Possible Cardiovascular Adverse Effects Profile of Acute and Chronic AripiprazoleAdministration, in Comparison to Olanzapine, in Male Wistar Rats: Contribution of Serotonin Receptors

Thesis

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Introduction and Aim of the Work

Second-generation (atypical)antipsychotics have been substantially used in treatment of psychiatric disorders during the past decade(McIntyre and Jerrell, 2008). Although the cardiovascular toxicity of conventional antipsychotics is well-established (Pacher and Kecskemeti, 2004), the cardiovascular profile of members of the atypical class is a subject of investigation. Some drugs, such as olanzapine (OLA), pose known metabolic and cardiovascular risk. On the other hand, the 'newer' atypical antipsychotic aripiprazole (ARI) has been shown to have an adverse effect profile comparable to that of placebo (Blonde et al., 2008).A significant weight gain on administration of aripiprazole was, however, observed in a long-term double-blind controlled trial (McIntyre et al., 2011). Regarding cardiovascular toxicity, several case reports have linked development of hypertension with commencement of aripiprazole therapy (Borras et al., 2005, Bat-Pitault and Delorme, 2009, Pitchot and Ansseau, 2010). This adverse effect was observed from as early as the first dose. Moreover, a 24-month study reported significant increase in both systolic and diastolic blood pressures as well as significant mild increase in QTc interval (Gulisano et al., 2011). Earlier reports, however,

tend to associate orthostatic *hypotension* with the use of antipsychotic drugs (Buckley and Sanders, 2000). This conflict might echo the lack of systematic evaluation of the comparative safety and tolerability of this agent (Pae, 2009).

Aripiprazole is the first atypical antipsychotic with potent partial agonist activity at D_2 and 5-HT_{1A} receptors (Jordan et al., 2002). Efficacy of aripiprazole, as well as its undesirable effects, is attributed, in part, to its effect on serotonergic receptors. These receptors are involved in either modulation of blood pressure, or change in cardiac rhythm, or both (Pytliak et al., 2011).

Research Hypothesis

The study hypothesis is that aripiprazole administration would be associated with an increase blood pressure, upon acute and/or chronic administration to rats, as well as QTc interval prolongation, and these effects would be mediated, in part, through serotonin receptors.

Aim of the Work

The present work aims at investigating the cardiovascular adverse effect profile of acute and chronic administration of aripiprazole, and comparing its chronic

administration with that of olanzapine.Effects of combination of 5-HT receptor antagonist will be examined to explore a possible contribution of serotonin to cardiovascular effects of both drugs.

Research Questions

1. Are cardiovascular adverse effects, namely, elevation of blood pressure and prolongation of QTc interval, consistent and dose-dependent with acute administration of aripiprazole?

2. Could aripiprazole in chronic use induce such cardiovascular adverse effects?

3. Could antagonism of serotonin receptors, simultaneously with aripiprazole administration, alter these cardiovascular adverse effects?

The experimental work was divided into:

I. Acute Study

The acute study aimed at examining the effect of acute administration of aripiprazole in graded doses (1, 3 and 10 mg/kg) and in combination with serotonin receptor antagonist (cyproheptadine) in the dose of 10 mg/kg, on the blood pressure and QTc interval.

The outcome measures were:

1. Measurement of the systolic (non-invasive) blood pressure using the tail cuff technique for each animal, 60 and 90 minutes after injection of the tested drugs.
2. Measurement of QTc interval 2 hours after injection of the tested drugs, by recording ECG for each animal after giving anesthesia.
3. Measurement of the mean (invasive) blood pressure using P23XL (ViggoSpectramed Inc.) pressure transducers introduced into the aorta, for each animal, 2 hours after injection of tested drugs.

II. Chronic Study

The chronic study aimed at examining the effect of chronic administration of aripiprazole (6 mg/kg), chronic administration of olanzapine (10 mg/kg) and their combined chronic administration with serotonin receptor antagonist (cyproheptadine) (10 mg/kg), on the blood pressure, body weight, QTc interval and ex-vivo aortic reactivity.

The outcome measures were:

- Measurement of the systolic (non-invasive) blood pressure using the tail cuff technique for each animal, at the days 1,7,14 and 21 of the duration of the experiment.

- Measurement of body weight gain for each animal, on the days 1,7,14 and 21 of the duration of the experiment.
- Measurement of QTc interval at the end of the 3 weeks, by recording ECG for each animal after giving anesthesia.
- *Ex- Vivo* aortic reactivity studies:

Isolated rat's aortic ring is studied to examine endothelial dysfunction induced by the tested drugs through examining:

- Phenylephrine-induced contractile response.
- Acetylcholine-induced relaxation expressed as percentage reduction of phenylephrine-induced contraction.

