State of clinical and pharmacological data

Clothiapine: highlights of the pharmacological and clinical profile of an undervalued drug

Calogero Crapanzano[a], Chiara Amendola[b], Claudia Conigliaro[c], Ilaria Casolaro[d]

[a] ASPAG, CSM Licata, Licata, Italy; [b] Azienda USL Toscana Centro, CSM Scandicci, Firenze, Italy; [c] ASPPA, CSM Termini Imerese, Termini Imerese, Italy; [d] ASST Lariana, Como, Italy

Summary

Clothiapine is a quite widely used, but understudied, first-generation antipsychotic with the pharmacodynamic properties of aliphatic phenothiazines and clozapine. The aim of our comprehensive review was to summarise state of the art clinical and pharmacological data concerning the use of clothiapine in several psychiatric conditions. The main evidence is from short-term studies evaluating efficacy in schizophrenia versus active comparators. Off-label use in alcohol abstinence and insomnia is also reported with preliminary promising findings. Few studies systematically investigated the tolerability and safety of clothiapine, specifically extrapyramidal symptoms and its effect on the QT interval, which appear comparable to other first-generation antipsychotics. From the scientific literature, we believe that this drug has not been adequately investigated and consequently it risks being a valid, but underutilised, pharmacological tool in psychiatry.

Introduction

Clothiapine, also known as "clotiapine", is a first-generation antipsychotic dibenzothiazepine derivative, available since the late 1960s [1]. It is indicated for the management of schizophrenia and psychosis-related disorders, bipolar disorder, psychomotor agitation, anxiety.

In Spain, Belgium, Italy, Switzerland, Israel, Taiwan, South Africa and Argentina, clothiapine is available as 40-mg tablets, in Italy, Belgium and South Africa as 40 mg/4 ml vials, and in Italy only as a 10% oral solution.

In acute psychosis and/or exacerbations of chronic psychosis, daily doses of 100–120 mg are recommended, either intramuscularly or intravenously, to be gradually reached in 4–5 days; if the patients collaborates, multiple daily oral doses can be administered. The daily dose can be increased to a maximum of 360 mg during acute phases, whereas for maintenance therapy in psychosis a dosage of 40–60 mg per day may be sufficient [1–2].

Calogero Crapanzano

Data from survey studies showed high prescription rates, although four of these were before the extensive use of atypical antipsychotic medications. In Belgium, in a survey published in 2015, 108 psychiatrists and emergency physicians from Flanders were asked to choose their preferred drug class and first-choice molecule for the treatment of psychomotor agitation, from a list of 80 drugs. Antipsychotics were the first-line pharmacological tool. For patients in compulsory hospitalisation, clothiapine and olanzapine were the first-choice drug for 21.3% of respondents each; in the case of patients in voluntary hospitalisation clothiapine was preferred by 19.4% of respondents, ranked after olanzapine (22.2%) [3]. In a 1999 Swiss retrospective survey over 1 year in 1083 patients, clothiapine was the most pro re nata prescribed antipsychotic drug for sedative purposes [4]. In South Africa, a 1999 survey study, based on a questionnaire and semi-structured interviews to investigate drug therapy used in alcohol abstinence, showed that among a sample of 58 physicians, 65.5% preferred benzodiazepine monotherapy, 10.3% clothiapine and 24.1% combination therapy [5]. In Israel, a 1998 survey of 454 hospitalised patients found that clothiapine was prescribed in 9% of patients, while no data are available about prescription rate of other neuroleptics [6]. In Italy, a survey of antipsychotic prescriptions on 1141 patients belonging to four services, published in 1991, found that clothiapine had a prescription rate of 9% [7].

However, evidence on clothiapine is limited in quantity and quality, at least in part due to a lack of profitable investment opportunities leading pharmaceutical companiesto not promote research into off-patent drugs [8]. The aim of our study wass to provide an overview of the available research evidence on the clinical psychopharmacology of clothiapine, in order to support and promote its use in daily clinical practice. This could lead to the rediscovery of a potentially understudied valid treatment.

EMHMedia

Methods

We conducted a comprehensive review of the literature available up to August 2021. PubMed and Web of Science were searched using the search builder (clothiapine OR clotiapine) to identify the most relevant literature. Duplicates were removed. The remaining studies were independently evaluated by two reviewers (CC and IC), and included or excluded after a final consensus regarding relevance and compliance with the inclusion criteria was reached. In the end, we included all English-language papers evaluating studies concerning use in schizophrenia and other psychiatric disorders, and its pharmacological properties.

