

Asian American Psychiatrists

Pharmacotherapy of Asian Psychiatric Patients

by KEH-MING LIN, MD, MPH and RUSSELL E. POLAND, PhD

In contrast to other forms of psychiatric therapeutic modalities originally developed in Western countries, which have thus far achieved very limited successes in Asian countries,¹ the introduction of various psychotropic medications into these communities has encountered very little resis-

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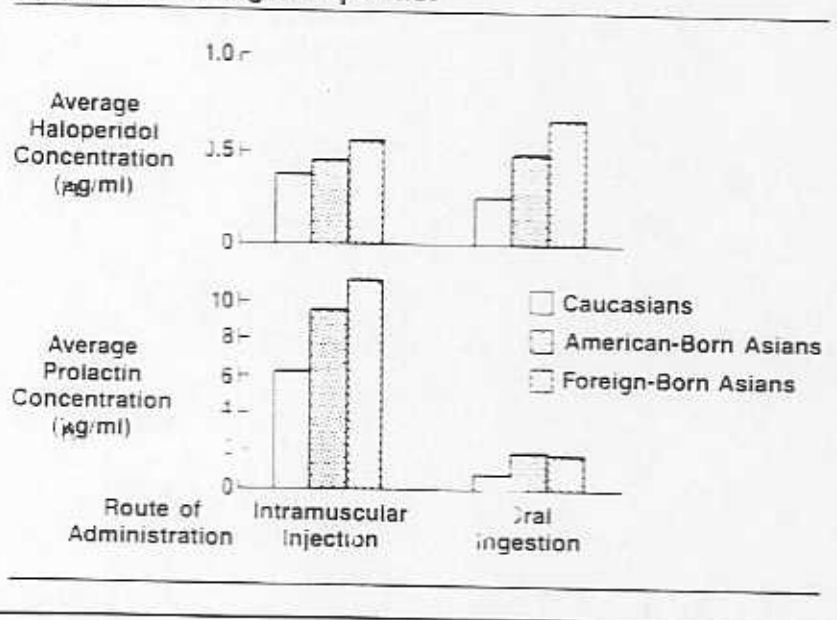
tance, if at all.² Practically all major categories of psychotropics currently available in the United States and Europe are also widely used in Asian countries for similar clinical indications.

However, over the past 40 years clinicians with cross-cultural experiences have repeatedly reported dramatic differences in the therapeutic dosages of many of the psychotropics that are used on both sides of the Pacific Ocean.³ With the rapid in-

crease of the Asian populations in the major metropolitan areas of the United States, reports of similar cross-ethnic dosage contrasts also have emerged.⁴⁻⁶ However, until most recently, these observations were based only on surveys, chart reviews, or clinical impressions and were not derived from systematic studies with vigorously designed methods.

Since 1982, our research group has conducted a series of studies in

FIGURE 1
Average Haloperidol and Prolactin Concentrations After Intramuscular Injection of 0.5 mg Haloperidol and Oral Ingestion of 1 mg Haloperidol



this area using different study designs. The major impetus behind these studies has been our shared conviction of the importance of genetic and environmental factors in shaping intergroup and interindividual differences in drug responses. Additionally, these studies also have their roots in our cross-cultural clinical experiences. In 1974, one of the authors (KML) left Taiwan and entered the residency program at the University of Washington in Seattle for further psychiatric training. Among the many things he had to adapt to during this difficult transition, one he least expected was the dramatic differences in psychotropic dosages.

For example, whereas most Chinese schizophrenic patients in Taiwan seemed to respond well to haloperidol in a dose range between 0.5 and 2 mg/day, many psychotic American patients received the same medicine at a dosage level of around 50 mg/day, and some patients even received dosages of up to 100 mg

per day. In subsequent years, he often pondered upon such huge differences in the "therapeutic dose ranges" in the two countries and wondered whether they could be completely caused by differences in the "practice styles" of the psychiatrists in the two places (ie, either a tendency among psychiatrists in Taiwan to undermedicate or the opposite tendency among their American counterparts, or both)⁶ or whether biological factors also were an important component underlying such differences.

Interestingly, in subsequent years the prescription patterns of both countries have changed significantly. In Taiwan, the introduction of rapid neuroleptization in recent years has resulted in dramatic increases in the neuroleptic doses used in the clinical settings. Conversely, in the United States, the increasing awareness of the risk of tardive dyskinesia in association with long-term use of neuroleptics has discouraged clinicians from using excessively high doses of neuroleptics. Thus, the current cross-cultural differences in dosage requirements may not be as dramatic as they were 15 years ago.

