Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Dose equivalents for second generation long-acting injectable antipsychotics: The minimum effective dose method

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ARTICLE INFO

Article history:
Received 5 April 2017
Received in revised form 11 July 2017
Accepted 14 July 2017
Available online xxxx

Keywords:
Longactinginjectable
Equivalentdose
Minimumeffectivedose
Meandose
Schizophrenia
Antipsychotic
Olanzapine
Paliperidonepalmitate
Aripiprazole
Risperidone
Haloperidol
Olanzapinepamoate
Paliperidone
Aripiprazolemaintena
Risperidonemicrospheres
Haloperidoledecanoate

ABSTRACT

Background: The concept of dose equivalence of depot medication is important for many scientific and clinical purposes.
Methods: A systematic literature search on four second-generation antipsychotics available as long-acting injectable drugs and haloperidol was conducted. We used the minimum effective dose method which is based on randomized fixed dose studies where the smallest dose which was significantly more efficacious than placebo in the primary outcome was declared as minimum effective dose. We calculated equivalent doses from acute phase studies but we also reported the minimum effective doses found in relapse prevention studies.
Results: The acute phase minimum effective doses/olanzapine equivalents were: aripiprazole lauroxil 441 mg (300 mg aripiprazole)/4wks/0.71; aripiprazole 400 mg/4 weeks/0.95 (aripiprazole maintena); paliperidone palmitate 25 mg/4 weeks/0,06; risperidone 25 mg/2 weeks/0,12; RBP-7000 90 mg/4 weeks/0,21; olanzapine 210 mg/2 weeks/1.
Conclusions: The minimum effective dose method is an operationalized and evidence-based approach for determining antipsychotic dose equivalence which can also be applied to long-acting injectable formulations. Doses may not have been chosen low enough to find the truly minimum effective dose. Comparisons with other methods will be necessary to come to ultimate conclusions.

1. Introduction

Equivalent doses of antipsychotics can be useful for many purposes. Within the clinical situation, it is important to use this method when it becomes necessary to switch one antipsychotic for another or when two drugs need to be combined. Dose equivalence estimates are also needed for the design of fair comparisons in trials or meta-analyses (Heres, 2006; Leucht et al., 2013) or when doses of different antipsychotic drugs need to be converted into 1 unit. Cost calculations and treatment guidelines may also make it necessary to estimate equivalent doses of antipsychotic drugs.

Patel et al. (2013) discussed in a comprehensive review different methods to define dose equivalence: The classical mean dose chlorpromazine equivalent method by Davis, 1974 (Davis, 1974), the dose-response curve method to define near-to-maximum doses by Davis and Chen (2004), methods based on the maximum licensed doses of different antipsychotic drugs (MacE and Taylor, 2005; Milton et al., 1995a), daily defined doses (DDD) of the World Health Organization and Consensus methods (Andreasen et al., 2010; Gardner et al., 2010; Kane et al., 2003b).

As all these methods have advantages and limitations, recent reviews used them on a one by one basis to provide dose equivalencies for second-generation antipsychotics and to compare the findings. (Woods, 2003), (Leucht et al., 2014), (Leucht et al., 2016; Leucht et al., 2015). However, these reviews were restricted to oral forms of administration; long-acting injectable (LAI) "depot" formulations have so far not been addressed. With this current systematic review we tried to fill the gap by deriving dose equivalencies of haloperidol decanoate and all second-generation antipsychotics available as LAI's with the minimum effective dose method first presented by Woods (2003) and later updated by Leucht et al. (2014): paliperidone palmitate, aripiprazole lauroxil®, aripiprazole maintena®, risperidone depot and olanzapine pamoate.

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http://dx.doi.org/10.1016/j.schres.2017.07.033
0920-9964/

2. Methods

We included studies on adult patients with schizophrenia or schizoaffective disorder according to DSM-III, DSM-IV, DSM-IV-TR, Feigner Criteria, ICD-9, ICD-10 and the four SGAs available as a long-acting injectable formulation: paliperidone palmitate, aripiprazole depot, risperidone depot, olanzapine pamoate. The aripiprazole drugs "maintena®" (prolonged-release suspension for injection) and "lauroxil" (an extended-release prodrug of aripiprazole for injection) were analysed separately, due to their different release mechanism. The same holds true for paliperidone palmitate one monthly (Xeplion®) and three monthly (Trevicta®), and for Risperidal Consta® (an extended-release microspheres formulation) and RBP-7000 (Reckitt BeckiserPharmaceuticals-7000, a sustained-release formulation of risperidone for monthly subcutaneous injection).

We also included haloperidol decanoate which is the standard first generation antipsychotic drug, which is also available as LAI.

We excluded studies in populations with special considerations such as adolescents, elderly, first-episode patients, treatment resistance patients, patients with predominant negative symptoms and other diagnosis than schizophrenia or schizoaffective disorder. These specific patients were excluded as different dosages might be required for them (currently there are no relevant studies in this area known to the author). An electronic search was conducted with "MEDLINE", "EMBASE", "PsycINFO", "Cochrane Library", "Pubmed". "BIOSIS Citation Index", "Clinicaltrials.gov" and "Platform of the World Health Organisation". For search terms see webappendix 1. The last search was performed in April 2016. We also researched the medical reviews that pharmaceutical companies submitted to the FDA and we inquired with the providers of paliperidone palmitate and risperidone depot (Janssen-Cilag), aripiprazole maintena (Otsuka/Lundbeck), aripiprazole lauroxil (Alkermes), olanzapine pamoate (Lilly) and Indivior PLC (RBP-7000) for literature concerning the aforementioned medications. Data was extracted independently by at least two reviewers (P.H.R., S.L.) and remaining questions were clarified with SH. The analysis was conducted with Excel 2010.

