COMPARATIVE EFFICACY OF HALOPERIDOL AND RISPERIDONE: A REVIEW

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ABSTRACT:
Psychosis is a mental state of illness in which person is detached from reality. Psychosis is of many form, including: Hallucinations, Delusions, thought insertion, withdrawal, block broadcasting, lack of insight etc. Different theories suggest that the cause of psychotic illness may be, inherited, problem in brain, neurochemical imbalance, anxiety or stress, any combination of the above, using drugs [e.g., cannabis, Lysergic acid diethylamide (LSD)], infections (e.g., meningitis), brain tumours (cancer), epilepsy, head injuries. Psychosis has been shown to respond well to treatments such as anti-psychotic medication, and more recently cognitive-behavioural therapy has been suggested as working well. Family and group therapies are often found to give successful results in certain individuals. Haloperidol is a psychotropic agent indicated for the treatment of schizophrenia. It also exerts sedative and antiemetic activity. Haloperidol has actions at all levels of the central nervous system-primarily at subcortical levels as well as on multiple organ systems. Risperidone is a novel antipsychotics, it is a uniquely balanced serotonin/dopamine antagonist (SDA) that offers considerable advantages in the first-line treatment of schizophrenia. This review examines the efficacy of haloperidol versus risperidone.

Keywords: Psychosis, Schizophrenia, Antipsychotic, Mania, Major-bipolar disorder, Cognition.

INTRODUCTION

Psychosis
Psychosis comprises a cluster of medical symptoms, but a precise and universally accepted definition has been elusive. The most restrictive definition is limited to symptoms of delusions or hallucinations – the hallucinations occurring in patients who lack insight into their illness. A broad definition can include psychiatric manifestations such as the positive symptoms of schizophrenia like disorganized speech or catatonic behavior. The term psychosis can conceptually include the loss of ego boundaries or a gross impairment in reality testing.

Psychotic symptoms are a defining feature of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and brief psychotic disorder. However, other disorders can present with psychotic symptoms, including bipolar disorder and depression with psychotic features, substance-induced psychosis, medical illness such as neurological disorders like Parkinson’s disease and with environmental circumstances e.g., in the intensive care unit (ICU). ICU psychosis can occur in some patients due to a variety of situations: post-surgical anesthesia, waking up with numerous intravenous lines in place, noises in the ICU area, the constant flow of staff, and an unfamiliar environment for that could result in agitation and other psychotic symptoms (Wallace, 2001; Sato et al., 2006 and Krakoski et al., 2006).

Antipsychotic Drugs
Antipsychotics drugs have been the mainstay of the treatment for psychosis since
chlorpromazine’s discovery in the mid-1950s and its record of achievement earned in clinical application during use in the early 1960s. From 1960s to 1989, anti-psychotics drugs were effective in treating psychotic symptoms in psychiatric disorders, but had numerous adverse side effects, most notably extra pyramidal side effects (EPS). The food and Drug Administration’s (FDA) approval of clozapine started a new era of developing anti-psychotics drugs with fewer EPS.

Agents prior to 1989 can be classified as “conventional” or “typical” anti-psychotics; those approved after that date are termed “atypical” anti-psychotics (Lee et al., 1997 and Stollberger et al., 2005).

Behavioral Effects in Humans:

When administered acutely, anti-psychotics produce profound effects in psychotic individuals, including patients with schizophrenia, acute mania, and others displaying agitation, aggression or paranoia. Soon after administration individuals become less agitated, restless, aggressive and impulsive without becoming excessively sedated. Initiative and interest in the environment may be reduced, in addition to displays of emotion or effect. However, while there may be drowsiness and some slowness in response to external stimuli, subjects are easily aroused, capable of giving appropriate answers to direct questions, and seem to have intact intellectual functions. Because of the dramatic tranquilizing effect of these drugs in individuals without schizophrenia, this calming of acute psychosis is less selective than the long-term effects (Wallace, 2001; Zuidema et al., 2006 and Sato et al., 2006).

With continuous administration of the anti-psychotics more selective effects on psychosis emerge. Following two to six weeks of administration, hallucinations, delusions, and disorganized thinking tend to diminish or disappear. Although negative symptoms are less likely to be affected than positive symptoms, patients displaying social withdrawal may sometimes become more responsible and communicative. Anti-psychotics drugs are therefore not simply tranquilizers, decreasing the ability of psychotic individuals to express their disturbances, but instead appear to somewhat selectively reverse many of the symptoms of schizophrenia. Anti-psychotics do not cure schizophrenia, they simply alleviate symptoms. Since schizophrenia is a lifetime disorder, treatment with anti-psychotics typically continues throughout the lifetime of the patient (Krakowski et al., 2006; Molina et al., 2004 and Spanarello et al., 2005).

