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Concentrations: A Preliminary Report

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Divergence in the Therapeutic Ranges of Serum Haloperidol Concentrations: A Preliminary Report

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In a longitudinal follow-up study of 40 schizophrenic patients treated with haloperidol according to a standard protocol, the optimal haloperidol doses were bimodally distributed. While approximately two-thirds of patients who completed the study were best treated with "small" doses of haloperidol (less than 0.15 mg/kg), the other one-third required significantly higher doses for the optimal control of their psychotic symptoms. The two dosing groups also differed significantly in terms of their serum haloperidol concentrations, the severity of extrapyramidal side effects (EPS), and the need for anti-cholinergic medications. Thus, the differences in the therapeutic dose ranges between the two groups could not be explained by pharmacokinetic factors or receptor sensitivity as reflected by drug induced EPS, and may be a reflection of the heterogeneity of the schizophrenic syndrome. Further, approximately half of the patients were Asians and the other half Caucasians, and the similarity of the findings for both ethnic groups further strengthen the validity of our observations.

Key words: neuroleptics, schizophrenia, pharmacokinetics, pharmacodynamics

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Introduction

More than three decades after the introduction of neuroleptics into psychiatry, the therapeutic dose ranges of these potent and widely prescribed therapeutic agents remain uncertain^(1,2). Controversies continue to persist regarding the efficacy and utility of "megadose"⁽³⁻⁷⁾ and rapid neuroleptization regimens^(8,9), as well as the definition of "minimal effective doses"⁽¹⁰⁻¹⁴⁾. Furthermore, major efforts in searching for the therapeutic serum or plasma concentration ranges, or

"therapeutic window," also have resulted in contradictory findings⁽¹⁾. There is thus currently no rational guidelines for deciding what consists of optimal neuroleptic dosing for individual patients.

Methodological difficulties may have contributed to the slow progress in this field. These include problems in the selection of research subjects, the collection and processing of blood samples, and the assessment of drug effects^(1,15). However, in addition to these technical issues, several additional and potentially important factors may also contribute significantly to the inter-individual variability in

neuroleptic responses. These issues include receptor-coupled responsivity (pharmacodynamics) and the heterogeneity of psychotic syndromes and have received less attention clinically.

In a recently completed study⁽¹⁶⁾, we prospectively studied a group of Asian and Caucasian schizophrenic patients who were treated with a predetermined protocol, and assessed them longitudinally with standard rating instruments or clinical responses and side effects. Blood samples were obtained simultaneously for the determination of serum haloperidol concentrations. Using these data, we examined the contribution of both pharmacokinetic and pharmacodynamic factors in determining the therapeutic dose ranges of individual patients. Various comparisons were made to determine if clinical factors, in addition to kinetic and dynamic issues, also contributed to the dosages required for amelioration of their schizophrenic symptoms.

Methods

Study Design and Subjects

As has been described in detail in a previous report⁽¹⁶⁾, this was a prospective clinical follow-up study which aimed at clarifying inter-individual as well as inter-ethnic variations in pharmacokinetics and pharmacodynamics of haloperidol in the treatment of acutely decompensated schizophrenic patients. Only physically healthy Asian and Caucasian schizophrenic patients with a definitive diagnosis of schizophrenia or schizophreniform disorder according to DSM-III criteria were included in the study. For the establishment of the diagnosis, the Structured Clinical Interview Schedule for DSM-III (SCID)⁽¹⁷⁾ was conducted with each subject prior to entrance into the study. At the inclusion

of the study, all subjects manifested active symptoms as defined in the A Section of the DSM-III criteria and their initial (BPRS)⁽¹⁸⁾ total scores were all greater than 25.

After signing written informed consents, all patients were treated with haloperidol and followed approximately for three months. The treatment was divided into an initial fixed-dose phase and then a clinically-determined variable dose phase. The fixed-dose phase took place immediately following intake and lasted for two weeks, during which time subjects were treated with an oral dosage of haloperidol (0.15 mg/kg) in tablet form. Starting from the third week of the study, the dosage of haloperidol was adjusted on a weekly or biweekly basis according to titration procedure specified below. Benzotropine 4.0 mg per day was given routinely in the first two weeks for the prevention of acute dystonia. It was discontinued at the end of the second week unless clinically indicated.