2.1. Minimum effective dose method

We included all available randomized, fixed dose, placebo-controlled studies on the mentioned compounds and followed the approach first presented by Woods (2003) and later refined by Leucht et al. (2014). This means that we identified the lowest fixed dose of the included LAIs that was consistently more efficacious than placebo in the primary outcome in at least one double-blind randomized controlled trial (RCT). As in Woods (2003), but differently to Leucht et al. (2014) we accepted RCTs in which a very low dose of the same drug that was assumed to be ineffective and thus a "pseudo-placebo" by the original authors were also included, because relatively few LAI dose-finding studies are available (e.g. in study Kane et al., 2009) the pseudo-placebo was a subtherapeutical dose of four weekly 45 mg olanzapine pamoate). Statistically significant superiority in one RCT compared to placebo was considered sufficient because due to various problems in trial methodology in recent years, such as increasing placebo response (Kemp et al., 2010; Khin et al., 2011) and high dropout rates (Spineli et al., 2013), it is currently difficult to demonstrate statistical superiority. These developments lead to an increasing number of failed trials (studies in which neither the new drug nor the active comparator was more effective than the placebo), so that even well-established compounds such as olanzapine (Kinon et al., 2011) sometimes do not show separation from the placebo. In this environment, we feel it is unlikely that superiority to the placebo is just a chance finding (Leucht et al., 2014).The primary outcome was the mean change of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) total score or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) total score from baseline in the intention-to-treat dataset for acute phase studies and relapse as defined by the individual studies for relapse prevention trials. The derived minimum-effective doses were then used to derive equivalent doses expressed in olanzapine equivalents for every examined drug. Olanzapine was chosen as the primary reference drug because it was also used in our prior publications which should be complemented by the current one (Leucht et al., 2016; Leucht et al., 2015; Leucht et al., 2014). 441 mg/4 weeks, which for the prodrug aripiprazole lauroxil would represent 300mg of aripiprazole. We first used the applied doses and their injection intervals to estimate daily doses for olanzapine pamoate (15 mg/d) and aripiprazole lauroxil (10.7 mg/d, derived from 300 mg/4 weeks aripiprazole which is equivalent to aripirazole lauroxil 441 mg/4 weeks). To obtain 1 mg/d olanzapine equivalents for aripiprazole lauroxil we divided the daily doses (10.7/15) and received an olanzapine equivalent for aripiprazole lauroxil of 0.71 mg/d. Thus 0.71 mg/d of aripiprazole lauroxil is equivalent to 1 mg/d olanzapine pamoate in our case (see Table 2).

Equivalent doses were only calculated based on the acute phase studies. Relapse prevention studies were not used for this purpose, because their primary outcome is different (relapse instead of mean PANSS change) and because theoretically for relapse prevention lower doses might be minimally effective than those for acute treatment. However, we displayed the minimum effective doses for relapse prevention in separate tables, because we felt that this information could be useful for readers. Here, we assumed that if a lower dose was minimally effective in the acute phase studies than in relapse prevention studies, we would have considered such a dose also as the minimum one for relapse prevention. This procedure again took into consideration the relative paucity of available studies.

3. Results

The PRISMA diagram shows the flow of the search (Webappendix 2). A description of the included studies is provided in Webappendix 3. The minimum effective doses and dose equivalents derived from acute phase studies are presented in Tables 1 and 2. Minimum effective doses for relapse prevention are presented in Table 3.

3.1. Acute phase studies

The duration of the 10 acute phase studies ranged between 8 and 13 weeks (median 12) and they had 247–648 participants (median 378). No acute phase study was available for paliperidone palmitate three monthly (PP3M) and haloperidol decanoate.

3.2. Aripiprazole lauroxil

We identified one study for aripiprazole lauroxil (Meltzer et al., 2015) which compared 441 mg/4 weeks (300 mg of aripiprazole) and 882 mg/4 weeks (600 mg of aripiprazole) with placebo. 441 mg/4 weeks was the lowest dose that was significantly superior to the placebo and it thus was defined as the minimum effective dose. The equivalent dose to 1 mg olanzapine was 0.71 mg.

3.3. Ariprazole maintena

Another study compared aripiprazole maintena (Kane et al., 2014) in a dose of 400 mg/4 weeks with placebo, and there was a statistical separation (Kane et al., 2014). The equivalent dose to 1 mg olanzapine was 0.95 mg.

3.4. Olanzapine pamoate

For olanzapine pamoate one placebo-controlled fixed dose acute study with doses between 150 and 405 mg/2 weeks/4 weeks (EliLilly2) was included. 210 mg/2 weeks was the minimum effective dose.

Please cite this article as: Rothe, P.H., et al., Dose equivalents for second generation long-acting injectable antipsychotics: The minimum effective dose method, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.07.033