A Comparison of Two Methods for Calculating Total Antipsychotic Dose

比較兩種計算抗精神病藥物總份量的方法

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Abstract

Objective: To compare two methods of calculating total antipsychotic drug dosage with a representative patient sample in Hong Kong.

Methods: Antipsychotic prescription data from 8,620 inpatients and outpatients in the New Territories West Cluster hospitals of Hong Kong were collected. The total antipsychotic dose was calculated using the chlorpromazine equivalent method and the percentage of maximum recommended method.

Results: There was 97.2% concordance between these two methods, with a Spearman’s rank correlation of 0.92. High doses of antipsychotic medications were prescribed for 3.2% and 2.8% of the sample based on the chlorpromazine equivalent and percentage of maximum recommended methods, respectively.

Conclusions: Total antipsychotic dose expressed as a percentage of the maximum recommended dose is easy to calculate and avoids the ambiguity associated with the chlorpromazine equivalent method, besides it helps to identify patients receiving high doses of antipsychotics, thus facilitating monitoring and adherence to current guidelines.

Key words: Antipsychotic agents; Chlorpromazine; Therapeutic equivalency

Introduction

Trainees in psychiatry have long been advised not to routinely prescribe high doses of antipsychotic medication. Generations of psychiatrists have been taught the chlorpromazine equivalent dose, as a standard method of comparing different antipsychotic regimens. In the ‘Consensus statement on the use of high-dose antipsychotic medication’, the Royal College of Psychiatrists proposed the percentage of maximum recommended dose as an alternative method.

Use of the chlorpromazine equivalent dose can be traced back to a classic paper by Davis. Equivalent doses were derived from randomised double-blind trials, in which two antipsychotics were shown to have the same clinical efficacy; chlorpromazine being the standard antipsychotic against which many first-generation antipsychotics were compared. For many reasons calculating equivalent doses is required when comparing antipsychotic medications. They include determination of clinical effects, side-effects, and...
costs of treatment. These comparisons become meaningless if the doses prescribed are not equivalent. A chlorpromazine equivalent dose above 1000 mg per day is considered high.

There are several problems using this method of calculation. Conversions are based on equivalence of antipsychotic effect, not toxicity. Extrapolation of equivalent doses to toxicity cannot be made accurately, particularly at high doses. The dose-response relationship is sigmoidal, not linear, and the concept of dose equivalence was challenged 30 years later by the original author. As equivalent doses are calculated from empirical studies and expert opinions, the ranges quoted in the literature can differ by up to 500%. Further difficulties arise in determining chlorpromazine equivalent doses for second-generation ('atypical') antipsychotic medications, although such data have been published. The lack of a uniform conversion system creates uncertainty and ambiguity.

As an alternative, the percentage of maximum recommended dose method has been suggested for calculating total antipsychotic dose. Each medication is converted to a percentage of the maximum recommended dose listed in the British National Formulary (BNF). If the sum of the percentages exceeds 100%, the patient is receiving a high dose. This method is less ambiguous, with almost all antipsychotics having a clear maximum recommended dose in the BNF, with the exception of trifluoperazine and non–United Kingdom registered medications. These maximum recommended doses are obtained from data submitted to regulatory authorities required for marketing authorisation, and are based on extensive animal and human studies.

The main reason for calculating total antipsychotic dose is to allay concerns over the safety of antipsychotics at high doses. Their safety at high doses is determined by their side-effects, not antipsychotic effects. Using a method of calculation based on toxicity is therefore more relevant. However, both methods have limitations, as neither takes into account the effects of combining drugs with contrasting mechanisms of action. Different combinations yielding identical chlorpromazine equivalents or percentage of maximum recommended doses may be very different in terms of clinical efficacy and side-effect profile. This paper aimed to compare these two methods, using a large, representative sample of psychiatric patients in Hong Kong.

**Methods**

**Study Population**
All inpatients and outpatients receiving psychiatric services in the New Territories West Cluster (NTWC) in Hong Kong, who received antipsychotic medications on 15 November 2006 were included. The NTWC covers a catchment area of 223.17 km² with a population of 1.1 million inhabitants. Outpatients receiving prescriptions prior to 15 November 2006 were included if antipsychotic medications were to be taken on that day. Patients receiving risperidone long-acting injection were excluded, as no chlorpromazine equivalent dose was available for calculation.