Although anti-psychotics have produced important benefits in the treatment of mental illness, they are also associated with significant side effects. Acutely, these drugs may produce extra pyramidal symptoms, movement problems similar to Parkinson’s disease. With long-term use these drugs may produce, in some individuals, a disturbing movement disorder known as tardive dyskinesia. Tardive dyskinesia is characterized by stereotypical, repetitive, involuntary movements of the mouth and tongue, trunk, and extremities. These symptoms are typically seen after two years or more of anti-psychotic drugs use and symptoms sometime persist indefinitely after discontinuation of the medication. Secondary medications are often administered with anti-psychotics to decrease the potential for the development of tardive dyskinesia (Ritchie et al., 2003 and Tarazi et al., 2003).

Haloperidol:

Haloperidol is a butyrophenone derivative with anti-psychotic properties that has been considered particularly effective in the management of hyperactivity, agitation, and mania. Haloperidol is an effective neuroleptic and also possesses anti-emetic properties; it has a marked tendency to provoke extra pyramidal effects and has relatively weak alpha-adrenolytic properties (Savaskan et al., 2005). It may also exhibit hypothermic and anorexiant effects and potentiate the action of barbiturates, general anesthetics, and other CNS depressant drugs. The mechanism of
action of haloperidol has not been entirely elucidated, but has been attributed to the inhibition of the transport mechanism of cerebral monoamines, particularly by blocking the impulse transmission in dopaminergic neurons (Alvarez and Skowronski, 2003; Karl et al., 2006; Ali et al., 2003; Kirkwood and Givone, 2003 and Zimbroff, 2003). Peak plasma levels of haloperidol occur within 2 to 6 hours of oral dosing and about 20 minutes after i.m. administration. The mean plasma (terminal elimination) half-life has been determined as 20.7 ± 4.6 (SD) hours, and although excretion begins rapidly, only 24 to 60% of ingested radioactive drug is excreted (mainly as metabolites in urine, some in faeces) by the end of the first week, and very small but detectable levels of radioactivity persist in the blood and are excreted for several weeks after dosing. About 1% of the ingested dose is recovered unchanged in the urine. Haloperidol is indicated in the management of manifestations of acute and chronic psychosis, including schizophrenia and manic states. It may also be of value in the management of aggressive and agitated behavior in patients with chronic brain syndrome and mental retardation and in the symptomatic control of Gilles de la Tourette’s syndrome (Zykov et al., 2005; Andrezina et al., 2006 and Kennedy et al., 2003), Comatose states and CNS depression due to alcohol or other depressant drugs; severe depressive states; previous spastic diseases; lesions of the basal ganglia; Parkinson’s syndrome, except in the case of dyskinesias due to levodopa treatment; sensitivity to haloperidol; senile patients with pre-existing Parkinson-like symptoms. Safety and effectiveness in young children have not been established; therefore, haloperidol is contraindicated in this age group. Safety for use in pregnancy and lactation has not been established; do not administer to women of childbearing potential or nursing mothers unless, in the opinion of the physician, the expected benefits of the drug outweigh the potential hazard to the fetus or child. Haloperidol is excreted in breast milk (Fredriksson & Archer, 2006; Diav-Citrin et al., 2005).

Haloperidol has been reported to interfere with the anticoagulant properties of phenindione in an isolated case, and the possibility should be kept in mind of a similar effect occurring when haloperidol is used with other anticoagulants. Haloperidol may antagonize the action of epinephrine and other sympathomimetic agents and reverse the blood pressure-lowering effects of adrenergic-blocking agents, such as guanethidine. Enhanced CNS effects may occur when haloperidol is used in combination with methyldopa. Haloperidol inhibits the metabolization of tricyclic antidepressants, thereby increasing plasma levels of these drugs. This may result in increased tricyclic antidepressant toxicity (anticholinergic effects, cardiovascular toxicity, lowering of seizure threshold) (Krieger et al., 2004).

When prolonged Carbamazepine treatment is added to haloperidol therapy, this results in a significant reduction of haloperidol plasma levels. Therefore, during combination treatment, the haloperidol dose should be adjusted, when necessary. After stopping Carbamazepine, it will be necessary to reduce the dosage of haloperidol. Haloperidol may impair the antiparkinson effects of levodopa. If an antiparkinson agent is used concomitantly with haloperidol, both drugs should not be discontinued simultaneously, since extrapyramidal symptoms may occur due to the slower excretion rate of haloperidol. When haloperidol is used to control mania in cyclic disorders, there may be a rapid mood swing to depression. The antieneptic action of haloperidol may obscure signs of toxicity due to over dosage of other drugs or mask the symptoms of some organic diseases, such as brain tumor or intestinal obstructions. Severe neurotoxicity (rigidity, inability to walk or talk) may occur in patients with thyrotoxicosis who are also receiving anti-psychotic medication, including haloperidol. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, which are presumed to be...
linked to elevated prolactin levels (Savaskan et al., 2006, Besag and Berry, 2006).