A total of 173 items (61 Web of Science, 112 PubMed) were retrieved from the search databases and reference cross-check; 47 duplicates were removed. Among them, we selected and reported 12 studies meeting the inclusion criteria and evaluating clinical efficacy (9 studies), tolerability/safety (3 studies) in schizophrenia and other conditions.

The main studies on pharmacokinetics (two studies) and pharmacodynamics (two studies) are also discussed.

Results

Pharmacokinetic properties

Trials with a marked compound administered orally and intravenously in preclinical studies showed that 2-chlor-1-(4methyl-1-piperazinyl)-dibenzo-1, 4-thiazepine (clothiapine/clotiapine) is absorbed quickly and to a considerable extent from the gastrointestinal tract. It is excreted mainly via the faecal route; urine excretion is as follows: 35% of the oral dose is eliminated in urine in the form of free bases (about 25%) or conjugated (about 10%). Nine metabolites have been identified in the urine; the main ones are: N-desmethyl derivatives (2.3%), sulphoxide (2.4%), N-desmethylsulphoxide (12.7%), N-oxidesulphoxide (6.9%) [2, 9]. Clothiapine half-life after a 15-mg single intravenous dose is 4.3 hours, and after a 40-mg oral dose it is 3.8 hours. A therapeutic reference range of 10–160 ng/ml has been suggested [10], although further studies are needed to confirm this.

Pharmacodynamic properties

According to Leysen and colleagues, the receptor binding affinity of clothiapine follows this order: 5HT2 > H1 > alpha 1 > D3 > D2 > D1 > sigma > M > 5HT3 > 5HT1a [11]. According to Yonemura and colleagues, receptor binding affinity would be, instead, in the following order: 5HT2 > D4 > alpha 1 > D1 > D3 > M > D2 > sigma > H1 > 5HT1a > 5HT3 (table 1) [12]. Differences of Ki values for the same receptor between these two studies may be due to heterogeneous laboratory conditions [13].

Clothiapine shares some pharmacodynamic features of dibenzodiazepine derivatives, in particular clozapine: (i) high 5-HT2A/D2 affinity ratio; (ii) high affinity to D4; (iii) moderate affinity to D2 (table 1) [14].

Clinical efficacy in schizophrenia

In a meta-analysis of five randomised controlled trials, assessing the efficacy of clothiapine in the treatment of acute psychosis, with a duration of 1 to 9 weeks and on an overall sample of 261 patients, the sedative effect of clothiapine (dose range 40–290 mg/d) appeared to be similar to that of other first-generation antipsychotics such as chlorpromazine (100–600 mg/d), perphenazine (24–64 mg/d), zuclopenthixol (150 mg intramuscularly every 3 days), trifluoperazine (10–40 mg/d), as well as lorazepam (maximum dose 4 mg intramuscularly every 6 hours). As the authors report, side effects were not sufficiently investigated: movement disorders were comparable between clothiapine and chlorpromazine, lower in the clothiapine than the zuclopenthixol group. The trial comparing clothiapine and perphenazine did not report any specific information on adverse effects and the trial comparing clothiapine and lorazepam found significantly fewer side effects with lorazepam, although the data were skewed and not included in statistical analysis [15].

Table 1: Receptor binding affinities of clothiapine, quetiapine and clozapine (expressed as Ki [nM]).

Compound	5-HT1A	5-HT2	5-HT3	D1	D2	D3	D4	Sigma	M	H1	Alpha 1
Clothiapine [11]	3110	1	368	40	16	10	–	193	245	5	9.1
Clothiapine [12]	430	1.4	2500	25	59	30	8.7	150	35	170	22
Quetiapine [14]	320	120[a]	170	4240	310	650	1600	–	1020	19	58
		3820[b]									
Clozapine [14]	180	3.3[a]	69	540	150	360	40	–	34	2.1	23
		13[b]									

5-HT: 5-hydroxy tryptamine receptor; D: dopamine receptor; M: muscarinic receptors; H: histamine receptor; alpha 1: alpha-1 adrenergic receptor
a: Ki value for the 5-HT2A receptor;
b: Ki value for the 5-HT2C receptor

According to a meta-analysis of four randomised controlled trials, comparing efficacy of clothiapine and chlorpromazine, with a duration <6 months and a sample of 276 patients, the global improvement with clothiapine was higher than with chlorpromazine, and no significant difference was found for negative symptoms. In three studies the doses of clothiapine and chlorpromazine ranged from 40 to 240 mg/d and from 40 to 600 mg/d, respectively. The other study reported only the mean doses (125.2 and 404.5 mg/d, respectively). Side effects were not sufficiently evaluated, but both drugs appeared comparable in their propensity to induce extrapyramidal symptoms. One trial evaluated nervous system adverse effects, with no difference between chlorpromazine and clothiapine for drowsiness, sleep disturbances, unsteadiness, and weakness. Another reported thirst and weight gain without differences between the two treatments [16].

