Chapter 3

CHLORPROMAZINE EQUIVALENTS VERSUS DEFINED DAILY DOSES:

HOW TO COMPARE ANTIPSYCHOTIC DRUG DOSES?

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Abstract

OBJECTIVE Classic chlorpromazine (CPZ) equivalents can be used to chart relative antipsychotic potencies of antipsychotic drugs. Values of CPZ equivalents per drug are ambiguous in literature. In drug use evaluation studies, antipsychotic doses are frequently compared by use of the Defined Daily Dose (DDD). The DDD is the assumed average maintenance dose per day for a drug, if used for its main indication in adults. The DDD is based on review of the available older and recent literature. In this report we evaluated discrepancy between CPZ-equivalent values and DDD-equivalent values.

METHOD We plotted CPZ-equivalent values against DDD-equivalent values and performed linear regression to determine the mean relationship between the two methods.

RESULTS In general, 67 % of the DDD-equivalent values demonstrated lower potencies per antipsychotic drug compared to CPZ-equivalent values. The slope of the regression line was 0.68 ($r^2 = 0.81$).

CONCLUSION Since we found a great discrepancy between these two methods of comparing antipsychotic drug doses, we think further research is necessary in order to develop a standardised way of antipsychotic drug comparison.
Introduction

Chlorpromazine (CPZ) equivalents can be used to chart relative antipsychotic potencies of antipsychotic drugs. This equivalency is most often based on antidopaminergic action and in general does not take into account the influence of antipsychotics on serotonergic, histaminergic, cholinergic and adrenergic receptors. Generally, CPZ-equivalent values per drug are ambiguous in literature [1]. The origin of the used equivalency value per study is in general quite opaque. Most likely, researchers base their equivalencies on pharmacological drug registration studies and other available literature. As a result of this non-transparency, an up to threefold variation in CPZ-equivalent values has been reported in the literature. For example, the CPZ-equivalent for haloperidol varies from 40 to 60 times more potent than chlorpromazine [1].

In drug use evaluation studies, doses are frequently compared by use of the Defined Daily Dose (DDD). DDDs are assigned and reviewed by researchers of the WHO Collaborating Centre of Drug Statistics Methodology [2]. The newly assigned DDD of a drug is nearly always a compromise, based on systematic review of the available literature [2]. A list of DDDs is available at the WHO, costs of access to this (updated) information are approximately $200 any one year. The DDD is the assumed average daily dose per day for a drug, if used for its main indication in adults. When establishing the DDD, usually the maintenance dose is calculated. Some drugs are used in different initial doses (e.g. antipsychotics), but this is not reflected in the DDD. A DDD will normally not be assigned for a substance before a product is approved and marketed in at least one country. All newly assigned DDDs are reviewed after three years considering recent literature. After the first three years period, the DDD normally remains unchanged for at least five years unless new information becomes available. Proposed changes will always be considered.

The DDD does not necessarily reflect the individual recommended or prescribed daily dose. Daily doses for individual patients and patient groups may differ from the DDD and will of necessity have to be based on individual characteristics, such as age, weight, pharmacogenetic and pharmacokinetic considerations [2,4].

All antipsychotic drugs have an individual DDD. For example, the DDD of chlorpromazine is 300 mg and the DDD of haloperidol 8 mg. Thus, this ratio (further called DDD-equivalent) claims haloperidol to be 37.5 times more potent than chlorpromazine.

To our knowledge, no comparison has been made yet to establish equality between values of CPZ-equivalents and DDD-equivalents.
Methods

We used three sources to obtain CPZ-equivalent values, which were consulted in order of availability of the equivalents. Initially, we conducted a search in the entire Medline-database (1966 – 2002) for methodological reports about the use of chlorpromazine equivalents. MeSH-headings used were neuroleptic drugs and/or antipsychotic drugs in combination with the keywords chlorpromazine and equivalent. We calculated the middle of depicted ranges as a mean CPZ-equivalent per antipsychotic drug. Subsequently, if no literature was available, we contacted manufacturers of antipsychotics in order to obtain the reported CPZ-equivalent value of each individual antipsychotic drug. Finally, if the manufacturer could not provide a CPZ-equivalent value, we retrieved dose-equivalency figures from the American Psychiatric Association’s (APA) “Practice guidelines for the treatment of psychotic disorders” [3]. These CPZ-equivalent values were compared to DDD-equivalent values.