Neuromuscular (extrapyramidal) effects such as Parkinson-like symptoms, akathisia, dyskinesia, dystonia, hyperreflexia, rigidity, opisthotonos, and, occasionally, oculogyric crisis are the most frequently reported side effects associated with the administration of haloperidol. Headache, vertigo and cerebral seizures have also been reported. The extrapyramidal reactions are usually dose related in occurrence and severity and, as a rule, tend to subside when the dose is reduced or the drug is temporarily discontinued. However, considerable interpatient variability exists, and, although some individuals may tolerate higher than average doses of haloperidol, severe extra pyramidal reactions, necessitating discontinuation of the drug, may occur at relatively low doses. Administration of an antiparkinson agent is usually, but not always, effective in preventing or reversing neuromuscular reactions associated with haloperidol (Galili et al., 2000; Balestrieri et al., 2000).

As with all anti-psychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmic, involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. There is no known effective treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all anti-psychotic agents be discontinued if these symptoms appear. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time the syndrome may not develop.

Tardive dystonia, not associated with the above syndrome, has been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible (Balestrieri et al., 2000; Luft, Taylor, 2006, Schneider et al., 2006 and Alvarez, Skowronski, 2006)

Insomnia, depressive reactions, and toxic confusional states are the more common effects encountered. Drowsiness, lethargy, stupor and catalepsy, confusion, restlessness, agitation, anxiety, euphoria, and exacerbation of psychotic symptoms, including hallucinations, have also been reported (Harvey et al., 2004, Hassaballa and Balk, 2003)

Tachycardia, hypertension and ECG changes including prolongation of the QT interval and ECG pattern changes compatible with the polymorphous configurations of torsades de pointes have been reported. Hypotension has occurred, but severe orthostatic hypotension has not been reported. However, should it occur, supportive measures, including i.v. vasopressors such as norepinephrine, may be required. Epinephrine should not be used, since haloperidol may block the vasoconstrictor effects of this drug.

Dry mouth, blurred vision, urinary retention, incontinence, diaphoresis and priapism have been reported. The overall incidence of significant hematologic changes in patients on haloperidol has been low. Occasionally there have been reports of mild and usually transient leukopenia and leukocytosis, decreases in blood cell counts, anemia, and a tendency toward lymphomonoctyosis. Agranulocytosis has rarely been reported with the use of haloperidol, and then only in association with other medication. Impairment of liver function (jaundice or hepatitis) has been reported rarely. One case of photosensitization is known and isolated cases of idiosyncratic cutaneous involvement have been observed.
Other untoward effects encountered include peripheral edema, hypocholesterolemia, alopecia, laryngospasm, bronchospasm and increased depth of respiration and stasis pneumonia. Hyperammonemia has been reported in a 5½ year old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

As with other neuroleptic drugs, a symptom complex sometimes referred to a neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated CPK, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of neuroleptic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported (Gerbershagen et al., 2001; Reeves et al., 2001; Magdalan et al., 2004; Lee et al., 1997).

**Risperidone**

Risperidone is a relatively new antipsychotic that is a potent antagonist at 5-HT2a and D2 receptors. It is the most potent serotonin/dopamine antagonist available today. It also demonstrates relatively high affinity for alpha, and H1 receptors but low affinity for beta-adrenergic or muscarinic receptors (Table 1). Preclinical studies indicate that while risperidone is approximately equipotent to haloperidol at D2 antagonism, it is several times less potent than haloperidol at inducing catalepsy (McDonald et al., 2003).

Risperidone is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 (5HT2), dopamine type 2 (D2), O1 and O2 adrenergic, and H1 histaminergic receptors. Risperidone antagonizes other receptors, but with lower potency. Risperidone has low to moderate affinity (47 to 253 nM) for the serotonin 5HT1C, 5HT1D, and 5HT1A receptors, weak no affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and to affinity (when tested at concentrations >10-5M) for cholinergic muscarinic or a1 and a2 adrenergic receptors (Marek et al., 2003, Aghajanian and Marek, 2000).

