods should be acceptable.

The availability of several sophisticated assays for neuroleptic drugs in different biologic fluids and tissues has been comprehensively and critically reviewed by Usdin (2) and Curry (29). The development of sophisticated methods for neuroleptic assay, from thin-layer chromatography, spectrometry, fluorometry, gas-liquid chromatography with electron-capture detector, mass fragmentography, and radioimmunoassay to the most recent radioreceptor assay, has outstripped the development of specific, critical, and structured clinical design and assessment of drug response in psychiatry. While drug assay is objective, clinical assessment and scoring for drug response are

subjective. Despite the availability of numerous validated diagnostic and clinical assessment scales (4–12), the users of these scales are so heterogeneous in skills and experience for subjective assessment of patients that reasonable concerns for the validity of clinical assessment of drug response are inevitable. This may be the foremost reason for the conflicting reports on the correlation of plasma neuroleptic concentration and clinical effects.

Radioreceptor Assay

The introduction of the radioreceptor assay for plasma levels of neuroleptics was claimed to be a solution to the question of whether the parent compound or a metabolite is the clinically therapeutic moiety (30). If both parent compound and its metabolites are suspected to be therapeutic agents, then an assay measuring "neuroleptic activity" in plasma or other biologic fluids based on dopamine receptor binding would be a logical approach.

Radioreceptor assay of neuroleptics is based on the hypothesis that effective antischizophrenic drugs act by selectively blocking the brain dopamine receptors. The principle of the assay is the in vitro competitive binding of plasma neuroleptics with radio-labelled butyrophenones (^{3}H-haloperidol or ^{3}H-spiroperidol) that bind selectively and with high affinity to striatal dopamine receptor sites in mammalian brain (30).

Possible pitfalls of the assay lie in the many assumptions that need to be met to insure accuracy and reliability of the method. Some of the assumptions that have not been documented are (*a*) that neuroleptic binding affinity to striatal or caudate dopamine receptors is identical to the binding to mesolimbic dopamine receptors; (*b*) that receptor binding affinity of the neuroleptic and all metabolites is at least equal to or higher than the binding affinity of spiroperidol or haloperidol and that the neuroleptic concentration in the plasma should be high enough to achieve displacement of the ligand; (*c*) that the active metabolites are proven to be dopamine antagonists and not partial agonists.

Some investigators have found that levels of active metabolites correlate better with clinical response than do the parent compound (8, 31–35). This evidence strengthens the claim that the radioreceptor assay would be a better technique to show correlation between plasma drug levels and clinical improvement.

However, this optimism may be premature, considering the complexities of receptor science, neuroleptic drugs, and psychiatric disease. To relate plasma "neuroleptic activity" to clinical response, several additional assumptions should be satisfied: (*a*) that the biochemical, physical, and physiological dopaminergic receptors of the bovine brain are identical to those in the human schizophrenic brain; (*b*) that the dopamine receptors of the striatal or caudate brain are identical to the mesolimbic ones; (*c*) that all schizophrenic abnormal behavior is explainable by altered dopamine receptor activity [this hypothesis is

questionable, since some therapeutically effective antipsychotics are weak dopamine blockers, e.g. clozapine (36)]; and (*d*) that the parent compound and its metabolites are identical in their pharmacokinetics, transport through the blood-brain barrier, and regional distribution in the brain.

Neuroleptics in general possess anticholinergic, α-adrenergic-blocking, and antihistaminic activities in addition to their dopamine-blocking properties. The relative potencies of the different neuroleptics and their differential affinities to the cholinergic, α-adrenergic, histamine, and dopamine receptors have not been well studied. It is possible that the neuroleptic parent compound and the metabolites that bind to dopamine receptors in the in vitro assay and are measured and expressed as "neuroleptic activity," or that get into the brain, may preferentially bind to other receptors (cholinergic, α-adrenergic, and histamine), with consequent reduction in the amount of drug available for dopamine receptors. This will obviously affect the correlation of plasma "neuroleptic activity" and clinical improvement. To date, the published reports claiming a correlation between radioreceptor plasma concentration and clinical improvement are not convincing (37–41).

There are numerous metabolites of neuroleptics that may be pharmacologically active but have not been conclusively proven to be psychoactive. If these metabolites with less or no psychoactive activity possess moderate- or high-receptor binding affinity, plasma "neuroleptic activity" as measured by radioreceptor assay can obviously not relate precisely to clinical improvement. Serum levels by radioreceptor assay may be a poor way to monitor blood levels, because psychiatrists may elect not to push dosage in patients with high levels, even if there are logical reasons to suspect that the high levels may be due to less active metabolites, with inadequate levels of active compound.

It has been proposed that the radioreceptor assay would be a convenient and practical method for monitoring plasma levels of neuroleptics such as haloperidol and fluphenazine with few or insignificantly active metabolites, in contrast to chlorpromazine or thioridazine. This is discussed below.