Review of Literature

Antipsychotic drugs represent a chemically various group of compounds. They can be classified into typical (first generation or older drugs) and atypical (second generation or newer drugs) (Pacher and Kecskemeti, 2004).

Typical Antipsychotics

The history of antipsychotics began since 1950 when the typical antipsychotics were introduced to treat psychotic disorders. This family included phenothiazines, butyrophenones, thioxanthenes (clopentixol, flupentixol, and thiothixene), benzepines (loxapine, clothiapine and zotepine), diphenylbutylpiperidines (spiperones), indolones (molindone and oxypertine) and other heterocyclic compounds (Tarazi, 2001).

The sedative effects of chlorpromazine were first reported in 1952 and entered into clinical practice in many countries the following year. This was a great step in the treatment of acute psychosis (Burn, 1954). This discovery prompted further investigation through a series of performed experiments that aimed at introduction of further antipsychotic drugs.

In patients with schizophrenia, the widely used typical antipsychotics were effective in the treatment of the positive symptoms of schizophrenia, and also in preventing relapses (Kane, 1989).

Haloperidol was known to be the most potent member of this family of drugs. It had high affinity to D2receptors, that is why it carried relatively high risks of extrapyramidal symptoms, even at moderate doses. These adverse neurologic responses include distressing motor restlessness (akathisia), acute dystonias, dyskinesias, parkinsonian bradykinesia as well as tardive dyskinesias(Gardner et al., 2005).Tardive dyskinesia was the most significant adverse effect associated with chronic use of this family of drugs, especially in elderly patients(Llorca et al., 2002).

Not only neurological adverse effects were the leading cause for the scientists to search for alternative agents in managing schizophrenia, but also cardiovascular, autonomic, and endocrine adverse effects (Kapur and Remington, 2001). Orthostatic hypotension was the most common due mainly to α-blocking effect. Anticholinergic effects and sedation were also common owing to muscarinic and H_1-blocking action. Hyperprolactinemia was reported with galactorrhea, amenorrhea, and infertility (Kinon et al., 2003). Also they were closely associated with

increased insulin resistance, diabetes mellitus, hypercholesterolemia and weight gain (Yogaratnam et al., 2013, Gagliardi, 2014).Cholestatic jaundice and skin disorders like drug eruption were also reported (Warnock and Morris, 2002). Rare but dangerous adverse effects included cardiotoxicity and retinitis pigmentosa (Fornaro et al., 2002, Testai et al., 2004, Pakpoor and Agius, 2014). Such adverse effects may reduce compliance of treating drugs.

Atypical Antipsychotics

During the nineteen nineties, as a result of the efforts produced to achieve greater efficiency and reduce the side effects produced by the first generation family, novel antipsychotics were invented (atypical or second generation antipsychotics; SGA)(Francesco and Cervone, 2014).

Studies indicate that the antipsychotic use increased over the last decades, shifting from typical to atypical antipsychotics(Shrivastava et al., 2012) as they are expected to have potent antipsychotic effect, broader range in improving the schizophrenic symptoms, including the ***positive*** symptoms (hallucinations, delusions, thought disorders, aggression as well as some psychomotor abnormalities, for example stereotypy, echolalia) and the ***negative*** symptoms (flat affect, social withdrawal, poverty of

speech and thought, lack of drive and motivation, and anhedonia)(Jasovic-Gasic et al., 2012). They became the treatment of choice for schizophrenic patients not only during their first episode, but also throughout their life course (Weiss et al., 2000). As regards long-term maintenance treatment, all atypical drugs have demonstrated a positive effect on relapse prevention in the controlled trials (Csernansky et al., 2002).

Clozapine, was the earliest member of this family and was approved for treatment of schizopherenia in 1989(Kane, 1989). Clozapine seemed "atypical" in that it did not cause extrapyramidal side effects in patients(Kapur and Remington, 2001, Gardner et al., 2005). Although experts could barely agree on a formal definition of atypicality, there was nearly common agreement that all the newly introduced antipsychotics were atypical (Kapur and Remington, 2001).

Clozapine was found to be effective in at least some patients for whom the typical antipsychotics failed to control their symptoms, effective in controlling negative symptoms and improving mood and cognition (Buchanan, 1995), as well as offering unique benefits in treatment of suicidal patients (Meltzer and Okayli, 1995).

