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Review Article

Risperidone in Schizophrenia: An Overview

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Abstract

Schizophrenia is a severe form of mental illness affecting about 7 per thousand of the adult population, mostly in the age group 15-35 years. Though the incidence is low (3-10,000), the prevalence is high due to chronicity. Antipsychotic medications are primarily indicated for the treatment of schizophrenia and other psychotic disorders [including schizoaffective disorder, delusional disorder and bipolar affective disorder (BPAD)]. They have traditionally been categorized as first-generation (formerly known as 'typical' or 'conventional') antipsychotics (FGAs) or second-generation antipsychotics (SGAs) (formerly 'atypical' antipsychotics). Risperidone, a benzisoxazole derivative, is a novel antipsychotic drug which binds with high affinity to serotonin type 2 (5-HT2), dopamine type 2 (D2), and α1-adrenergic receptors. Risperidone is equally or more effective than conventional antipsychotics. It is more effective in relapse prevention than conventional antipsychotics and may be more effective than other atypical antipsychotics. Further improvement is probable with long-acting injectable risperidone use even instable patients in remission. It leads to Improvement in attention, cognitive and motor speed, verbal fluency, secondary memory and executive functioning.

Keywords: Schizophrenia; Risperidone; Atypical Antipsychotics

Abbreviations

5HT2A: Serotonin Receptor 2A; D2: Dopamine Receptor 2; H1: Histamine Receptor 1; α1: Adrenergic Receptor 1; α2: Adrenergic Receptor 2

Introduction

Schizophrenia is associated with interferences in the thinking, perception and social behaviour. The psychotic symptoms persist for at least six months, and lead to the decreased functional ability of the person. The symptoms and duration of schizophrenia are subjected to inter-subject variation. Eugen Bleuler, a Swiss psychiatrist coined the word "Schizophrenia" for the first time in 1908 in medical history. It was derived from the combination of Greek words "skhizein" means split and "phren" means mind. So Bleuler emphasizes that this disorder was due to the breaking of the associative threads or the destruction of the forces that connect one function to the next. The prevalence rate for schizophrenia across the globe is 0.5% to 1%. It affects men at an early age than women. Patients with schizophrenia pose high risk for suicide. Schizophrenia is a chronic and debilitating illness that requires continuous long-term therapy, as the risk of relapse is significantly increased if medication is discontinued [1-3]. Use of the atypical antipsychotics has been reported to reduce relapse rates compared with conventional agents and, thus, to improve the prognosis in patients with schizophrenia [3-6]. Antipsychotic medications are primarily indicated for the treatment of schizophrenia and other psychotic disorders [including schizoaffective disorder, delusional disorder and bipolar affective disorder (BPAD)]. They have traditionally been categorized as first-generation (formerly known as 'typical' or 'conventional') antipsychotics (FGAs) or second-generation antipsychotics (SGAs) (formerly 'atypical' antipsychotics). The burden of side effects associated with FGAs, in particular debilitating extrapyramidal side effects (EPSEs), led to the introduction of the SGA medications in the 1990s. The SGAs have a lower propensity to cause EPSEs (i.e. acute dystonias, akathisia, parkinsonism and tardive dyskinesia) compared with the FGAs, and these properties, aligned with their differentiating receptor profiles, led them to be labelled as 'atypical' [7]. Risperidone is a commonly used second

generation antipsychotic agent (SGA) recently approved for the treatment of schizophrenia in adolescents, ages 13–17, and for the short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents ages 10–17. It has additional indications for bipolar mania and schizophrenia in adults, and irritability associated with autism in children and adolescents 5–16 years of age. Risperidone or similar SGAs, either alone or in combination with the mood stabilizers lithium, valproic acid carbamazepine, serve as first line treatment options for the treatment of pediatric bipolar disorder based on severity and acuteness of the illness [8,9]. The antipsychotic action of conventional neuroleptics, such as haloperidol, is essentially derived from their D2 antagonistic properties, as do their extrapyramidal side effects (EPS). Also, the efficacy of these substances is generally restricted to the positive symptoms of schizophrenia. In the 1980s, antipsychotics that block D2 and 5HT2 receptors simultaneously were successfully developed, in line with the serotonergic hypothesis of schizophrenia [10]. Clinical trials demonstrated that these agents were not only effective in treating positive symptoms but also had activity against negative symptoms of schizophrenia. Moreover, these agents were associated with a significantly lower incidence of EPS. Risperidone was among the first of these atypical antipsychotic agents. Early atypical antipsychotics were developed at a time when psychiatry was pursuing the concept of high-dose treatment. Consequently, in licensing trials risperidone was tested up to high doses of 16 mg/day, unlike the newer atypical antipsychotics [11,12].