Chronicity of Disease and Neuroleptic Treatment

If the plasma concentration of CPZ is a predictor of clinical response, then investigations on the wide variability of plasma concentration of CPZ after similar doses, and the failure of some patients to achieve adequate plasma concentrations of CPZ despite huge doses, become especially relevant. Abnormally low plasma levels of neuroleptic drugs have been reported in chronic schizophrenics by Smith et al (42). Prien et al (43) reported that chronic schizophrenic patients who had been hospitalized for ten years showed greater improvement on high CPZ doses (up to 2000 mg/day) than on low doses or placebo.

A number of studies (6, 44–48) using chronic psychiatric patients ill for over five years have shown abnormally low plasma levels of neuroleptic drugs (mostly CPZ) when compared to acute patients. It has been suggested that neuroleptic bioavailability is diminished and metabolism perhaps increased in such patients (3, 49, 50). Prolonged continuous treatment with neuroleptics has been implicated in the unusually low plasma levels of neuroleptics achieved in chronic institutionalized schizophrenics (44).

We reported that chronic schizophrenic patients achieved significantly lower plasma CPZ concentrations than did acute schizophrenics on similar doses (44). Data from 133 psychiatric patients in our study were submitted to multiple-regression analysis. With plasma CPZ as the dependent variable, the effects of independent variables (hospital, CPZ dose, presence or absence of anticholinergic medications, and years of neuroleptic treatment) were tested. The analysis showed that when all the independent variables are kept constant, the best predictor of plasma concentration is the dose of CPZ and that plasma concentration decreases with an increase in the duration of CPZ treatment. The analysis predicts that with prolonged CPZ treatment the plasma CPZ concentration will diminish 5–10% a year.

We attempted to determine whether chronic psychiatric patients would achieve higher plasma CPZ levels if the drug was given parenterally. After a one-month washout period (3), plasma CPZ pharmacokinetics after oral CPZ liquid concentration (400 mg) and intramuscular (i.m.) CPZ (100 mg) were compared in four chronic patients who had been under CPZ treatment for 15–30 years. The differences between the oral and parenteral values were analyzed by Student's paired-t test. There was no statistically significant difference in the total body clearance, plasma half-life, and volume of distribution between the oral and i.m. CPZ ($p > 0.05$). The plasma peak levels and total area under the curve after i.m. CPZ were significantly greater than after oral CPZ ($p < 0.01$).

The lack of statistically significant changes in plasma half-life, total clearance, and volume of distribution between oral and i.m. routes suggests that the low plasma concentrations of CPZ after oral administration in these chronically treated patients is entirely due to diminished oral bioavailability.

The calculated oral bioavailability in these chronic patients relative to the i.m. dose ranges from 6.2 to 13.6%, which is much lower than the 25% oral bioavailability reported by Hollister et al (51). Dahl (49) observed a decrease in CPZ plasma level after repeated dosing. His pharmacokinetic analysis suggested that the low plasma concentration could be due to induced metabolism of CPZ in the gut. Smith et al (42) also observed that there was no significant difference in the β-half-life between groups of patients with low and high plasma levels of butaperazine.

This diminished oral bioavailability could be due to an increased first-pass effect as a result of enzyme induction, to increased metabolism in the gut because of delayed gastric emptying, or to a biochemical or morphological action in the gastrointestinal mucosa, with consequent impairment of absorption.

Studies have indicated that biological changes in chronically treated schizophrenics significantly affect both the pharmacokinetics and pharmacodynamics of neuroleptics. It is commonly observed that chronic patients on very high doses of neuroleptics do better than those on low doses. (52–57).

Lately, studies have indicated that striatal dopaminergic supersensitivity is a sequela of prolonged dopaminergic blockade with neuroleptics. This is the most popular theory for the development of tardive dyskinesis. Chouinard et al (58) have proposed that some dopaminergic supersensitivity develops in the mesolimbic dopaminergic receptors and expresses itself by a sudden return of psychotic symptoms upon withdrawal of medication or lowering of the neuroleptic dose. It was observed that in two patients extremely high plasma fluphenazine levels were required to reduce the psychopathology. Clearance of fluphenazine at the end of the postinjection interval induces a return of psychiatric manifestations, even if the blood levels are still high (>100 units haloperidol equivalent). Theoretically, this concentration should have been sufficient to control psychiatric symptoms in acute cases. This phenomenon suggests a significant increase in numbers of receptors, so that a much higher concentration of neuroleptics would be required to block all the receptors.

Hershey et al (48) studied the effect of a "drug holiday" (stopping neuroleptic medication for two weeks) on several parameters in six chronically treated schizophrenic patients using a placebo-controlled double-blind design. The parameters included peak-plasma CPZ, steady-state CPZ, psychiatric symptoms, withdrawal symptoms, extrapyramidal signs, and cognitive capacity. Drug holidays appeared to improve CPZ absorption, as shown by a more uniform onset of significantly higher CPZ plasma peaks after a post-holiday CPZ dose as compared to the pre-holiday dose. During the drug holiday, some mild withdrawal symptoms (restlessness, giddiness, agitation, autonomic symptoms) were noted in some patients. Others, who required diazepam for sedation, had shown high baseline BPRS scores. This is consistent with a report that the probability of relapse during drug holiday is related to the severity of illness (59).

