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New Synthetic Procedure to Prepare Olanzapine Along With Its Related Compounds

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Abstract:- This study describes the analysis of piperazine-type stimulants [1-benzylpiperazine (BZP), 1-(3-trifluoromethylphenyl) piperazine (TFMPP), 1-(3-chlorophenyl)piperazine (mCPP) and 1-(4-methoxyphenyl) piperazine (MeOPP)] in low volume urine samples (0.1 mL) by microextraction in packed sorbent and liquid chromatography-diode array detection. Analyte extraction has been comprehensively optimized, and the influencing factors were screened by means of the fractional factorial design approach. Several parameters susceptible of influencing the process were studied, and these included extraction sorbent type (C8 and C18), sample dilution (1:2 and 1:4), number of aspirations through the device (2 and 8) and the amount of methanol on both the washing (0 and 10%) and eluting solvents (10 and 100%).

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1.1 INTRODUCTION

Olanzapine is structurally and pharmacologically similar to the atypical antipsychotic clozapine. The mechanism of action is not completely understood. Antipsychotic effects may be related to blockade of dopamine (D1, D2, D3, D4), serotonin (5HT2, 5HT3, 5HT6), histamine (H1), alpha-1 adrenergic and muscarinic (M1-M5, particularly M1) receptors. Typical antipsychotics such as the phenothiazines (e.g. chlorpromazine) or the butyrophenones (e.g. haloperidol) strongly block dopamine receptors. In contrast, olanzapine blocks serotonin receptors (5HT2) more strongly than dopamine (D2) receptors. Blockade of 5HT2 receptors is a proposed mechanism for effects on negative symptoms in schizophrenia. Muscarinic blocking (anticholinergic) effects and lower affinity for dopamine receptors may possibly account for the decreased incidence of extrapyramidal symptoms (EPS) seen with olanzapine. Effect on prolactin levels is minimal.

Well absorbed after oral administration; absorption is not changed by food. Peak plasma levels occur 5-8 hours after an oral dose. Plasma levels appear to have a correlation with therapeutic effect, requiring about 23 ng/mL for an antischizophrenic effect. Onset of antipsychotic effects is seen after 1-2 weeks of treatment. Half-life ranges from 21-54 hours (mean 30 hours). Highly protein bound (about 93%) with a volume of distribution of 10-18 L/kg. Metabolized in the liver to inactive metabolites mainly by cytochrome P450 isozyme CYP1A2, flavin-containing monooxygenase (FMO) 3, and N-glucuronidation. Minor pathways involve CYP2D6 and possibly CYPS2C19 isozymes. About 40% is metabolized in the first pass through the liver. Because of the number of possible routes of metabolism, inhibition of cytochrome oxidase pathways does not markedly affect elimination of olanzapine. About 57% of a dose is excreted in urine principally as metabolites (only 7% as unchanged drug) and about 30% in the feces.

In single dose studies, half-life was not affected by decreased renal function or clinically significant cirrhosis (in smokers). In general, olanzapine elimination is slower in women, the elderly and non-smokers. In a small single dose study, mean half-life in elderly women was 55 hours, compared to a mean of 49 hours in elderly men. Olanzapine is not removed by dialysis.

Olanzapine is a useful agent in acute and maintenance treatment of schizophrenia and related disorders. It has beneficial effects on both positive and negative symptoms, an early onset of antipsychotic action and a favourable side effect profile. In patients who responded to initial therapy, olanzapine maintained clinical improvement for one year in a continuation trial. Further trials are required to evaluate long-term efficacy and safety and its usefulness in patients refractory to other antipsychotics. Olanzapine is also used in the management of psychoses in the elderly.