This article summarizes some of our findings, reports two case vignettes, discusses our findings in light of other recent reports with comparable methods, and briefly describes our suggestions for future research directions.

FINDINGS

Our first study,⁵ conducted in 1982, retrospectively compared the dose range of neuroleptics between 15 consecutively hospitalized Asian patients and Caucasian counterparts matched for age, sex, diagnosis, and chronicity. As evidenced by their discharge Global Assessment Scale (GAS) ratings, patients in both groups benefited to a similar degree from neuroleptic treatment. However, the maximal, as well as stabilized, chlorpromazine (CPZ) equivalent doses for Asians (849 and 652 mg/day) were significantly lower than those for Caucasians (1066 and 827 mg/day). These differences remained statistically significant after controlling for body weight differences in the two groups.⁵

This was followed by two similarly designed studies^{7,8} examining the serum concentrations and effects of haloperidol and alprazolam in Caucasian, American-born Asian, and foreign-born Asian healthy male volunteers. All subjects were non-smokers and drank alcohol only occasionally. In the first study, haloperidol (1.0 mg orally or 0.5 mg intramuscularly) was administered in random order to all subjects on 2 separate days at least 2 weeks apart. Repeated blood samples were obtained for the measurement of haloperidol and prolactin concentrations as measured by radioimmunoassay.⁵ Previous studies had demonstrated that prolactin secretion is very sensitive to the effect of haloperidol in this dose range.

The haloperidol (after both intramuscular and oral administrations) and prolactin (after intramuscular administration) concentrations of both Asian groups were significantly higher than those of the Caucasians (Figure 1). The differences in haloperidol concentrations remained

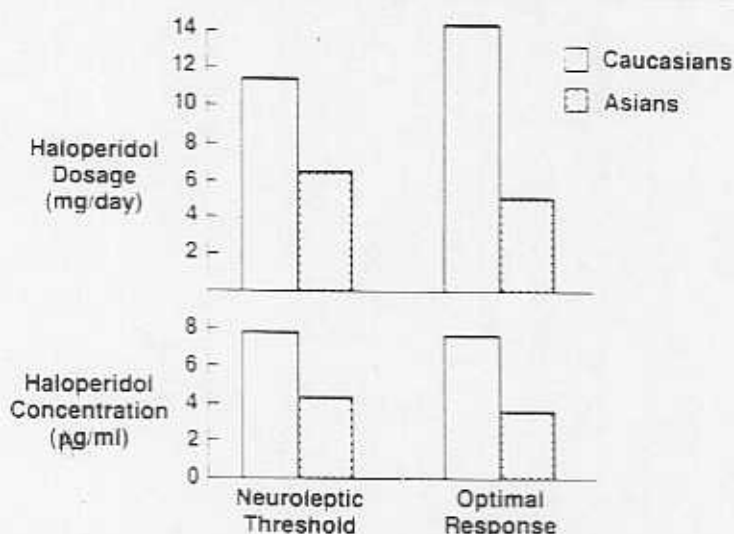
highly significant after controlling for body surface area. Further, when the influence of haloperidol is controlled statistically, the differences in prolactin concentration after intramuscular haloperidol remained statistically significant.

Although foreign-born Asians had slightly higher haloperidol and prolactin concentrations compared to American-born Asians in most of these measurements, these differences were not statistically significant in any of the comparisons. These results demonstrated that substantial and statistically significant differences exist between Asian and Caucasian healthy volunteers in their pharmacokinetic responses to haloperidol. The fact that ethnic differences in prolactin responses could not be explained completely by variations in haloperidol concentration suggests that in addition to and independent of the ethnic differences in haloperidol pharmacokinetics, Asians and Caucasians may also differ pharmacodynamically, i.e., there may be a difference between the two in their receptor coupled activities, and this may be part of the reason for the clinically observed differences in therapeutic dosage requirements between the two ethnic groups.

In the second of our cross-ethnic pharmacokinetic studies, we used alprazolam as a test drug, testing 28 Asian (14 foreign-born and 14 American-born) and 14 Caucasian volunteers with alprazolam. After a 12-hour overnight fast, 0.5 mg alprazolam was administered either as an oral tablet with 180 mL of water or as a slow intravenous injection on a separate day. Over the subsequent 36 hours, 14 post-drug blood samples were obtained.