Resumption of CPZ treatment after the holiday produced a worsening of extrapyramidal signs, greater sedation and hypotension, and alleviation of tardive dyskinesias. These observations indicate an increase in the bioavailability of CPZ to the tissues after the drug holiday. However, there was no appreciable change in the BPRS scores, possibly due to inadequate length of observation. Alternatively, this group of patients may be drug resistant, and

have much higher plasma concentration requirements, comparable to the two patients reported by Chouinard et al (58).

This study suggests that drug holidays may improve both the pharmacokinetics and pharmacodynamics of neuroleptics; relapse seems not to be a major problem.

Neuroleptic and Anticholinergic Drug Interactions

Another controversial issue that has plagued CPZ plasma kinetic studies is the interaction between CPZ and trihexyphenidyl (THP; Artane), an anticholinergic drug used widely for treating Parkinson's disease since 1949. Since extrapyramidal adverse effects are often observed with neuroleptic treatment, anticholinergics are often routinely and prophylactically prescribed to prevent the occurrence of extrapyramidal symptoms.

In recent years, the prophylactic use of antiparkinsonian drugs with neuroleptics has been shown to be unnecessary in many patients (60–64). Several investigators have reported that only 10–25% of neuroleptic-treated patients withdrawn from antiparkinsonian medication exhibit a recurrence of side effects, and Singh and colleagues (65–67) showed a reversal of the therapeutic effects achieved with neuroleptics when anticholinergics were added to the therapeutic regimen. Klawans (68) has suggested that injudicious use of anticholinergics may contribute to the genesis of tardive dyskinesias in prolonged neuroleptic treatment.

Drugs with anticholinergic effects, such as imipramine, trihexyphenidyl, propantheline, orphenadrine, and desmethylimipramine, have been shown to lower the plasma concentration of concomitantly administered drugs (69–72). Animal and human evidence indicates that anticholinergic action slows gastric emptying and delays delivery of the drug to the site of absorption. If the drug is unmetabolized in the stomach and upper intestine, the absorption of the drug will be delayed but the area under the curve will not change. However, if drugs are degraded in an acid environment or metabolized by the gut, then the rate and magnitude of absorption will be diminished as a consequence of delayed gastric emptying. For this interaction to be demonstrated, the following criteria have to be met: (*a*) baseline gastric emptying should be normal before treatment; (*b*) the test drug has to be metabolized in the gastrointestinal tract; (*c*) there should be adequate plasma concentrations of the anticholinergic drug; (*d*) the test drug should be devoid of anticholinergic activity.

The chlorpromazine-trihexyphenidyl interaction was first suspected by Rivera-Calimlim et al (18) when five patients who were receiving trihexyphenidyl could not achieve CPZ plasma levels higher than 30 ng/ml despite high does of CPZ. In 1976 (19) this CPZ-THP interaction was shown in 12 out of 15 patients who were prescribed THP together with CPZ after two weeks of treatment with CPZ alone. The patients showed a mean drop of 44% in plasma

CPZ levels after two weeks on THP. The CPZ-THP interaction was then studied in experimental animals (70); the absorption and tissue distribution of orally administered [^{14}C]chlorpromazine (CPZ) in THP-treated rats and control rats were compared. Total radioactivity (CPZ) in the plasma and brain of rats treated with THP was significantly lower and total radioactivity in the stomach was significantly higher than in rats not previously treated with THP. Gastric emptying in rats treated with THP was significantly delayed as measured by gastric clearance of the marker [^{14}C]polyethene glycol. THP had no effect on transport of [^{14}C]CPZ in everted sacs of rats or on CPZ metabolism by liver homogenates. This study thus showed that THP lowers plasma tissue CPZ after oral administration by inhibiting gastric emptying, thus diminishing bioavailability of CPZ at the absorptive site.

The association of low plasma neuroleptic levels with concomitant anticholinergic therapy was subsequently shown by Loga (50), Chouinard et al (73), and Gautier et al (74). Loga suggested that orphenadrine lowers chlorpromazine concentration by increasing CPZ metabolism, since orphenadrine is known to increase significantly the plasma half-life of antipyrine. Morselli et al (75) observed in eight patients that plasma haloperidol is diminished by concomitant administration of trihexyphenidyl and that discontinuance of trihexyphenidyl caused a significant rise in plasma CPZ. Johnstone et al (76) showed in 20 patients that procyclidine, an anticholinergic, lowered plasma concentration of fluphenthixol.

However, several studies have failed to show an interaction between neuroleptics and anticholinergics (6, 77–79). Simpson et al (77) studied this interaction in a controlled double-blind split crossover design and did not find any lowering of plasma CPZ levels by trihexyphendiyl. These patients were chronic patients with a mean duration of hospitalization of 19.7 years. They showed very low plasma CPZ levels relative to dose and in all probability had been on chronic neuroleptic treatment.