In a controlled 28 week trial in 339 patients with schizophrenia and related disorders, the efficacy of olanzapine 10-20 mg per day was compared to that of risperidone 4-12 mg per day. A significantly greater number of patients in the olanzapine group (36.8%) had at least a 40% improvement in PANSS (Positive and Negative Syndrome total score) compared to

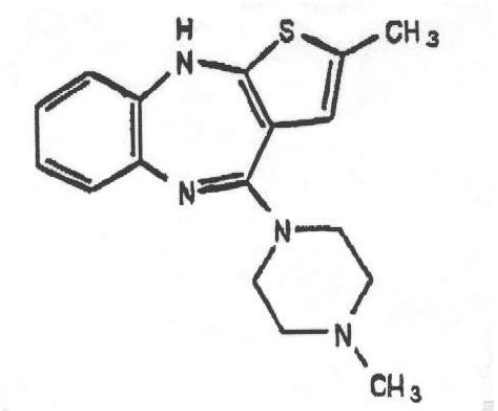
those in the risperidone group (26.7%) after 28 weeks of treatment.

Olanzapine was also more efficacious in treatment of negative symptoms (e.g. avolition, self-neglect, blunted affect). More olanzapine-treated patients maintained a response at 28 weeks (87.9%) than did risperidone-treated patients (67.7%). Fewer patients in the olanzapine group reported extrapyramidal events (18.6%) compared to patients in the risperidone group (31.1%). Akathisia and dyskinesia occurred with similar incidence in both treatment groups. Weight gain was greater and elevation in liver enzymes occurred more frequently in the olanzapine group. By the end of the 28 week study, 36% of the olanzapine group had elevated prolactin levels, compared to 90.3% of the risperidone group.

In short-term controlled clinical trials, olanzapine has been shown to be more efficacious than placebo and as effective or more effective than haloperidol in the treatment of schizophrenia and related disorders. In a 6 week trial in 335 patients, olanzapine in the dosage range of 15 ± 2.5 mg per day was more effective than haloperidol 15 ± 5 mg per day in the treatment of negative symptoms but was equally efficacious in overall improvement of symptom score. The percent of patients showing above 40% improvement in the Brief Psychiatric Rating Scale on olanzapine was 48%, and on haloperidol, 47%. In a large 6 week trial (1996 patients) primarily in treatment-resistant patients, the response to a mean modal dose of 13.2 mg per day of olanzapine was greater than the response to a mean modal dose of 11.8 mg per day of haloperidol. Overall efficacy was lower than in the previous trial possibly due to the fact that 77% of patients were resistant to prior antipsychotic treatment (excluding haloperidol). More patients in the haloperidol group discontinued therapy due to lack of efficacy (32.1%) than in the olanzapine group (20.7%); 7.3% of haloperidoltreated patients discontinued therapy due to adverse events, compared to 4.5% of olanzapine-treated patients. The only side effects that occurred with a higher incidence in the olanzapine group were excessive appetite (24%) and dry mouth (22.2%). The incidence of extrapyramidal events was 19.2% in the olanzapine group compared to 45.2% in the haloperidol group. Of the patients who responded to olanzapine or haloperidol in these comparative trials and subsequently continued therapy, it is estimated that 72% of haloperidol-treated patients and 80.3% of olanzapine-treated patients maintained response for at least a year. Olanzapine has been used in the management of acute mania in bipolar disorder.

Olanzapine, like other antipsychotics, is sometimes used as an adjunct to selective serotonin reuptake inhibitors (SSRIs) in the management of obsessive compulsive disorder. Investigations are underway for the use of olanzapine in autism, Gilles de la Tourette's syndrome and in treatment of behavioural problems such as aggression in children with pervasive developmental disorder.

Although olanzapine has been used to treat psychotic symptoms of Parkinson's disease, its use remains controversial as it may worsen parkinsonian symptoms. The FDA approved Olanzapine, an antipsychotic drug manufactured by the Eli, Lily and company, in October 1996, for the treatment of psychotic disorders. It is a thieno-benzodiazepine analog with the chemical name of 2-methyl-4-(4-methyl-1-piperazinyl)-10 thieno [2,3-b] benzodiazepine. Olz is a yellow crystalline solid and practically insoluble in water. Its structure is as given below.