Using the assay results, the plasma concentration curve for each individual subject was constructed. The area under the plasma concentration curve (AUC), the peak plasma concentration (C_{max}), the time required to reach the peak concentration (T_{max}), as well as the total plasma clearance (CL) and the volume of distribution were calculated.

FIGURE 2
Haloperidol Dosage and Concentration at the Neuroleptic Threshold and the Optimal Response Points for 13 Asian and 16 Caucasian Schizophrenic Patients



Ethnic differences of these parameters either reached statistical significance (AUC and CL after oral administration; C_{max} after intravenous administration) or approached significance (C_{max} after oral administration, AUC after intravenous administration). These statistical differences remained unchanged after body surface area was covaried. Asians also had substantially longer elimination half life, which, however, did not quite reach statistical significance.

In contrast to the differences between the Asians and the Caucasians, the pharmacokinetic parameters of the two Asian groups were again remarkably similar. These results confirmed the findings of the previous study with haloperidol in regard to the similarity between the two Asian groups and the significant divergence between Asians and Caucasians in their pharmacokinetic responses to psychotropics.

Following these pharmacokinetic studies with normal volunteers, we

conducted a prospective cross-ethnic study of clinical responses to haloperidol between Asian and Caucasian schizophrenic patients.¹⁰ Over a 3-month period, 13 Caucasian and 16 Asian schizophrenic patients were prospectively and sequentially treated with haloperidol, first with weight-adjusted fixed doses (0.15 mg/kg) for 2 weeks and then with clinically-determined (variable) doses of haloperidol for the next 10 weeks.

During the clinically determined phase of the study, efforts were first made to titrate for the "neuroleptic threshold" and then for the determination of the optimal dosage. The neuroleptic threshold is defined as the point where very mild rigidity first emerges without the use of anticholinergics.^{11,12} The results revealed that during the initial fixed-dose phase, Asians had non-significantly higher serum haloperidol concentrations and significantly higher ratings of extrapyramidal symptoms (EPS). During the subsequent clinical

cally determined phase. Asian patients required significantly smaller doses of haloperidol that resulted in lower serum haloperidol concentrations (Figure 2). These results further support previous clinical observations of ethnic differences between Asians and Caucasians in terms of therapeutic dose ranges and side effect profiles, but suggested that in contrast to normal volunteers, brain receptor responsivity may be more important than kinetic factors in determining such differences in schizophrenic patients.

CASE VIGNETTES

To illustrate the clinical significance of the above findings, the case histories of two Asian patients who responded to "unusually" low doses of neuroleptics are presented.

Vignette 1

Mr A was a 44-year-old, twice-divorced, unemployed third-generation Chinese-Panamanian who had lived in the United States since the age of 18. Despite several psychotic episodes requiring hospitalizations since his late twenties, he was able to complete a PhD degree in biochemistry and later a DDS degree. This enabled him to practice dentistry until the recurrence of his psychosis about 2 years prior to his contact with us. When he was first brought to our outpatient clinic by his older sister who was visiting from Panama, he was financially destitute and was completely incapacitated by his psychotic symptoms. These symptoms included looseness of association, persecutory delusions involving FBI agents, a firmly-held belief that his enemies were attempting to control his mind because "electronic waves" frequently interfered with his thinking, and bizarre and grandiose delusions (such as beliefs regarding his ability to disapprove Einstein's relativity theory) that were not accompanied by euphoric mood or other signs of mania.

With strong support and urging from his sister, he agreed to a treatment plan that included the stabilization of his living and financial situation, psychosocial interventions, and medication. Because of his past experiences of severe EPS when receiving psychotropic medication, he was only willing to take 2 mg/day of thiothixene, which he had

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taken several years ago when recovering from a previous psychotic episode. Over the next 8 months, he became progressively less preoccupied with his delusions. He was able to resume his dental practice and social activities. When last seen 5 years later, Mr A was remarried, and his private dental practice was successful. Although there was no sign of overt psychosis, he continued to take the small dose of thiothixene. When asked about his previously held delusions, he insisted that all those bizarre events did happen in the past. However, he added, now he was too busy to think about any of them.