In a small trial of 34 male patients with acute schizophrenia, clothiapine 160 mg/d and chlorpromazine 800 mg/d were equally effective in improving psychot-

Adverse reactions associated with clothiapine are related to its anticholinergic, antiadrenergic, antidopaminergic, antihistaminergic activities.

ic symptoms assessed after the first 48 hours of intramuscular treatment and the subsequent 2 weeks, as well as for up to 9 months of follow up [17].

In a double-blind controlled crossover trial with 26 patients affected by "severe chronic active psychosis" not responsive to at least three neuroleptics, clothiapine was significantly superior to chlorpromazine on both positive and negative symptoms after 3 months of monotherapy with clothiapine and chlorpromazine, in random order [18].

In an open-label randomise controlled trial of 101 patients with "acute schizophrenia" or "toxic psychosis", clothiapine (120 mg/d) was associated with a higher discharge rate at 12 weeks, 77.7% compared with 73.5% in the thioridazine (600 mg/d) group, and 55.5% in the chlorpromazine (600 mg/d) group; moreover, clothiapine was the first-line therapy when the diagnosis was undefined [19].

In a one month-controlled trial of 49 patients with "acute schizophrenia", clothiapine (40–220 mg/d) was comparable to chlorpromazine (200–600 mg/d) in terms of efficacy, overall tolerability and extrapyramidal symptoms [20].

In Italy, a retrospective study of 2019, 77 patients on clothiapine (n = 21), zuclopenthixol (n = 7), or promazine (n = 26), were assessed for efficacy and tolerability in the treatment of psychomotor agitation caused by several

conditions (schizophrenia: n = 27). No significant differences were observed as regards efficacy or tolerability [21].

Alcohol abstinence treatment

In a pilot study conducted in Israel, 59 subjects with alcohol use disorder and immediate suspension of alcohol intake were treated with clothiapine intravenously or intramuscularly at a dosage of 80–240 mg/d for a period of 2 weeks, then continued with oral administration (providing trihexyphenidyl or promethazine as needed against any extrapyramidal symptoms) for up to 2 months to relieve their withdrawal symptoms. Among these, 39 patients responded to the treatment in a "good and good" way, 13 in a "poor" way, and seven patients needed no medical therapy. All patients were discharged without withdrawal symptoms and/or craving for alcohol [22].

Insomnia

In an experimental prospective study, 320 patients with substance use disorder were assessed for the efficacy of trazodone, mirtazapine, quetiapine, clothiapine and gabapentin in the treatment of insomnia that arose during hospital detoxification. It was observed that mirtazapine and clothiapine showed the best results in the treatment of insomnia. Clothiapine succeeded in particular on poly-drug abuse sub-groups and on psychotic patients [23].

Tolerability and safety

Adverse reactions associated with clothiapine are related to its anticholinergic, antiadrenergic, antidopaminergic, antihistaminergic activities and include: movement disorder (parkinsonism, akathisia, dystonia, tardive dyskinesia), gastrointestinal, ocular, genitourinary, liver, nervous system, neuroendocrine, cardiovascular system, haematological, metabolic side effects [1, 11–12].

Specifically, selected adverse reactions of clothiapine were investigated in three studies: (i) in a cross-sectional study of 6790 patients in Switzerland, 0.9 % of patients showed a drug-related QT interval increase. Antipsychotics associated with an increased risk for QT prolongation (QTc ≥500 ms) included clothiapine, haloperidol, sertindole, promazine and levomepromazine [24]; (ii) in a case-crossover study on 17718 patients in Taiwan, the use of antipsychotic drugs was associated with a 1.53-fold increased overall risk of ventricular arrhythmia or sudden cardiac death; specifically, first generation and second generation antipsychotics were associated with increased risk of 1.66-fold and 1.36-fold, respectively; clothiapine showed a 2.16-fold increased