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Haloperidol</th>
<th>Risperodone</th>
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<tbody>
<tr>
<td>D1</td>
<td>36.0</td>
<td>50.0</td>
</tr>
<tr>
<td>D2</td>
<td>7.5</td>
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<td>2.7</td>
<td>6.7</td>
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<tr>
<td>D4</td>
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<td>5-HT2A</td>
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<tr>
<td>5-HT2C</td>
<td>2100.0</td>
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<tr>
<td>Alpha 1</td>
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<tr>
<td>Alpha 2</td>
<td>2000.0</td>
<td>2.3</td>
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<tr>
<td>H1</td>
<td>&gt;1000.0</td>
<td>110.0</td>
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<tr>
<td>Muscarinic</td>
<td>5500.0</td>
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Table 1

The relative in vitro binding profiles of (haloperidol)

Risperidone is well absorbed. Risperidone is extensively metabolized in the liver by cytochrome P450IID6 to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity (A second minor pathway is N-dealkylation). Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg bid). The relative oral bioavailability of risperidone from a tablet was 94% when compared to a solution. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70%. The enzyme catalyzing hydroxylation of risperidone to 9-hydroxy-risperidone is cytochrome P450IID6, also called debrisoquin hydroxylase, the enzyme responsible for
metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome P450IID6 is subject to genetic polymorphism. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. The apparent half-life of risperidone was 3 hours in extensive metabolizers and 20 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers (Aghajanian and Marek, 2000; Zhou et al., 2006).

Risperidone is indicated for the management of the manifestations of psychotic disorders. The antipsychotics efficacy of risperidone was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (Kontaxakis et al., 2006). The effectiveness of risperidone in long-term use, that is, more than 6 to 8 weeks, has not been systematically evaluated in controlled trials. Therefore, the use of risperidone for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (Klebovich et al., 2005).

The interactions of risperidone and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when risperidone is taken in combination with other centrally acting drugs and alcohol (Poewe, 2005).

Because of its potential for inducing hypotension, risperidone may enhance the hypotensive effects of other therapeutic agents with this potential.

- Risperidone may antagonize the effects of levodopa and dopamine agonists.
- Chronic administration of Carbamazepine with risperidone may increase the clearance of risperidone.
- Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

✓ Fluooxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxy-risperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

*In vitro* studies indicate that risperidone is a relatively weak inhibitor of cytochrome P450IID6. Therefore, risperidone is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

**Overdose:**
Acute risperidone over-dosage with estimated doses ranging from 20 to 300mg and reported signs and symptoms are resulting from an exaggeration of the drug’s known pharmacological effects (i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms). One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36mg, was associated with a seizure (Magdalan et al., 2004 and Lee et al., 1997).

Another acute over-dosage with estimated doses of up to 360 mg, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug’s known pharmacological effects (i.e., drowsiness, sedation, tachycardia, and hypotension). Other adverse events reported which were temporally, (but not necessarily causally) related to risperidone overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose (Aichhorn et al., 2006 and Llerena et al., 2004).

It is recommended that responding patients be continued on risperidone, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment (Silke et al., 2002).
Among patients with clinically stable chronic schizophrenia or schizoaffective disorder, the risk of relapse was significantly lower during treatment with risperidone than during treatment with haloperidol. The benefit with risperidone was substantial. The means of the modal daily doses of risperidone (4.9mg) and haloperidol (11.7mg) were similar to those used in clinical practice (Nyberg et al., 1999). The relapse rate among subjects receiving haloperidol (39.9 percent) was similar in magnitude to that found previously among patients receiving conventional anti-psychotic agents (Glick et al., 2006).

The reduced risk of relapse with risperidone could be due to that drug’s superior efficacy, better tolerability, or both. Patients who received risperidone had both early and late improvements in symptoms overall, as well as an amelioration of extrapyramidal symptoms. In contrast, patients receiving haloperidol had a slight worsening of both psychotic and extrapyramidal symptoms (Hertel, 2006 and Nyberg et al., 1999). These findings are similar to those previously reported for an eight-week comparative trial of risperidone and haloperidol. Another trial the rate of relapse, was similar in the two treatment groups (Halbreich and Kahn, 2003). Improvements in cognition or other symptoms of schizophrenia produced by risperidone but not well assessed by the positive and negative syndrome scale may also have contributed to the reductions in the rate of relapse. Receptor profiles and mechanisms of action vary among atypical anti-psychotic agents. Therefore, other agents should be assessed individually with regard to their ability to prevent relapses (Fe-Bornstein et al., 2002; Kirkwood and Givone, 2003).

Extrapyramidal side effects can occur with risperidone treatment. However, in clinical trials patients treated with risperidone experienced much fewer EPS than those treated with haloperidol. The use of antiparkinsonian medication (to alleviate EPS) reflects the finding with significantly fewer patients treated with risperidone requiring antiparkinsonian medication compared to haloperidol (Garver, 2006).

Risperidone is at least as (and possibly slightly more) effective than atypical anti-psychotics drugs (chiefly haloperidol). It has a low incidence of EPS and may be more acceptable to patients with schizophrenia. Whether risperidone offers any advantages over the other atypical anti-psychotics is yet to be established (Kirkwood and Givone, 2003; Conley and Kelly, 2002; Glick et al., 2006).

REFERENCES


