Response from Ehmann and Associates

Editors:

Dr. Jones contends that the use of a crossover design in our comparison of flupenthixol and haloperidol may have tainted the results because of a carryover effect generated by the length of the half-life of haloperidol. He also suggests that crossover designs should be limited to rare populations and, because schizophrenia is a common disorder, we should not have used such a design.

The main advantage of a within-subject design lies in the control of individual differences that leads to a reduction in error variance and an increase in the sensitivity of the statistics to uncovering experimental effects. Typically, each subject is able to act as his/her own control for variables that would need to be matched in a between-subjects design such as ward environment, sex, age, and weight. This design is also economical both in terms of organizational effort and the number of subjects needed to achieve a given level of statistical power. The choice of any experimental design is determined by both practical and theoretical issues. Given the size limits of the subject pool meeting entry criteria and the support resources available, we considered a within-subject design desirable and appropriate. Theoretically, we still see no reason that this design is unacceptable for evaluating drug treatment of schizophrenic patients.

As Dr. Jones points out, a danger of this design is the possibility of carryover effects. We anticipated this possibility and set a duration of at least 11 weeks on each drug as a reasonable period for the elimination of one medication and the instatement and adjustment of another. This time period was based on the literature extant when the study was planned.[1, 2] The recent report from Hubbard and coauthors[3] of a much longer half-life for haloperidol is interesting. Their estimation of a

21-day half-life, which appears to be based on two data points on one subject, at the limits of sensitivity of the assay, must be considered preliminary data and in need of confirmation. Even if we accepted a terminal elimination plasma half-life of 21 days, at the end of 11 to 14 weeks, four to five half-lives would have passed and the majority of drug acting in the patients would be the new one. However, our analysis of the data provided by Hubbard and coauthors does not support their suggestion that the elimination half-life of haloperidol increases continuously as plasma drug concentration declines. We modeled their data with a computerized exponential curve stripping program which uses a maximum of five exponential terms.[4] The data were best described ($R^2 = 0.80$) by a two compartment open kinetic model with first order absorption according to the equation: $C = -1667e^{-0.44t} + 1488e^{-0.043t} + 179e^{-0.0041t}$ (where C is the plasma concentration at any time t hours) with a lag time of 0.893 hours. This corresponds to a terminal half-life of 7.2 days. Calculation of this terminal half-life is based on the final three data points described by Hubbard and coauthors. Clearly, arbitrary selection of pairs of drug concentration-time data points can lead to a range of calculated half-lives. A reliable description of plasma drug concentration with time requires the data be examined together. In sum, the relevant issue does not appear to be whether some minute fraction of the initial drug is still lingering in the body 3 months following its withdrawal, but whether this amount is likely to contribute meaningfully to assessments made after 3 months of daily dosing with the second drug.

A recent study of haloperidol and flupenthixol decanoates by Eberhard and Hellbom[5] found haloperidol superior to flupenthixol in controlling symptoms after 24 weeks on each medication. They reported a modest decline in symptom scores over the first 24 weeks with both drugs. After crossover, symptoms were further reduced with haloperidol but increased with flupenthixol. A reexamination of our data revealed a similar trend but, unfortunately, the small sample size precludes further statistical exploration.

Dr. Jones raises the possibility that our patients may have appeared more disturbed on flupenthixol in phase 2 because of greater side effects generated by haloperidol in phase 1 and carried over into phase 2. He further suggests the agitation-excitement subscale scores of the Brief Psychiatric Rating Scale may reflect drug-induced akathisia rather than psychopathology. Data collected during our study but not presented earlier may clarify this issue.

First, each drug generated one case of clinically diagnosed akathisia during phase 1. Clinical diagnosis was made by an assessor blind to the independently collected akathisia ratings. A plot of the means of the 7-point akathisia rating scale (a score of 3 or more indicates akathisia) reveals elevated means at weeks 3 and 5 during the first phase. These elevations reflect the two cases of akathisia. Both cases were successfully treated with anticholinergic medication. At the end of phase 1 the four patients receiving haloperidol all received scores of 0 while the mean scores of the five flupenthixol patients was 0.4. The haloperidol patients who then began flupenthixol continued to exhibit no symptoms as evidenced by mean scores of 0 at weeks 1, 3, and 7 while the mean score for week 5 was 0.25. Final assessments for this group showed three patients with a score of 1 each for a final mean of 0.75. Scores of one are not specific for akathisia. Patients treated with haloperidol in phase 2 received slightly elevated scores at weeks 5 and 9 but no patient received a score of more than 2. An analysis of variance for the akathisia ratings with both weeks and drug considered within factors yielded no significant main effects (drug: $F = 0.22, p = 0.65$; time: $= F = 1.38$, $p = 0.23$) or a drug $\times$ time interaction ($F = 0.31, p = 0.94$). We agree that scores on akathisia and agitation may correlate. It is, however, as plausible that low akathisia scores reflect psychogenic agitation as it is that agitation scores reflect akathisia. In any event, our data do not indicate that haloperidol-induced akathisia was carried over and rated as agitation when patients were receiving flupenthixol. Furthermore, the problem of overlap in the ratings of these phenomena is not resolved by the use of a between-subjects design.

Finally, in a comparative study of antipsychotic medications, a washout is generally conducted to eliminate medication from the patients' bodies and/or ascertain the presence of psychotic symptoms when patients are unmedicated. Active psychotic symptoms were observed in all our patients during the rediagnosis conducted before inclusion. With respect to the removal of drug(s), a washout must be of ample duration if one is intending to collect baseline data and/or track responses over time. A washout to eliminate previous medication is not required if the trial is long enough to assure that measurements at the time of the researchers' main assessments reflect the effects of the drug under study. Because 11 to 14 weeks appear to be a reasonable period for drug elimination, and because we were not addressing questions related to short-term effects on symptoms, we did not attempt a washout. Of course, drug withdrawal periods carry attendant ethical concerns and potential problems of ward management, dropouts, and staff resistance.

We expect that the consistent results of our trial and that of Eberhard and Hellbom,[5] which we believe to be the first to directly compare haloperidol and flupenthixol, will be confirmed by further research. Furthermore, we do not believe that the use of a crossover design necessarily yields questionable results but that this design may be extremely useful in examining the relationship between dopaminergic systems and schizophrenic symptoms.

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