Several studies have shown that chronically institutionalized patients achieve very low plasma CPZ levels despite high doses of CPZ, which could be due to the intrinsic anticholinergic effect of CPZ. Chlorpromazine, like other phenothiazines, has significant anticholinergic action and can slow gastric emptying per se and thus affect absorption. Thus, in patients who have been chronically treated with neuroleptics, baseline gastric emptying is already prolonged, so that the effect of the addition of antiparkinsonian drugs will not be dramatic enough to be appreciated. Furthermore, CPZ medication was shown to inhibit intestinal active transport of amino acids in vivo and in vitro in rats (80, 81). Considering the local anesthetic property, CPZ can possibly affect membrane permeability in the intestinal mucosa and inhibit passive absorption of other drugs.

Hence, in chronically treated CPZ patients, even the absorption of trihexyphenidyl or other anticholinergics may be diminished (82). This is another

possible reason why CPZ-anticholinergic interaction may not be evident. It is noteworthy that studies that showed negative results for CPZ-anticholinergic interaction were all carried out in patients with initially low plasma concentrations of CPZ.

The conclusions of Simpson's study (77) were derived from statistical means of data generated from patients receiving variable doses and having undergone variable lengths of hospitalization. Inspection of individual data presented in this study shows that in over 50% of the patients plasma CPZ with trihexyphenidyl treatment was lower than without trihexyphenidyl in both steady-state and plasma-peak experiments.

Bolvig Hansen et al (78) studied plasma levels of perphenazine and its major metabolites during simultaneous treatment with anticholinergic drugs and reported no interaction. Plasma concentrations were measured at the seventh hour after the oral dose. If the CPZ-THP interaction is due to delayed gastric emptying after an oral dose of perphenazine, the peak time concentration will be more prompt in the group without concomitant anticholinergic than in the group with anticholinergic. Most likely by the seventh hour plasma concentrations in both groups would be comparable, since in the group with anticholinergic drug absorption is still going on because of delayed gastric emptying. This was shown by Morgan et al (69) in their study of the anticholinergic effect of imipramine on plasma kinetics of levodopa in rats and in man.

Again, one notices in this study unusually low baseline concentrations of perphenazine in all groups, but especially in the orphenedrine and biperidine group. Apparently these patients were chronically treated previous to the study with perphenazine, which in itself has intrinsic potent anticholinergic and antihistamine effects.

Kolakowska et al (6) likewise studied the interaction of benzhexol (trihexyphenidyl) in 13 chronic psychiatric patients with a history of 5–17 years of neuroleptic treatment. Plasma CPZ was measured before and after seven days' treatment with benzhexol. The study showed an increase in 12-hour and 23-hour plasma CPZ after benzhexol treatment. Seven patients had not received CPZ but were on other neuroleptic drugs and therefore were exposed to CPZ de novo during the study. The six patients who had been on CPZ for 8–17 years were given a placebo for 4–6 weeks before reinstating CPZ treatment in the study. In both groups, the increased plasma CPZ concentration seen after benzhexol could be the rise of plasma CPZ after simulated drug holidays reported in the study by Hershey et al (48).

In 1982, a statistical analysis of the effect of the anticholinergic THP on CPZ plasma levels in 38 acute psychiatric patients was reported (3). Each patient was prescribed an individual therapeutic dose of CPZ for four weeks. Eleven patients received THP (2 mg three times a day) in the first two weeks of the CPZ treatment; THP was then stopped for the next two weeks. Twenty-seven patients received the anticholinergic in the second two weeks. Plasma CPZ was

assayed at the end of each week by the gas liquid chromatography with an electron-capture detector.

All patients had a decrease in plasma CPZ after THP treatment, and this decrease was significant at $p < 0.004$. There was an increase in plasma CPZ levels when the THP was withdrawn after two weeks' administration in 8 of the 11 patients. A one-way repeated analysis of covariance was used to test for anticholinergic effect.

The variables available for each patient were weekly plasma CPZ level, CPZ dosage for each week, anticholinergic for each week (yes/no), and years of CPZ treatment. The basic question considered by the analysis was the effect of anticholinergic drug on plasma CPZ level. The approach taken in analysis was to use a one-way repeated-measures (each patient is observed at two time points) analysis of covariance. Since the anticholinergic effect was not crossed with the trial (time) effect, no fixed effects were included in the analysis of variance. Only the random-effect "trial" (first two weeks/second two weeks) was included. The anticholinergic effect was a within-patient effect since each patient was observed both with and without anticholinergic. Histograms of the two plasma level variables indicated that a logarithmic transformation would reduce a certain amount of skewness in these variables, so that the assumption of normally distributed errors would not be violated. The dependent variables in the analysis were thus the logs of the two mean plasma levels for each patient. The analysis is summarized in Table 1.

As Table 1 indicates, the anticholinergic effect is highly significant. Furthermore, the sign of the regression coefficient for anticholinergic effect (recall that this variable was included as a covariate) indicated that patients not taking anticholinergic were predicted by the analysis of covariance model to have approximately 50% higher plasma levels (when all other independent variables are held constant). There was no trial (time) effect. Furthermore, dose did not account for a significant amount of variation within patients.