Clinical Assessment

Clinical interviews were conducted weekly or biweekly in the morning approximately 12 hours after the last dose of haloperidol. Each session began with the drawing of a 10 ml blood sample for the measurement of serum haloperidol concentrations. Following the blood drawing, subjects' clinical status was assessed with the BPRS⁽¹⁸⁾. Their extrapyramidal side effects were evaluated with the Neurological Rating Scale (NRS)⁽¹⁹⁾. Dosage and other side effects were recorded on a modified version of the Dosage and Treatment Emergent Symptoms Scale (DOTES)⁽²⁰⁾. Subjects also were asked to record the exact amount and timing of medications (haloperidol and benzotropine) taken between interviews, and a pill count was performed after each interview.

In the subsequently clinically determined dose phase of the study, attempts were made to titrate the dosage to obtain the optimal therapeutic effect. This was done clinically with the aid of the BPRS results. Hence the optimal dose was at the point where the BPRS rating was at the lowest. In the majority of the cases, this was also the maintenance dosage the subject continued to receive after completing the research protocol. Differences between the optimal BPRS scores and the baseline BPRS scores were also calculated. Cases with the change scores less than 6 were regarded as non-responsive.

Inter-individual variation in the steady-state pharmacokinetics was assessed in two ways: (1) mean serum haloperidol concentrations during the fixed-dose phase; and (2) mean adjusted serum haloperidol concentrations which were the average of the serum haloperidol concentrations for all sessions divided by the daily dosage given during the preceding week. Since the two parameters are highly correlated ($r=0.64$, $n=39$, $p < 0.0001$), in the data analysis, only the results of the mean relative haloperidol concentrations will be reported.

Sample and Data Analysis

Blood samples were allowed to clot overnight at 4°C, centrifuged at 500g for 30 minutes, and aliquots of the serum were frozen at -70°C. Serum haloperidol was measured by radioimmunoassay⁽²¹⁾. Maximum intra- and interassay coefficients of variations were 9% and 13% respectively. All clinical and laboratory data were analyzed using the CRISP⁽²²⁾ and BMDP⁽²³⁾ software programs. Since these data were not Gaussian distributed, they were log transformed prior to statistical analyses. Significance levels of $p \leq .05$ were considered statistically significant.

Results

Out of a total of 40 subjects (20 Asians and 20 Caucasians) initially included in the study, 9 (23%) were judged to be unresponsive to the treatment according to the criteria defined above (4 Asians and 5 Caucasians). 21 (52%) required haloperidol dosage equal to or below their initial fixed-dose (0.15 mg/kg) for their optimal treatment (11 Asians and 10 Caucasians), and the remaining 10 (25%) needed haloperidol in the dosage range far exceeding their initial fixed-dose (5 Asians and 5 Caucasians). The proportion of patients belonging to these three outcome groups were similar between the two ethnic groups. In the following discussion, the two treatment responsive groups with different dosage levels in regard to their neuroleptic threshold will be simply called "low dose" and "high dose" groups.

As expected, the optimal haloperidol doses of the two groups were drastically different (for both ethnic groups combined: 5.7 vs 27.2 mg/day; $t=4.90$; $p < .00001$; for Asians: 3.2 vs 18.0 mg/day; $t=4.26$; $p < .001$; for Caucasians: 8.5 vs 36.4 mg/day; $t=3.92$; $p < .0025$). The differences in the dose requirements could not be explained by pharmacokinetic factors, since the two dose groups did not differ in their dose-adjusted haloperidol concentrations (for both ethnic groups combined: 0.91 vs 0.71 ng/ml x mg; $t=1.04$; NS; for Asians: 1.14 vs 0.71 ng/ml x mg; $t=1.69$; NS; for Caucasians: 0.66 vs 0.69 ng/ml x mg; $t=0.24$; NS). Thus, corresponding to the substantial differences in the optimal doses between the two groups, the high dose group also had significantly higher optimal haloperidol concentrations (for both ethnic groups: 3.2 vs

20.0 ng/ml; $t=5.23$; $p<.00001$; for Asians: 2.1 vs 13.5 ng/ml; $t=5.53$; $p<.00001$; for Caucasians: 4.4 vs 26.5 ng/ml; $t=3.94$; $p<.0025$).