Vignette 2

Mr B was a 58-year-old married Chinese computer programmer who was first evaluated by us because of his frequent angry outbursts, hostility, and verbal altercations with his neighbors and other tenants of the office building where his computer store was located. The initial interview with him and his wife revealed that he had been experiencing severe psychiatric symptoms, including auditory hallucinations and persecutory delusions for several years, although he had never had any previous psychiatric contact and had been able to function at work until very recently. One year prior to this initial clinical contact, he resigned from a well-paying job at a major aerospace company because he believed his colleagues were spying and reporting on him; he started his own business selling microcomputer systems and components. He also had been hearing different voices ridiculing him, commenting on his actions, and threatening to hurt him for quite some time; he became convinced they came from his neighbors

and symptoms included agitation, irritability, and insomnia. There was, however, no evidence of blunting of affect and no looseness of association. There was no evidence of depressive mood, mood swing, or manic-like behavior in the past. Family history revealed that he had an older brother who had been suffering from similar symptoms.

After the establishment of the diagnosis as schizophrenia, paranoid type, he was entered into our clinical haloperidol study and placed on 8 mg of haloperidol at bedtime and 2 mg of benztropine twice daily. He called the next morning and complained of severe side effects, including palpitation, hot flushes, insomnia, increased feeling of agitation, restlessness, aches and pains all over the body, and rigidity of the extremities. After much discussion, he reluctantly agreed to continue the treatment with 5 mg/day of haloperidol and 2 mg/day of benztropine. His psychotic symptoms responded dramatically to this regimen, and by the end of the second week of treatment he was no longer experiencing any hallucinations. However, he continued to believe that he had been persecuted by various people in the past. Despite the small dose of haloperidol, and the use of benztropine, he continued to suffer from a moderate degree of muscular rigidity, which subsided only when the dosage of haloperidol was further decreased to 1 mg/day. He was satisfactorily maintained on this dose for the next 2 months without signs of recurrence of active psychotic symptoms. He subsequently became less preoccupied with his delusional beliefs and was able to handle his increasingly thriving computer business without difficulty.

Serum haloperidol concentrations during treatment revealed the following: when he was on 5 mg/day the steady-state haloperidol concentration was 5.5 ng/mL. When the dosage was titrated down to 1 mg/day, which was his neuroleptic threshold as well as optimal dosage, the average haloperidol concentration was 2.8 ng/mL. These results showed that he was both a slow metabolizer of haloperidol and at the same time also required lower haloperidol concentrations for optimal clinical effects. These suggested that indeed both pharmacokinetic and pharmacodynamic factors were operative in causing his unusual initial reaction to the "regular" dosage of haloperidol, and his sub-

sequent satisfactory responses to lower doses of the same medication.

DISCUSSION

We have briefly described several of our recent studies which, although using very different research designs, have reached remarkably similar conclusions regarding the importance of ethnicity as a factor in determining patients' responses to psychotropic medications. The results indicate the importance of both pharmacokinetic and pharmacodynamic factors underlying such differences. However, despite the consistency of these findings, many issues remain to be clarified. First, in the past several years, quite a few similarly designed studies have been conducted by other research groups.¹³⁻¹⁹ The results of these studies have not been consistently positive. Factors responsible for the inconsistency of these results may include:

- psychotropic medications have divergent pharmacological properties, interact with different brain receptor-neurotransmitter systems, and are biotransformed by divergent enzyme systems;^{20,21} ethnic differences in responses to some of these psychotropics are not necessarily generalizable to all the others in the same category;
- cross-ethnic differences in drug responses could be masked by interindividual variations within each ethnic group in pharmacokinetics and pharmacodynamics; this heterogeneity in the subject populations could be further aggravated if different subcultural groups are lumped together in the studies;
- the sample size of many of these studies has been small, contributing to type II statistical errors; and
- nonpharmacological factors, such as degree of compliance, stress,

social support, and family interactions, may further complicate the interpretation of cross-ethnic comparison of drug responses in clinical studies.

In addition to the need to pay attention to these issues, future studies in the field should also attempt to go beyond the mere documentation of ethnic differences in psychotropic responses and also try to elucidate the mechanisms that may be responsible for these differences. In terms of pharmacokinetics, it is ultimately important to identify the enzyme systems that are responsible for such differences and to determine whether these differences are genetically or environmentally determined. In terms of the pharmacodynamics, it may be especially fruitful to explore newer and more direct assessment methods of receptor-drug interactions. These newer imaging techniques include the single photon emission computerized tomography (SPECT) and computerized electroencephalography.²²

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