The Relationship Between Serum Concentration and Therapeutic Effect of Haloperidol in Patients with Acute Schizophrenia

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Summary

Haloperidol is the most commonly used antipsychotic drug in the therapy of acute schizophrenia. Clinicians have been using therapeutic drug monitoring in an attempt to improve clinical application of this drug. The scale of interest in this area is emphasised by the large number of studies (about 50) concerning the serum concentration-therapeutic effect relationship (SCTR) of haloperidol, including 35 studies on patients with acute schizophrenia. However, conflicting results concerning the existence and position of a therapeutic window have emerged.

This article aims to provide a comprehensive review of the study design of studies in patients with acute schizophrenia before the study data are used for decision-making. For this purpose, a reproducible system for the evaluation of studies in this special area, a so-called total study score (TSS), was developed on an empirical basis. Thus, insufficient study design was found to be a reason for negative results. On the other hand, in spite of a great variability, the majority of studies with good design provided evidence for a significant SCTR: a bisigmoidal dependence of clinical effect on haloperidol serum concentration.

The therapeutic effects of haloperidol increase at low concentrations, and the concentration has a maximum effect at about 10 μg/L and again decreasing at higher concentrations. The data of 552 patients also fit to this model in a single scatter plot (pseudo-r² = 0.076, p < 0.001). The position of the therapeutic window was determined at about 5.6 to 16.9 μg/L. Patients treated with serum concentrations within this optimal range had a significantly better response compared with outside this range (p < 0.001, Student t-test). Therefore, a quantitative synthesis of all available data by means of effect-size analysis provides a mean effect-size ($\hat{g}$) = 0.499 ± 0.182 (standard deviation) for the comparison of haloperidol-treatment with serum concentrations within versus outside the therapeutic window.

Thus, because of this moderate positive effect, serum concentration assay of haloperidol is recommended for patients with acute schizophrenia in a therapeutic drug monitoring programme. The modalities of haloperidol therapeutic drug monitoring in clinical practice are discussed, e.g. patient selection, method and time for serum concentration measurement, influence of premedication and comedication, interpretation of results and dose adjustment. Clinical investigations into this subject should focus on covariates which are responsible for the variability of the SCTR. Serum concentration assay is advised for investigations of nonresponse to exclude patients with pseudo-drug resistance.

1. Serum Concentration–Therapeutic Effect Relationship (SCTR) of Antipsychotic Drugs

The introduction of antipsychotic drugs in the 1950s was a fundamental advance in the therapy of schizophrenia and schizoaffective disorders.[1] The first drug introduced was chlorpromazine, a phenothiazine, followed a few years later by haloperidol, the guiding compound of the butyrophenone group. In combination with a new strategy of public healthcare in psychiatry, which could only be based on these drugs, a decrease in the number of psychiatric inpatients was achieved (fig. 1) and a qualitative improvement in the treatment of the remaining patients became possible.[2-4]

In spite of this success, it rapidly became clear that this was often at the cost of considerable adverse effects, such as extrapyramidal adverse effects, tardive dyskinesia, circulatory disturbances and antipsychotic malignant syndrome. Furthermore, it was recognised that the negative symptoms of schizophrenia were not sufficiently improved and,