If it is true that anticholinergic-neuroleptic plasma kinetic interaction is only observed in acute patients who tend to achieve high concentrations of chlorpromazine and is absent in those who achieve very low plasma CPZ, then the clinical significance of this drug interaction in the two situations will be

Table 1 Effect of anticholinergic drugs on plasma CPZ level

Source	Sum of squares	DF	Mean square	F-ratio	P-value
Trial effect	.126	1	.126	2.83	.10
Anticholinergic	.448	1	.448	10.06	.004
Dose	.032	1	.032	.721	.40
Error	1.29	29	.045	—	—

different. The plasma CPZ lowering effect of anticholinergic drugs should be kept in mind when prescribing neuroleptics to acute cases so as to avoid inadequate concentrations of CPZ.

It had been a practice to prescribe anticholinergics routinely with neuroleptics to prevent extrapyramidal adverse effects. Because of this drug interaction, unnecessarily high doses of neuroleptics may be required to achieve clinical response in acute schizophrenic patients. On the other hand, in patients chronically treated with neuroleptics, dopaminergic hypersensitivity and cholinergic hyposensitivity may develop, so that prescribing anticholinergics may contribute to the induction of tardive dyskinesias and anticholinergic toxicity.

HALOPERIDOL

When Cooper reviewed the literature on antipsychotic plasma-level monitoring in 1978 (83), there were too few published studies on haloperidol (HDL) to recommend using drug-level measurements as a clinical tool. Since that time, however, a number of new analytic techniques have been introduced, and several groups have addressed the question of whether serum HDL levels correlate with dose and/or clinical response. Because haloperidol has no significant active metabolites, it is an ideal medication to use to study the relationship between clinical efficacy and neuroleptic levels. For adult schizophrenic patients, there is now evidence to suggest a therapeutic plasma range for HDL. While the exact limits for this range are still poorly defined, it appears that concentrations on either side of a "therapeutic window" may be associated with poor clinical response.

Assay Methods

Gas-liquid chromatographic (GLC) methods for measuring HDL have been described by Marcucci et al (84), Zingales (85), Forsman et al (86), Bianchetti et al (87), and Shvartsburd et al (88). The latter authors also demonstrated the usefulness of their GLC method (with nitrogen detection) in measuring red blood cell HDL levels in addition to plasma HDL levels.

Clark and others showed radioimmunoassay (RI) of HDL to be sensitive and specific (89), although they did not compare it to other analytic methods. Creese & Snyder developed the neuroleptic radioreceptor assay (NRRA) for antipsychotic drugs, including HDL (90). This assay is based on the ability of neuroleptic agents in serum to displace binding of tritiated ligand to brain dopamine receptors. Since HDL has no known active metabolite, the results of chemical (GLC) and biologic (NRRA) assays should be roughly comparable. Correlation coefficients of 0.75 or better have been reported when GLC and NRRA are compared (91, 92). Nevertheless, GLC has the advantage of greater sensitivity than the NRRA. GLC can reliably detect HDL concentrations of

0.5–1.0 ng/ml (92), while NRRA assays can rarely detect levels below 3 ng/ml–10 ng/ml (92). Rimon and others (93) showed the two biologic methods (NRRA and RI) to correlate poorly (r=0.51), although Creese & Snyder found the correlation to be good in the narrow range of 18–37 ng/ml (90). Rimon et al suggested that some patients have an immunoreactive metabolite of HDL that does not bind to receptors; conversely, other patients may have a receptor-active metabolite that is not immunoreactive (93).

More recently, high-pressure liquid chromatographic methods have been developed to measure HDL (94, 95), but the lower limit for useful quantitation with this method is similar to that of NRRA (2–3 ng/ml). A more sensitive (but more expensive) method is gas chromatography-mass spectrometry (GC-MS). It can accurately measure HDL levels in the range of 1 ng/ml, and it can perform the task in the presence of other drugs (96). Kurland et al found correlation coefficients of 0.73 and 0.97 when GC-MS and NRRA were compared in a group of schizophrenic patients (97).

Dose-Level Correlation

Using RI to measure HDL levels in pediatric patients, Morselli and his colleagues reported a poor correlation (r=0.56) between plasma levels and dose (mg/kg/day), but this could be explained by age-related differences in drug clearance in patients under the age of 20 (98). Using GLC to measure HDL levels in adults, Forsman et al also found a poor correlation (r=0.55) between plasma levels and dose (mg/kg/day), but their patient population was not defined in terms of age or clinical diagnosis (86). In adult schizophrenic patients, several authors have reported a good correlation between HDL levels and dose (mg/kg/day) over a wide range of doses using GLC (r=0.95), NRRA (r=0.83), or RI (r=0.90) (92, 99, 100). The next step will be to use these dose-level relationships to choose the starting dose for acutely psychotic patients. This method could potentially save time and prevent the persistent psychiatric distress associated with inadequate dosing.

Response-Level Correlation

The therapeutic range of HDL appears to vary as a function of the disease entity being treated. For example, Morselli and his co-workers (98) showed that children with motor tics or Gilles de la Tourette syndrome required lower levels of HDL to achieve a therapeutic response (1–3 ng/ml) than did children with psychoses (5–10 ng/ml). Similarly, Singer et al reported that older Gilles de la Tourette syndrome patients required about a tenth of the HDL dose (and level) that is required to treat young adults with schizophrenia (102).