**Calculating Total Antipsychotic Dose**
Chlorpromazine equivalent doses were calculated based on published data, there being no published chlorpromazine equivalent dose for risperidone long-acting injection. The maximum recommended dose for each antipsychotic medication was obtained from the 51st edition of the BNF. For trifluoperazine, a maximum recommended dose of 50 mg per day was used, following the level used in an audit performed by the Royal College of Psychiatrists’ Research Unit. For thioridazine, which was withdrawn from the British market in 2005, the maximum recommended dose prior to withdrawal was used.

**Data Collection**
Inpatient prescription data were collected using a pro forma to collect information on all antipsychotic medications prescribed between 00:00 and 23:59 on 15 November 2006. Depot medications that were given prior to this date were included if this date fell within the period between successive injections. Outpatient prescription data were collected using the Clinical Management System database of the Hospital Authority, which stores information on all outpatient prescriptions. Data were analysed using the Statistical Package for the Social Sciences (Windows version 13.0; SPSS Inc., Chicago, US).
Results

There were 1,114 inpatients and 7,506 outpatients receiving antipsychotic medications and fulfilling the inclusion criteria. Twenty five patients receiving risperidone long-acting injection were excluded. The results are shown in the Figure. The prescriptions can be conveniently divided into four groups:

- **Group 1**: patients not receiving a high dose according to either method ($\leq 100\%$ of the maximum recommended dose and $\leq 1000$ mg chlorpromazine equivalents);
- **Group 2**: patients receiving a high dose using the chlorpromazine equivalent method only ($\leq 100\%$ of the maximum recommended dose and $> 1000$ mg chlorpromazine equivalents);
- **Group 3**: patients receiving a high dose using the percentage of maximum recommended method only ($> 100\%$ of the maximum recommended dose and $\leq 1000$ mg chlorpromazine equivalents);
- **Group 4**: patients receiving high doses according to both methods ($> 100\%$ of the maximum recommended dose and $> 1000$ mg chlorpromazine equivalents).

The Table shows the antipsychotics prescribed for patients in groups 2, 3, and 4. The mean prescribed dose was $29\%$ of the maximum dose (range, 0.4-273.3; SD, 29.9) and $278$ mg chlorpromazine equivalents (range, 2.5-3,600; SD, 304). In this study sample, $96\%$ of the prescriptions were categorised as group 1, with antipsychotic doses below the maximum using both methods described. High doses of antipsychotic medications were prescribed for $1.6\%$ of the sample using the chlorpromazine equivalent method recommended by the Royal College of Psychiatrists, $1\%$ patients receiving doses in group 2 would not be classified as receiving high doses, whereas patients in groups 3 and 4 would. There was a $97.2\%$ concordance between these two methods for calculating the total antipsychotic dose, and Spearman’s rank correlation was $0.92$ ($p < 0.001$). When the prescriptions were separated according to atypical antipsychotic usage, Spearman’s rank
correlation was 0.94 for non-atypical antipsychotics, and 0.88 for atypical agents (p < 0.001 for both).

Discussion

The percentage of maximum recommended dose method identified more cases of olanzapine prescribed at high doses (69 cases), while the chlorpromazine equivalent identified more high dosages of clozapine and amisulpride (59 and 14 cases, respectively). Using either method of calculation, there was a large group of patients (73 cases) receiving high doses of olanzapine, mainly as monotherapy, but also in combination with other antipsychotics. There was also a large group of patients (121 cases) receiving high doses of haloperidol, mainly in combination with other antipsychotic medications.

Recent reviews have failed to show any clinical benefit in prescribing high doses of antipsychotic medications. However, high doses and polypharmacy are both linked to increased mortality. Care should also be exercised in prescribing atypical antipsychotics, due to their association with diabetes mellitus. The Royal College of Psychiatrists’ consensus statement currently recommends the use of high doses only after evidence-based strategies have failed, and as a carefully monitored therapeutic trial.

The method of calculating the total antipsychotic dose as a percentage of the maximum recommended dose is easy and less ambiguous than the chlorpromazine equivalent method. It helps to identify patients receiving high doses of antipsychotic medications, which facilitates monitoring and adherence to current guidelines.

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References