However, the discovery of life-threatening agranulocytosis was associated with clozapine treatment

dampened its use, in addition to myocarditis, cardiomyopathy, arrhythmogenic risk (Pacher and Kecskemeti, 2004) and high incidence of development of metabolic syndrome (Mitchell et al., 2013).

Attempts to develop ***clozapine–like*** antipsychotic drugs that lack its risk of agranulocytosis led to the introduction of other new drugs. The development of atypical antipsychotics aimed at titration for the doses that produce therapeutic effects, avoid adverse effects, and have better efficacy and broader spectrum (Lieberman, 1996). These include risperidone, olanzapine, quetiapine, ziprasidone, and amisulpride.

Unlike the typical antipsychotics, it has been difficult to find a common mechanism explaining the actions of these drugs. With the exception of quetiapine, the atypicals have 5-HT_{2A}/D_2 affinity ratios greater than 10, but they also interact with other receptors from the serotonin (5-HT_{1A}, 5-HT_{2C}, 5-HT_6, 5-HT_7), dopamine (D_3, D_4), muscarinic, and histamine families (Shapiro et al., 2003).

Risperidone and quetiapine were reported to have significant metabolic adverse effects including weight gain, hypercholesterolemia, and diabetes tendency in chronic clinical studies (Arango et al., 2014, Boyer et al., 2014, Yogaratnam et al., 2013). Also risperidone was reported to cause sudden death (Pacher and Kecskemeti, 2004).

On the other hand introduction of amisulpride and ziprasidone showed lower metabolic risk, better tolerability profile(Arango et al., 2014, Boyer et al., 2014), andmay even reverse dyslipidemia associated with administration of other antipsychotics(Yogaratnam et al., 2013).

Ziprasidone had a unique receptor binding profile and a presynaptic reuptake inhibition of serotonin and norepinephrine effect which probably made it effective in controlling negative symptoms (Schmidt et al., 2001). Few years after introduction, ziprasidone was considered the most risky to produce torsades de pointes, through prolongation of QT interval (Zuddas et al., 2011, Pakpoor and Agius, 2014).

By time, it was demonstrated that atypical antipsychotics were associated with greater incidence of metabolic changes in comparison to typical antipsychotics such as hypercholesterolemia, hypertriglyceridemia, increased incidence of type 2 diabetes, hypertension and increased myocardial infarction risk. These metabolic alterations collaborate for increased risk of mortality by cardiovascular causes, as well as increased risk of morbidity (Francesco and Cervone, 2014, Vancampfort et al., 2013, Gagliardi, 2014).

Typical Versus Atypical Antipsychotics

Whether using first or second generation, it was shown in many studies that they are important contributors to higher risk of morbidity in psychiatric patients (Hung et al., 2014). Recent studies put a spotlight on pros and cons of both families of antipsychotics in comparison to each other. A twenty-years observation study found that patients on typical antipsychotics reported satisfactory and better glycemic and lipid profile than patients on atypical ones (Francesco and Cervone, 2014). The same desired effect was observed in a retrospective study on 72 psychiatric children which found that typical antipsychotics didn't affect weight gain significantly in comparison to atypical ones (Ebert et al., 2014).

Some reviews found that there was no significant difference between typical and atypical antipsychotics in the point of metabolic alterations like hyper-cholesterolemia, hypertriglyceridemia, type 2 diabetes, obesity (Cuerda et al., 2014), hyperprolactinaemia with subsequent galactorrhoea, gynaecomastia, menstrual irregularities, sexual dysfunction and osteoporosis (Pakpoor and Agius, 2014).

Although atypical antipsychotics are more efficacious than typical ones, the efficacy needs to be

balanced against side effects, as well as side effects being balanced against each other when choosing antipsychotic medication for a particular patient. For example, the higher efficacy of clozapine needs to be balanced against its low propensity to extrapyramidal side effects and its high propensity to weight gain, while on the other hand, the low propensity of aripiprazole to hyperprolactinaemia, weight gain and extrapyramidal side effects needs to be balanced against its lower efficacy compared to olanzapine, which in turn is more likely to cause weight gain and metabolic syndrome (Pakpoor and Agius, 2014).

In this study, a spotlight will be put on the possible cardiovascular and metabolic adverse effects that could be associated with administration of atypical antipsychotics (olanzapine and aripiprazole) and the possible contribution of the serotonin receptors in the occurrence of these adverse effects.