risk, similar to clozapine (2.03-fold) [25]; (iii) in a retrospective study of 98,320 hospitalisations lasting 5 years, the co-prescription rate of anti-parkinson drugs with 14 antipsychotics was analysed using the population database to compare the prevalence of extrapyramidal symptoms between first-generation antipsychotics (typical) and second-generation antipsychotics (atypical). The ranking of the rate of co-prescription of anti-parkinson drugs with antipsychotics, in ascending order, were: quetiapine, clozapine, olanzapine, thioridazine, zotepine, chlorpromazine, risperidone, sulpiride, clothiapine, flupentixol, haloperidol, zuclopenthixol, trifluoperazine and loxapine [26].

Conclusions

All selected studies in this review showed that clothiapine has a favourable efficacy profile in the treatment of schizophrenia and other conditions, comparable and in some cases superior to the comparators. However, most of the evidence is too low quality to allow conclusions on the comparative safety and efficacy.

Furthermore, no studies have compared clothiapine with placebo; active comparators were either first-generation antipsychotics (zuclopenthixol, chlorpromazine, trifluoperazine, perphenazine) or lorazepam. Tough head-to-head trials may give important clinical data on comparative effectiveness, safety and efficiency, but they have several disadvantages (eg., uncertain assay sensitivity, equivalence/noninferiority not suitable as proof of efficacy, active comparator not standard therapy, noninferiority margin clinically questionable), making them not suitable for regulatory purposes [27, 28]. According to the authors of both meta-analyses [15, 16], available data do not support the use of clothiapine as first-line therapy for acute psychosis. Evidence is not robust enough to define its superiority regarding onset of action and sedative action; no evidence confutes its clinical efficacy as well. Likewise, studies concerning disorders other than schizophrenia are very few. Given the lack of large well-designed clinical trials evaluating the use of clothiapine in patients with schizophrenia, neither safety nor tolerability do not appear sufficiently investigated. Although evidence remains scant, clothiapine was one of the most frequently prescribed first-generation antipsychotics in our selected surveys. The Adult Hospital Level and Primary Health Care Expert Review Committees of the Department of Health of the Republic of South Africa 2017 recommended intramuscular clothiapine as a second-line drug after haloperidol + promet-

hazine for the treatment of psychomotor agitation [29]. However, this is not in line with the current international guidelines [30, 31] and available algorithms/protocols [32, 33] for the management of psychomotor agitation, where intramuscular atypical antipsychotics and haloperidol are first-line therapy, and clothiapine is not even mentioned.

Globally, efficacy and tolerability profiles appear not to substantially differ from those of first-generation antipsychotics; a balanced block of D2/5-HT2/H1/M1/alpha 1 receptors comparable to aliphatic phenothiazines may explain its antipsychotic, anxiolytic and sedative properties [1, 2, 11, 12, 15, 16, 34, 35]. Clothiapine does not show advantages in terms of tolerability although it has a high 5HT2A/ D2 ratio and weak D2 affinity [36], therefore other typicality features, i.e. a lower value of Koff (slow dissociation), may be involved [37]. Clothiapine remains an established, but undervalued and understudied, antipsychotic with a favourable efficacy and tolerability profile for the treatment of schizophrenia and related psychotic disorders. As a speculative consideration, the oral formulation may be helpful for patients suffering from schizophrenia and concomitant anxiety and insomnia, thanks to its sedative and anxiolytic action; additionally, the intramuscular formulation, thanks to a strong sedative effect, may represent a valid alternative when atypical antipsychotics fail to control psychomotor agitation. Favourable preliminary results were found regarding its off-label use in alcohol abstinence and in the treatment of insomnia. Nevertheless, our research found quite a few studies describing its clinical efficacy, despite our extensive promising experience in clinical practice. This leads us to believe that this drug is not adequately investigated in scientific literature and consequently risks being a valid, but underutilised, pharmacological tool in psychiatry.

Limitations

Some studies included in the meta-analysis are old and dated, so we were not able to obtain their full texts. Thus, we decided to use the data provided by the meta-analysis, although filtered and indirect.

References
You find the complete bibliography in the online version of the article at http://doi.org/10.4414/sanp.2022.10065.

Calogero Crapanzano, MD
Psychiatry Ward
Department of Mental
Health and Addiction
IT-92027 Licata (Agrigento)
calogerocrapanzano87[at]
gmail.com