The first authors to quote a therapeutic range for HDL in adults with psychiatric illnesses were Forsman & Ohman (103). They pointed out that the ranges vary according to the disease being treated. For example, the range for

acutely psychotic patients was 0.8–32.9 ng/ml (mean=6.5), for chronically psychotic patients 0.6–12.1 ng/ml (mean=9.7), and for senile dementia 0.5–18.6 ng/ml (mean=3.4). The authors acknowledged the weaknesses of their study design (other antipsychotic drugs were permitted, and no baseline or followup psychiatric ratings were performed). Subsequent authors have taken care to control these factors.

Magliozzi et al (104), for example, had each patient examined at baseline by two raters using the brief psychiatric rating scale (BPRS) of Overall & Gorham (105). No other antipsychotic agents were permitted, and a final interview was performed 3–12 weeks later. Subjects were classified as responders if there was a 50% or greater decline in BPRS scores from baseline to the final determination. The authors reported a "therapeutic window" of 8–18 ng/ml because patients with lower or higher levels did not achieve therapeutic benefit by their criteria. Two criticisms can be leveled at this study: (*a*) the patients were diagnostically too heterogeneous (acute and chronic schizophrenia; subacute and chronic schizoaffective disorders); and (*b*) the timing of the followup examinations was too variable (3–12 weeks). Subsequent authors have been careful to control for these factors.

Extein et al (106) used only newly admitted acutely psychotic patients in their study (14 had schizophrenia and four had schizoaffective disorder). Each patient was examined at baseline and again at four weeks with the BPRS. Responders were defined as those showing a decline of 10 points or more on the BPRS. The authors reported a "therapeutic window" of 5–15 ng/ml even though two of their 12 responders had much higher levels and three of their six non-responders had levels within the "therapeutic window."

Smith et al (107) examined red blood cell levels of HDL in a fixed-dose study on inpatients with schizophrenia or schizoaffective disorder. Unfortunately, we do not know whether these patients had acute or chronic disease. The BPRS was done twice weekly and "estimated" BPRS scores for days 0 and 24 were used to compute the percentage improvement. Only three of their 26 patients had a 50% improvement or better. Nevertheless, the authors described a therapeutic "window" of 2.4–5.4 ng/ml for red blood cell levels of HDL at three weeks. They found a similar, though less significant, relationship between plasma HDL level and clinical response with a "window" of 5–14 ng/ml.

Some authors have suggested a broader "therapeutic window" than the 8–18 ng/ml range of Magliozzi et al (104) or the 5–15 ng/ml range of Extein et al (106). We examined psychotic patients who had deteriorated acutely with GLC and NRRA and found responders to have levels in the range of 10–40 ng/ml (92). We defined responders as those who had a 50% or greater decline in BPRS scores from the baseline to week two. Our patient population included those with acute and chronic schizophrenia, paranoid state, and schizoaffective disorder. Ericksen et al (108) compared low-dose to high-dose HDL treatment

in a double-blind fashion. They found no difference in clinical improvement between those two groups as judged by total BPRS scores (reduction of about 30% was seen in both groups). Nevertheless, steady-state plasma levels in the low-dose group had a mean within the accepted "window" (9.9 mg/ml), while levels in the high-dose group were much higher (24.8 ng/ml). The latter patients thus improved with levels outside the currently accepted therapeutic range. Smith et al (107) showed that while an average improvement of 37% was seen in those with plasma HDL levels of 5–14 ng/ml, an average of 23% improvement was seen in those whose levels were above 14.1 ng/ml. There was a great deal of overlap between these two groups in the improvement seen in individual patients. It is also of interest to note that the six patients reported by Creese & Snyder had HDL levels by NRRA of 21–31 ng/ml (90).

With all this discussion of a "window," where is the evidence that high plasma HDL levels can be deleterious? Morselli et al (109) discussed the effects of high-dose HDL treatment in six patients with "resistant" paranoid schizophrenia. Oral doses were increased from 20 mg/day to 150 mg/day over seven weeks. Mean levels were initially within the "window" but quickly exceeded 40 ng/ml. None of the six patients improved clinically, and two patients developed increased psychomotor agitation and hallucinations with higher doses (and higher levels). These authors do not specify the exact levels obtained at the time of the clinical deterioration.

Bjorndal et al (100) also discussed the effects of high-dose HDL treatment in a group of chronic schizophrenics. Among 12 patients dosed with up to 120–240 mg/day of HDL for a twelve-week period, five deteriorated as judged by a rise in BPRS scores. Three of the high-dose patients exhibited attacks of violent aggression during which they struck fellow patients and staff. In all three of these patients, the aggression disappeared when their HDL doses were reduced by 50%. Unfortunately, the concomitant plasma levels achieved in these patients were not given. Extein et al (110) recently reported a schizophrenic patient in whom the initial antipsychotic effect of HDL was lost when the level reached 25.7 ng/ml. The antipsychotic effect was regained when the dose was adjusted so that the plasma levels came down to 10 ng/ml. All this suggests that high levels of HDL can indeed be deleterious.