Behavioral pharmacological in vivo studies show that olanzapine is an antagonist of dopamine, serotonin, and acetylcholine (Moore et al., 1993; Tye et al., 1992). This receptor profile parallels that of Clozapine (Borison, 1995; Moore et al., 1992). Olanzapine displays a very broad pharmacological profile, with potent activity at dopamine, serotonin, muscarinic, histamine and adrenergic receptors (Bakshi & Geyer, 1995; Bymaster et al., 1996; Coyle, 1996; Fuller & Snoddy, 1992; Moore et al., 1992; Saller & Salama, 1993; Stockton & Rasmussen, 1996; White & Wang, 1983). Its antagonism to muscarinic receptors may explain its anticholinergic properties. Animal behavioral studies show that olanzapine has atypical antipsychotic characteristics, by virtue of its in vitro receptor profile (Bakshi & Geyer, 1995; Coyle, 1996; Fuller & Snoddy, 1992; Moore et al., 1992; Saller & Salama, 1993; Stockton & Rasmussen, 1996; White & Wang, 1983). The initial animal screening tests suggested that olanzapine possessed antipsychotic efficacy by virtue of its dopaminergic blocking properties.

Furthermore, the animal tests suggest that the clinical efficiency with minimum EPS could be due to its specific action on the firing of the A10 region of the hippocampus the brain. The animal behavioral and electrophysiological studies show that at low doses, it might act as an atypical antipsychotic whereas at very high doses, it might resemble the typical antipsychotic.

It is metabolized extensively in humans via glucuronidation, allylic hydroxylation, N-oxidation, N-dealkylation and a combination thereof. This is the

most important pathway both in terms of contribution to drug related circulating species and as an excretory product in the species (Kassahun et al., 1997). The major metabolites found in humans are 10-N-glucuronide and 4-desmethylolanzapine (Kando et al., 1997). In vitro evaluations of the human cytochrome P450 isoenzymes involved in the formation of the three major metabolites of olanzapine have found that CYP 1A2, CYP 2D6, and the flavin containing mono-oxygenase system are involved in the oxidation of olanzapine (Ring et al., 1996).

The major route of elimination seems to be urine (first pass metabolism) in humans (Kassahun et al., 1997). It displays linear kinetics over the clinical dosing range. The systemic clearance of olanzapine takes about 26.1 ± 12.1 hrs The plasma elimination half-life (t1/2b) is 33.1 ± 10.3 hrs (Obermeyer et al., 1993). Compared with young men, young women demonstrated decreased clearance. Similarly, elderly subjects showed a decreased clearance compared to younger patients (Bergstrom et al., 1995).

1.2 ANTI-DEPRESSIVE EFFECTIVENESS OF OLANZAPINE

Anti-depressive properties have been indicated for several second generation antipsychotics (SGAs). Different hypotheses exist regarding the mechanisms by which the SGAs mediate their anti-depressive effects, including antagonism of serotonergic 5HT2 receptors; agonism of 5HT1 receptors; antagonism of adrenergic a2 receptors and inhibition of trans-membrane monoamine transporters. The evidence for efficacy is strongest in bipolar depression in which some SGAs have become agents of first choice. Pragmatic studies of anti-depressive effectiveness of SGAs in more heterogeneous, naturalistic samples with psychosis are scarce. Short-term studies do, however, indicate antidepressive effects of several SGAs in non-affective psychosis. Olanzapine was superior to haloperidol in reducing depressive symptoms in a 6-week study. In patients with treatment refractory schizophrenia, quetiapine was found to be superior to haloperidol in reducing depressive symptoms during the 8-week follow-up. Both studies were sponsored by the pharmaceutical industry. Some studies have indicated a marked superiority of clozapine in reducing the risk of suicide and depressive symptoms compared to the other antipsychotics. In some recent studies quetiapine has demonstrated anti-depressive properties in both clinically depressed and non-depressed populations.

There are indications that studies sponsored by the pharmaceutical industry selectively report data in favour of the sponsored drug. Clearly, more long-term studies are needed on the highly prevalent occurrence of depressive symptoms in psychosis. In particular, comparative effectiveness trials of first-line SGAs funded independently of the pharmaceutical industry are called for in order to provide clinically relevant evidence on whether or not differential antidepressive effectiveness exists among the drugs. We have previously reported the superior effectiveness of quetiapine on several outcomes other than depression. The overall depression outcome was reported only briefly. Depression and depressive symptoms are, however, the main foci in the present study with a larger sample.