Of the 21 patients on low doses, only two (9.5%) required benztropine for extrapyramidal side effects (EPS). In contrast, all high dose patients required concurrent use of benztropine for the control of EPS ($X^2=19.7$; $p<.0001$). This difference between the two dose groups in the use of benztropine for EPS occurred for both ethnic groups (for Asians: $X^2=8.6$; $p<.005$; for Caucasians: $X^2=7.8$; $p<.01$).

The two groups were similar in their demographic characteristics, and to a large extent in their clinical manifestations at the initial assessment. Although the high dose group had a somewhat longer duration of illness (77.6 ± 55.5 vs 73.6 ± 96.4 months), this difference did not reach statistical significance ($t=0.12$; NS). As reflected in the reduction in the total and psychotic sub-scale BPRS scores, patients in both dose groups experienced substantial symptomatic improvement to a similar degree. This similarity in improvement notwithstanding, at the end of the treatment protocol, all the patients belonging to the low dose group either achieved complete resolution of their psychotic symptoms, or only suffered from residual negative symptoms (flat affect, withdrawal, lack of motivation). In contrast, 10 out of the 14 who required high doses of haloperidol continued to manifest some residual positive symptoms (hallucination or delusion).

Discussion

Due to the potentially hazardous effects of inappropriate dosing of neuroleptics, such as tardive dyskinesia⁽²⁴⁾ and debilitating akathisia⁽²⁵⁾, research-

ers in recent years have become more interested in searching for the "minimal effective doses" of neuroleptics⁽¹⁰⁻¹⁴⁾. However, in light of the wide inter-individual variations in neuroleptic pharmacokinetics, it is doubtful whether such therapeutic dose ranges can be meaningfully defined. As is demonstrated in our data, as well as those reported by other researchers^(11,15), the same dose of a neuroleptic, administered to a group of patients or normal volunteers, typically results in up to a 20 fold variation of the serum neuroleptic concentrations. In order to take these inter-individual variations in pharmacokinetics into account, numerous studies have attempted to define the therapeutic "window" for various neuroleptics^(11,15,26). Unfortunately, these efforts have thus far also led to controversial results. Many factors have been listed as possible reasons for the lack of consistency of these findings, including the existence of pharmacologically active metabolites, variations in protein binding, and the heterogeneity of the patient populations included in these studies^(11,15,26).

The fact that about one-third of our patients required substantially higher neuroleptic doses for the optimal management of their psychotic symptoms is hardly a surprise. As suggested by clinical lore and confirmed by survey studies⁽²⁰⁻²⁹⁾, this indeed appears to be a wide-spread practice. However, two major questions exist regarding the interpretation of such a phenomenon. First, it has often been argued that high doses of neuroleptics may have been prescribed unnecessarily by physicians inpatient with their patients' progress and were misled by a belief that superior antipsychotic efficacy occurs with higher doses of neuroleptics (i.e. "more is better"). Second, it has not

been clear whether and to what extent the requirement of the high dosages in these patients can be explained by unique kinetic or dynamic profiles of these patients. In other words, whether they need higher doses because they are unusually fast metabolizers or whether their neuronal systems are for some unknown reasons much less responsive to neuroleptics. Based on our data, it appears that neither of these explanations apply to our patients.