FLUPHENAZINE

As early as 1961, Moore (111) used a naturalistic design to study the neuroleptic effect of oral fluphenazine in 174 patients aged 20–80 years. Doses ranged from 2.5 mg to 40 mg daily. Clinical improvement was observed as early as after one week of therapy in a few patients. Some improved after six weeks; some required continuous treatment up to eight months before improvement was observed.

One of the biggest problems in the maintenance treatment of chronic and remitting psychiatric patients is drug compliance. It is estimated that 30–70% of chronic patients fail to take their oral medication (112). This could explain the high incidence of relapse in outpatients. The introduction of parenteral depot fluphenazine is perhaps the most important advance in phenothiazine therapy since the introduction of chlorpromazine.

Fluphenazine decanoate and enanthate are long-acting versions of fluphenazine, a trifluoromethyl pipirazine derivative esterified with fatty acids for depot use. Fluphenazine is released to the blood stream after the hydrolysis of fluphenazine (FPZ) decanoate; it provides good control of symptoms in most chronic schizophrenic patients and reduces their rate of relapse (113–119). However, despite continuous treatment some 37% of chronic schizophrenics relapse within two years of starting treatment and 30–40% show extrapyramidal side effects. The plasma pharmacokinetics of fluphenazine in man has been studied using several methods of assay (120–123).

Using GLC-electron capture detector, fluphenazine was assayed in the plasma of six patients who were treated with parenteral fluphenazine decanoate (25–50 mg) every two weeks for an average of 2–4 weeks (121). Plasma concentrations ranging from 9–12 ng/ml were observed 7–14 days after injection. One patient achieved 15 ng/ml 24 hours after one injection of 50 mg FPZ decanoate.

Nasrallah et al (124) studied the relationship of plasma concentration of fluphenazine to clinical response and prolactin concentration in 10 chronic schizophrenic patients in a controlled study. There were wide intra- and interpatient variations in the plasma FPZ concentrations following an intramuscular dose of 50 mg. Concentrations from 6–28 ng/ml were observed within 1–6 hours after injection. Peak values occurred at different times in different patients. In most patients, daily oscillations of plasma concentrations from trace amounts to 22 ng/ml were observed. Two patients achieved 100 ng/ml, one at six days after injection and the other on the twenty-second day after injection. There was no relationship between fluphenazine concentration and prolactin plasma levels in these patients. Prolactin levels fluctuated but remained high for all patients throughout the period, including the days with undetectable plasma fluphenazine. There was no significant clinical change in any of the subjects in the study.

The kinetics of fluphenazine after fluphenazine dihydrochloride, enanthate, and decanoate administration to seven subjects were studied by Curry et al (120) using radioactive fluphenazine. Subjects who received fluphenazine hydrochloride orally achieved much lower concentrations than subjects who received the fluphenazine hydrochloride by intramuscular injection. The half-lives were shortest with the dihydrochloride (14–19 hours) and longest with the decanoate preparation (6–9 days). It appeared that the rate-limiting step in

achieving plasma concentrations of depot fluphenazine is the clearance and release of the compound from the site of injection. There was no evidence of esters in plasma, urine, and feces. Jorgensen's group (125), using radioimmunoassay, studied two concentrations of fluphenthixol decanoate, 2% and 10%, in eight schizophrenic patients in a crossover design and showed no significant difference in the plasma concentration achieved by the two different concentrations. Maximum concentration was observed by 4–7 days. Tune et al (117), using the radioreceptor assay, monitored the serum levels of fluphenazine in nine chronic schizophrenic patients who received various doses of fluphenazine decanoate injected every two or three weeks. All these patients were in remission. Individual variations in plasma concentration were observed but intrapatient plasma concentrations tended to be stable. Concentrations were generally related to dose. Concentrations measured and expressed as chlorpromazine equivalents were amazingly low in this group of patients (<30 ng/ml) and yet maintained them in remission without significant adverse effects. Harris et al (126) reported plasma fluphenazine concentrations from oral and parenteral doses in 12 patients, measured by both high-pressure liquid chromatography (HPLC) and radioreceptor assay. NRRA was able to detect the drug in 94% of the samples. The sensitivity of the HPLC is 2 nanomolar fluphenazine and it detected no drug in all samples with less than 5 nM as measured by NRRA.

There was no correlation between doses (10 mg for oral and 25 mg depot injection every two weeks) and concentrations of fluphenazine. Plasma concentration of fluphenazine and metabolites appeared to correlate with clinical improvement, but the number of subjects was too small to be conclusive. Patients had florid symptoms of hallucinations and delusions and clinical improvement assessment was measured by the brief psychiatric rating scale.

Wiles & Gelder (122) claimed a correlation between the doses of fluphenazine decanoate (3 mg–75 mg weekly) and the mean plasma concentrations of fluphenazine measured by radioimmunoassay. In this complicated study, 33 patients were given different doses at different intervals. Examination of the raw data from three patients suggested that the plasma profile of patients receiving 25 mg/2 weeks was no different from that of patients receiving 12.5 mg/3 weeks, while one patient who received 25 mg/4 weeks achieved much higher concentrations. The raw data from the 33 patients showed a wide variation of plasma concentrations in patients within a dose level; some patients receiving 12.5 mg/week achieved much lower plasma concentrations than some who received 6.25 mg/week. These receiving 50 mg/week or higher had definitely higher plasma concentrations (3–6-fold) than those receiving 12.5 mg/week. It must be noted that the radioimmunoassay is not specific and can cross-react with both active and inactive metabolites.