1.3 OLANZAPINE: ZYPREXA

Olanzapine (Zyprexa) is an antipsychotic medication approved to treat schizophrenia, and acute mania or mixed episodes of bipolar disorder. Olanzapine can improve symptoms of schizophrenia such as: hallucinations, delusions, and disorganized thinking; in some people, improvement in social isolation, reduced speech productivity and motivation. Olanzapine can improve symptoms of mania which include: racing thoughts, having an inflated sense of importance, an elevated mood, being impulsive, being irritable as well as a decreased need for sleep. Olanzapine has also been approved for the treatment of agitation associated with schizophrenia or bipolar I mania.

Relapse is very common in schizophrenia and bipolar disorder and the most frequent cause is that individuals stop taking their medication. Even when medication is taken exactly as prescribed, relapse may still occur for some people. Therefore, it is recommended that you take your medication exactly as prescribed by your healthcare provider as this has been shown to delay relapse.

Schizophrenia and bipolar disorder require long-term treatment. Only your healthcare provider can determine the length of olanzapine treatment that is right for you. Olanzapine is an atypical antipsychotic, these medications have been given warnings by the FDA for the possibility that the following adverse effects may occur: diabetes, severe hyperglycemia, increases in blood cholesterol and/or triglycerides. When taking olanzapine consider nutritional and exercise lifestyle changes to reduce this risk.

Do not stop taking olanzapine or change your dose without talking to your healthcare provider first. Some people may develop side effects on olanzapine such as extrapyramidal effects (restlessness, tremor, stiffness) or tardive dyskinesia (slow or jerky movements that one cannot control). These symptoms are likely to be less severe and occur less often than with the older antipsychotic medications (e.g.,: Haldol [haloperidol], Prolixin [fluphenazine], Thorazine® [chlorpromazine]). If you develop movements that you cannot control, call your healthcare provider immediately. Olanzapine

treatment may be associated with strokes and/or transient ischemic attacks (TIAs) in elderly people with dementia and accompanying behavior problems. This safety concern has not been proven confidently, but there is some evidence. Talk with your health care provider if you are concerned or have questions.

Olanzapine treatment must be monitored by a healthcare provider. Be sure to keep all of your scheduled appointments so that you stay healthy while on olanzapine. You should not take illegal drugs or drink alcohol while taking olanzapine. Smoking can affect the amount of olanzapine that gets into the body. Tell your healthcare provider if you smoke.

Treatment with olanzapine is usually well tolerated. However, common adverse effects include: daytime sleepiness, dizziness, increased appetite, weight gain, and restlessness.

Olanzapine's more common side effects are usually relatively minor, especially when taken at doses of 15 mg/day or less. Some people may experience low blood pressure or dizziness, especially when standing up suddenly. Heart palpitations, sleepiness; dry mouth; constipation; weight gain; sexual dysfunction; and fatigue are also possible. These side effects may also include extrapyramidal symptoms "EPS" (muscle stiffness, tremors, and body shakes).

Some of these problems may be reduced or eliminated by increasing the dose slowly. At higher doses, extrapyramidal side effects often increase. Cogentin (benztropine) or Benadryl (diphenhydramine) can be prescribed to reduce or eliminate stiffness as well as tremors. Patients who already have low blood pressure, have kidney or liver impairment, are elderly, or are in a weakened condition may require close monitoring and even more gradual dose adjustment. The concurrent use of benzodiazepines like (diazepam) Valium or (lorazepam) Ativan® with olanzapine may lead to very low blood pressure or dizziness upon arising.

Zyprexa® may also cause more serious side effects such as increases in glucose, cholesterol, or triglyceride blood levels. The FDA has had all makers of atypical antipsychotics include warnings to prescribers and consumers, that these medications may place individuals at risk for developing diabetes. If you get high blood glucose you may feel very tired, have to go to the bathroom often, and have blurry vision. Also, you might be very thirsty and feel sick to your stomach. If you have any of these symptoms please talk to your health care provider as soon as possible.

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