Information about DDDs of antipsychotics was extracted from the ATC classification index with DDDs [4]. We used chlorpromazine as the reference DDD and calculated equivalent values according to the DDD amount per antipsychotic drug. For example, the DDD-equivalent of haloperidol, according to DDD values, is 37.5 (300mg / 8mg). We plotted CPZ-equivalents against DDD-equivalents in order to establish discrepancies in values between these two ways of comparing antipsychotic drug doses. Furthermore, we performed linear regression to determine the mean relationship between the two methods.
Results

Only one study fulfilled the inclusion criterion of a methodological report [1]. It reviewed all literature until 1989 about CPZ equivalents of 27 classic antipsychotics and depicted ranges of unweighted arithmetical mean values reported. For the atypical antipsychotic drugs clozapine, risperidone, sertindole and quetiapine, we contacted manufacturers for CPZ-equivalent values. For olanzapine and ziprasidone we applied CPZ-equivalency data from the APA [3]. Figure 1 shows CPZ-equivalent values plotted against DDD-equivalent values. Thirty-three different antipsychotic drugs were included. 67% of the DDD-equivalent values demonstrated lower potencies per antipsychotic drug compared to CPZ-equivalent values. The slope of the regression line was 0.68 ($r^2 = 0.81$). Of only three substances, trifluromazine, thioridazine and perphenazine, the CPZ-equivalents were equal to the DDD-equivalents. The extremest discrepancy was found with butaperazine. According to the CPZ-equivalent value it had a 12.5 times higher potency than chlorpromazine, while the DDD-equivalent value claimed a potency of 30 times stronger.
Figure 1: Classic chlorpromazine (CPZ) equivalent values versus Defined Daily Dose (DDD) equivalent values*

* Inset: close-up of bottom left of figure 1.


The line represents the regression line, which in case of equal CPZ- and DDD- equivalencies should cross the 100,100 point.
Discussion

In this explorative investigation we found a major discrepancy between the two methods for comparing antipsychotic potencies of antipsychotics. The relevance of this finding is slightly limited, because most CPZ-equivalent values were calculated from publications in which it was not defined if patients were treated for the main indication of the antipsychotic drug [1]. However, this fact cannot be the only explanation of the big difference between CPZ-equivalent values and DDD-equivalent values.

A substantial advantage of DDD-equivalents is their update at least every 5 years, based on new available literature. In contrast, CPZ-equivalency is generally not reviewed after marketing the antipsychotic [1].

Furthermore, CPZ-equivalency is mainly based on dopamine-2 receptor activity, which is the main point of action of classic antipsychotics. However, atypical antipsychotics act through a complex spectrum of receptor binding properties, which should be taken into account when comparing antipsychotic doses. DDDs are based on research involving general effectivity of an antipsychotic drug, which makes DDDs possibly more suitable for comparing atypical drug doses. In addition, for marketing purposes first studies might have compared atypical antipsychotic drug doses with high doses of chlorpromazine, resulting in a distorted image of the actual equivalency. This distorted value may be part of the explanation for the substantial lower DDD-equivalent values we found, since DDD values are based on a broader, more recent range of literature.

When using DDDs, caution should be taken in situations where the recommended dose differs from one indication to another. In general, for antipsychotics this implies that comparison of doses by DDDs is justified for schizophrenia, psychosis and bipolar disorder. On the other hand, CPZ-equivalents are usually not uniformly based on one indication, so by using DDD-equivalents a more unified way of comparing antipsychotic dosages may be achieved.

In conclusion, we suggest further research to develop a standardised way to compare antipsychotic drug doses. Since the relevance of evidence based medicine is increasing nowadays, reliable tools for comparing drug doses are required. Although using DDDs is not allowed in all indications and, in principle, they are developed for drug use evaluation studies, they may present a more reliable way of comparing both typical and atypical antipsychotic doses. CPZ-equivalents may represent a relatively old-fashioned way to compare antipsychotic doses. With the development of more atypical antipsychotics, it will be of increasing importance to compare antipsychotic drugs not only on D2-antagonism, but on the whole spectrum of receptor binding patterns, effectiveness and side effects.


Chapter 3

Reference list