One of the central foci of this study was to search and define the minimal effective haloperidol dose and serum concentration for each individual patient. During the three month treatment study, we routinely attempted to reduce the dosage in the high dose group when clinical stabilization had been achieved. This typically resulted in significant re-emergence or worsening of symptoms and a need to return to the previous dosage with patients eventually classified in the high dose group. Two of these patients actually suffered from acute relapses requiring short-term hospitalization and restoration of the previous dosage. Thus, we are confident that the high doses of neuroleptics received by these patients was indeed determined by patients' clinical need rather than by over-aggressive treatment. This finding is in congruence with previous reports of a subgroup of schizophrenic patients responding only to extra-ordinarily high doses of neuroleptics¹³⁻⁷⁾.

Although the mean relative haloperidol concentrations are somewhat lower for the high dose patients than for their low dose counterparts, this difference was not statistically significant. Furthermore, this difference was quite small when compared to the huge differences in the optimal haloperidol doses between the two groups. It is thus clear that the

need for high doses in these patients cannot be explained by pharmacokinetic factors.

The concept of supersensitivity psychosis⁽²⁰⁻²²⁾, although still controversial and unproven, could provide the basis for explaining why some patients required "excessive" doses of haloperidol for optimal effect. However, our high dose patients showed no sign of increasing tolerance to neuroleptics throughout the study period. Some have been followed by us far longer than the study period and still show no signs for the need to further escalate the dosage, which would be the case according to the hypothesis of supersensitivity psychosis. Reviewing the drug history obtained at intake, it is also clear that, although high dose patients typically received higher doses of neuroleptics in the past, there was no evidence for the need to increase the dosage further over time.

This leads to the tentative conclusion that the two dose groups in our study indeed represent two subtypes of schizophrenia identifiable by their quantitatively different patterns of drug responses, and simultaneously raises an even more important and interesting question: what makes them different? Admittedly this is a complicated question that may not have easy answer. Our data suggest that although the two groups were similar in the severity of their psychosis at the beginning of the treatment, and improved to a similar degree, a closer look revealed that the high dose patients tended to have more "typical" schizophrenic symptoms at the initial interview, and after stabilization continued to manifest residual psychotic symptoms. A review of history also showed that although the two groups did not differ in the length of illness and number of re-

lapses requiring hospitalization, the low dose group patients tended to experience no positive schizophrenic symptoms during these remissions, while the high dose patients typically continued to have some of these symptoms even though otherwise they functioned relatively well.

These characteristics are similar to two of the subtypes recently described by M. Bleuler⁽³³⁾, who prospectively followed a large group of definitively schizophrenic patients for several decades. Other researchers have also reported different types of schizophrenic patients responding to different doses of neuroleptics^(24,34,35). This possible association between subtyping, as classified according to clinical course and neuroleptic dose requirement, is evidently of potential clinical significance and should be further clarified by carefully designed studies with larger sample sizes.

The two dose groups not only diverge in their dosage requirement, but also differ significantly in their optimal serum haloperidol concentrations. This might explain why previous studies regarding the therapeutic serum haloperidol concentrations have come up with ranges drastically different from one another⁽¹⁾. It is possible that, depending on the setting of the studies, the ratio between patients who would have belonged to the two dose groups as defined in our study would change, which then resulted divergence in findings regarding therapeutic ranges.

To ultimately test this hypothesis of the existence of two distinctive subtypes of schizophrenic patients who require different neuroleptic dosages, similar dose-finding studies should be conducted with first-break patients. Ideally, such studies should be combined with other research strategies looking at structural abnormalities (e.g. sizes of the ventri-

cles), frontal lobe functions, neurological soft signs, and biochemical parameters such as metabolites of dopamine (e.g. homovanillic acid [HVA]), in order to further identify mechanisms which may be responsible for the differences in drug response.

Finally, it is also noteworthy that most of the findings discussed in this report hold true for both the Asians and the Caucasians who participated in the study. A comparable proportion (about one-third) of patients in both ethnic groups required doses higher than threshold. When data analysis was done separately for each ethnicity, the results parallel each other and are in the same direction as those derived from analysis with the whole sample. It is in a sense as if these were two independent studies which came up with strikingly similar results, further suggesting that the observations derived from them were not merely chance findings, but represented core aspects of the pathobiology of schizophrenia.

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