A double-blind study to investigate the relationship of oral plasma fluphen-

azine and therapeutic response was conducted in 29 patients using GLC with nitrogen detector and acetylation procedure (127). There was no correlation between dose and plasma concentrations. Patients with less than 0.2 ng/ml and greater than 2.8 ng/ml deteriorated clinically, while patients in between these concentrations improved significantly. The study also showed no relationship between plasma concentration and extrapyramidal symptoms. The mean values of both the two-hour peak and the area under the curve of the six patients without dystonia were actually higher than for those with dystonia.

Megadoses and Neuroleptics

Certain chronic, drug-resistant schizophrenic patients respond to megadoses of neuroleptics. Whereas the majority of patients receive 25–50 mg FPZ i.m. every week or two weeks, a few patients may need doses up to 250–500 mg i.m. every two weeks. Itil (54) in 1970 reported the treatment of resistant schizophrenics with extremely high doses (up to 2000 mg daily) of fluphenazine hydrochloride.

Dencker et al (52) reported on the use of megadoses of fluphenazine enanthate in 30 chronic schizophrenics who also had been drug-refractory for 10 years. Fourteen patients responded so well that megadoses were continued as their treatment. The dose was 250–500 mg weekly, with withdrawal intervals, continued for 4–8 years. The total dosage received during the period ranged from 13.9–61.2 grams as ester. Plasma concentration was measured on four and five days after a megadose by ion-pair partition chromatography. Concentration ranged from < 0.4–55.1 ng/ml. Several parameters were monitored during the megadose treatment, such as skin and eye changes, EEG, ECG, chest X-rays, hematology, blood chemistry, and site of injections. The significant findings noted were leukopenia and low neutrophil percentage, EEG abnormalities, and ocular changes. Dyskinetic movements were usually slight. The authors concluded that the changes observed were not life-threatening and were not specific to megadose therapy.

Although megadoses have been tried and reported on (128, 129) from various parts of the world and have been shown to be beneficial for chronic drug-refractory non-responders compared to standard doses, careful evaluation of patient candidates for megadoses and judicious monitoring of side effects are indicated.

Effect of Age on Plasma Neuroleptic Concentration

Several reports (130–133) have shown that mentally ill children 7–15 years of age who were treated with neuroleptics achieved much lower plasma concentrations relative to dose than did adults. This observation is not unique for neuroleptics, however, since this is similarly observed with phenytoin, isoniazid, antibiotics, and tricyclic antidepressants. Studies have shown that

children are rapid metabolizers of drugs. Recently (134), higher plasma-protein binding and a shorter plasma half-life of haloperidol (4–16 hours) were reported in children compared to adult values, which are 16–24 hours.

Our study (3) noted, however, that in six mentally ill children whose plasma concentrations were followed for 8–16 weeks, the optimum therapeutic CPZ plasma concentration (35–80 ng/ml) tended to be lower than values reported for adults (50–300 ng/ml).

Similarly, adverse effects were noted even in concentrations as low as 30 ng/ml. There was wide variations of plasma concentration on comparable doses, but plasma concentration increased with dose/kg body weight.

CONCLUSION

The dilemma of establishing a therapeutic range from neuroleptics in order to provide a guideline for psychiatric chemotherapy has not been resolved, despite experimental maneuvers to circumvent possible pitfalls in assay methodology, clinical design, and clinical diagnostic therapeutic assessment.

It is evident that there are significant individual variations in the pharmacokinetics and pharmacodynamics of the neuroleptics in psychiatric patients. Measurements of serum neuroleptic levels or "neuroleptic activity" are probably most useful in people who are not achieving optimum therapeutic benefit, those experiencing significant adverse effects, and those in whom poor compliance is suspected. Future studies are needed to define the limits of the therapeutic range for various sub-groups of psychiatric patients. High doses may be required in chronically treated patients and children because of bioavailability problems. However, clinical improvement and toxicity have been observed to occur at lower plasma concentrations in such patients than those required for patients showing acute deterioration in a chronic schizophrenic process. Maintenance treatment of chronic patients is conveniently and effectively achieved by long-acting parenteral fluphenazine. Bioavailability may improve with drug holidays in some patients and with megadoses in non-responding, treatment-resistant patients.

Early assessment of the treatment is needed (at 1–2 weeks) so that appropriate dosage adjustment can be made in non-responding patients. An important goal of monitoring neuroleptic levels in acutely psychotic patients is to shorten the duration of the patient's disability and hospital stay. Long-term studies will also be needed to see whether keeping patients at the low end of the therapeutic range can eventually reduce the incidence of tardive dyskinesia. To compulsively adhere to a rigid "therapeutic window" or therapeutic range without regard to clinical monitoring diminishes the usefulness of monitoring plasma concentrations of neuroleptics.

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