EPV1611

Effect of clozapine and olanzapine on the production of malondialdehyde in reaction to free radical attack on deoxyribose

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Introduction: Clozapine and olanzapine are among the most effective antipsychotic drugs. However, their use is associated with the development of metabolic syndrome and lipid profile disorders. It is therefore interesting whether they can affect the level of oxidative stress associated with the Fenton reaction, which is a source of harmful hydroxyl radicals in the blood that damage DNA.

Objectives: The aim of our study was to test the in vitro antioxidant properties of two known neuroleptics – clozapine and olanzapine, which are commonly used in the treatment of schizophrenia and bipolar disorder.

Methods: The study was based on the ability of the hydroxyl radical to split deoxyribose into malondialdehyde (MDA). In the experimental system, the Fenton reaction was used as a source of the hydroxyl radical, in which the divalent iron cation reacts with hydrogen peroxide to form a highly toxic hydroxyl radical. For this purpose, deoxyribose was incubated under appropriate conditions with FeSO4 (0.5 mM), EDTA (1 mM), H2O2 (14 mM) and cloazpine or olanzapine at concentrations of 1, 5, 20 or 50 µmol/l. These concentrations corresponded to the concentration of drugs in the cerebrospinal fluid. A clean system (containing no drugs) was used as a positive control. Then, thiobarbituric acid (TBA) was added to the reaction mixtures in the presence of trichloroacetic acid.

Results: Both olanzapine and clozapine inhibited the formation of malondialdehyde (MDA) from deoxyribose under the influence of the Fenton reaction. At concentrations of 1 and 5 µmol/l, both neuroleptics did not inhibit the reaction. At concentrations of 20 µmol/l, olanzapine inhibited the reaction by 15%, and clozapine by 20%. At concentrations of 50 µmol/l, olanzapine inhibited the reaction by 30%, and clozapine by 37%. The difference between the two neuroleptics was not statistically significant.

Conclusions:

1. At concentrations of 1 and 5 umol/l, both neuroleptics did not inhibit the studied reaction.
2. At concentrations of 20 and 50 umol/l, both neuroleptics inhibited the reaction.
3. The difference in the degree of inhibition of the reaction between clozapine and olanzapine was not statistically significant.

The similar results of inhibition of the reaction by both neuroleptics probably result from a similar chemical structure. The fact that clozapine and olanzapine inhibit the Fenton reaction may have a beneficial effect in protecting tissues from oxidative damage.

Disclosure of Interest: None Declared

EPV1611

Clinical Pharmacist Recommendations for Rational Benzodiazepine and Zolpidem Use During Daily Ward Rounds in Inpatients with Mental Disorders: A Retrospective Pre-Post Study

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Introduction: Benzodiazepines and zolpidem are commonly prescribed as long-term treatments for anxiety and insomnia, although recommendations generally do not support their extended use. These medications are often prescribed for longer durations than necessary, at inappropriate doses, and with potential drug-drug interactions. In this context, rational prescribing strategies are essential. One potential strategy is the integration of a clinical pharmacist into the inpatient team for daily interdisciplinary ward rounds. However, this approach remains under-researched in the context of inpatients with mental disorders.

Objectives: This study aimed to evaluate the impact of a clinical pharmacist on medication-related problems (DRPs) focused on benzodiazepine and zolpidem use during daily ward rounds within an interdisciplinary team in a Slovenian psychiatric hospital.

Methods: A retrospective observational pre-post study was conducted at Ormož Psychiatric Hospital in Slovenia, including patients treated between 2019 and 2020. During this study, clinical pharmacists provided recommendations focused on benzodiazepines and zolpidem. The primary outcomes assessed were the difference in the total number of DRPs observed at the time of hospital discharge compared to admission. The secondary outcomes evaluated adherence to existing treatment guidelines.

Results: The study involved 20 participants with a mean age of 57.2 years (SD = 17.1). A total of 23 recommendations related to DRPs associated with benzodiazepine and zolpidem use were performed (1.15 per patient). Of these, 19 DRPs (82.6%) were identified as potential issues, while 4 DRPs (17.4%) were already expressed. Most DRPs concerning benzodiazepines and zolpidem were classified as unnecessary treatment, with 18 recommendations (78.3%). The remaining five recommendations (21.7%) addressed treatment effectiveness. The most common recommendation was the discontinuation of benzodiazepine and zolpidem therapy, suggested in 12 cases (56.5%), followed by adjustments to the treatment regimen, predominantly dose reductions, in 9 cases (39.1%). In only one case (4.3%) was the recommendation to initiate benzodiazepine treatment. Initially, the acceptance rate of recommendations was 100.0% (N = 23) at the time of discharge, but this decreased to 82.6% (N = 19) three months after discharge. Adherence to treatment guidelines improved ($p < 0.05$).

Conclusions: The results indicate that this approach led to fewer DRPs, improved adherence to treatment guidelines, and a high

acceptance rate. This is the first retrospective pre-post study in the European Union to include this collaboration in daily rounds at psychiatric hospitals, focusing on these medications. However, the study has notable limitations (non-randomized design and small sample size), which should be addressed in future research.

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EPV1613

MM120 demonstrates no evidence of abuse potential in rodent preclinical studies

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Introduction: Generalized anxiety disorder (GAD) is a chronic and disabling disorder with an estimated lifetime prevalence of up to 7.8% in the US. MM120 (lysergide D-tartrate), a tartrate salt of D-lysergic acid diethylamide (LSD), is currently under development as a potential treatment for GAD. The mechanism of action (MOA) by which MM120 may elicit profound lasting psychological changes is not fully understood. Studies suggest that it has significant effects on functional brain activity across several networks, likely a result of serotonergic agonism mediated by 5HT2A activity and subsequent changes in neural network connectivity.
Objectives: A series of Good Laboratory Practice (GLP) compliant studies were conducted to evaluate abuse potential of MM120.
Methods: In vitro assessments of MM120, and its main metabolite 2-oxo-3-hydroxy LSD, receptor binding activity were performed using Eurofins CEREP BioPrint. To examine single dosing effects, MM120 was administered by oral gavage to male Sprague Dawley rats (n=6/group) at doses of 0 (vehicle only), 0.5, 2.0, and 6.0 mg/kg. A Modified Irwin test evaluated shorter acting drug effects at 15, 60, 120, and 240 minutes post-dosing compared to pre-dose baseline, with long-term, single dose neurological effects studied in a functional observation battery (FOB) on the day of dosing and 24 hours post dose. To compare potential chronic MM120 effects, male and female Sprague Dawley rats were dosed daily for four weeks via oral gavage at 0 (vehicle only), 0.5, 2.0, and 6.0 mg/kg (n=10-15/sex/group) followed by a 4-week recovery phase. FOB was performed pre-dose, dosing day 27, and day 25 of recovery phase. Additional assessments included toxicological and toxicokinetic evaluations.
Results: Receptor binding assay confirmed MM120's MOA is mediated by the serotonin system and hallucinogenic effects are driven by agonism at 5-HT2A and 5-HT2C receptors. MM120 demonstrated agonist activity at 5-HT1A, 5-HT1B, 5-HT1D, 5-HT5A, 5-HT6, and 5HT7 receptors and only nanomolar affinity at D2 dopaminergic receptors. Single dose MM120 at 0.5 mg/kg, had no effects on behavioral or physiological states. Following 6 mg/kg MM120, vocalization was recorded in 1/6 rats 2-4 h post dose, and incidences of mild piloerection were recorded in 3/6 rats from 4 to 24 h post dose. In the chronic study, there were no MM120-related changes in basic or fine movements, total ambulation, total rears, or total distance traveled.
Conclusions: Binding studies suggest no indication for elements of abuse for MM120 even with binding at serotonergic and, to a smaller degree, dopaminergic receptors. in vivo studies with MM120 evaluated supratherapeutic doses and demonstrated no evidence of physical dependence or withdrawal after sustained, daily administration for four weeks.

Disclosure of Interest: J. Tripp Employee of: Mind Medicine, Inc., G. Smagin Employee of: Mind Medicine, Inc.

EPV1614

Clozapine for the treatment of resistant psychosis – CLOZAPINE UNIT

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Introduction: Treatment resistant schizophrenia (TRS), according to HOWES et al. 2017, is defined as a patient's condition in which, despite two or more treatment cycles with adequate dosage and duration of antipsychotic treatment, the patient's condition does not improve to the extent expected with positive or negative or cognitive symptoms persisting. The heterogeneity of patients with resistant psychosis is high, and some may show the resistance in the course of the disease after years. However, several patients show resilience from the first psychotic episode.
Objectives: Treatment resistant psychosis is probably a distinct subtype of schizophrenia, with a different etiopathogenetic mechanism. Clozapine is currently considered the drug of choice with proven efficacy, whereas atypical antipsychotic drugs are inferior in efficacy in the treatment of resistant psychosis.
Methods: The mechanism of action of the drug is unknown and there is a potential for serious side effects to occur, which necessitates the adoption of a specific protocol for clozapine administration and patient monitoring in regular psychiatric clinical practice.
Results: The Adult Psychiatric Clinic of Sismanoglio General Hospital in Athens, Greece, in its effort to create a systematic and integrated treatment and monitoring of patients who take clozapine, has created, in collaboration with the cardiology and hematology department of Sismanoglio Hospital a special unit for paients with treament resistant scizophrenia.
Conclusions: The unit called "CLOZAPINE UNIT" will ensure the regular and continuous monitoring of patients receiving clozapine during and after their hospitalization in the psychiatric clinic.

Disclosure of Interest: None Declared

EPV1615

Vitamin E and Clonazepam in the treatment of tardive dyskinesia secondary to atypical antipsychotic treatment: a case report

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Introduction: Tardive dyskinesia is a movement disorder mostly associated with long-term antipsychotic use. Patients may present