Pharmacokinetics of antipsychotic drugs [13]

	Usual dose mg/day (maximal dose)	T_{max} (h)	$T_{1/2}$ (h)	V_d (l/Kg)	F (%)	BPP (%)
Haloperidol	2-30 (100)	3-6	15-30	15-20	40-80	90-94
Clozapine	150-450 (900)	1-6	12-36	4-8	40-60	97
Risperidone	4-16 (16)	2	2,8	1-1,5	66-82	89
Olanzapine	10-30 (20)	5-8	33	10-20	60-80	93
Quetiapine	150-750 (800)	1-1,5	5,8-6,6	10	100	83
Ziprasidone	80-160	3,8-5,2	3,2-10	1,5	60	> 99
Amisulpride	400-1200 (1200)	1,5-4	12	5,8	48	16
Aripiprazole	10-30 (30)	3-5	75-94	4,9	87	99
Paliperidone	3-12 (15)	1,5	24,8	6,9	28	74

Table a

F (Bioavailability); BPP (Binding plasmatic proteins).

The chemical designation of risperidone is 4-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl] ethyl]-3-methyl-2, 6-diazabicyclo [4.4.0] deca-1, 3-dien-5-one. It has the following structural formula.

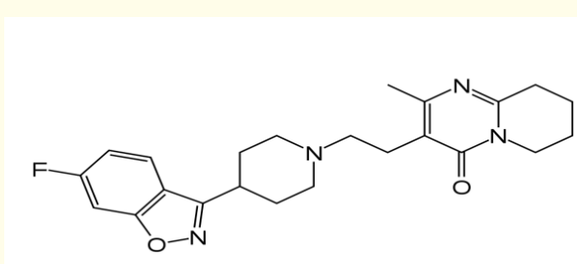

Figure 1

Route of administration: Oral [14].

Action and clinical pharmacology

Mechanism of Action

Risperidone, a benzisoxazole derivative, is a novel antipsychotic drug which binds with high affinity to serotonin type 2 (5-HT2), dopamine type 2 (D2), and α1-adrenergic receptors. Risperidone binds with a lower affinity to the α2-adrenergic and histamine H1 receptors. Risperidone does not bind to dopamine D1 receptors and has no affinity (when tested at concentrations > 10-5 M) for muscarinic cholinergic receptors. Due to the lack of muscarinic receptor binding, risperidone is not expected to produce anticholinergic adverse effects. Receptor occupancy was also demonstrated *in vivo* in humans. Using positron emission tomography, risperidone was shown to block both 5-HT2A and dopamine D2 receptors in three healthy volunteers. Although risperidone is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy in animal models than classical antipsychotics. Risperidone has also been found to be one of the most potent known antagonists of 5-HT2A (cloned human receptor); 5-HT2A antagonism has been shown to reverse deficits in several *in vivo* animal models predictive of novel antipsychotic activity (PCP-induced social deficit, microdialysis assessment of dopamine output in prefrontal cortex, glutamate antagonist-induced hyperlocomotion). Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side-effect liability [12].

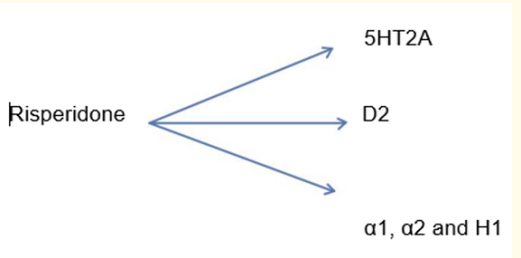

Figure 2

Mechanism of action of risperidone [15].

Pharmacokinetics

- **Absorption:** Risperidone is well absorbed after oral administration, has high bioavailability, and show dose-proportionality in the therapeutic dose range, although inter-individual plasma concentrations vary considerably. Mean peak plasma concentrations of risperidone and 9-hydroxyrisperidone are reached at about 1 hour and 3 hours, respectively, after drug administration. Food did not affect the extent of absorption; thus, risperidone can be given with or without meals [16].
- **Distribution:** Risperidone is rapidly distributed. The volume of distribution is 1–2 L/kg. Steady-state concentrations of risperidone and 9-hydroxyrisperidone were reached within 1–2 days and 5–6 days, respectively. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein (AGP). The plasma protein binding of risperidone is approximately 88%, that of the metabolite 77% [17].
- **Metabolism:** Risperidone is extensively metabolized in the liver by CYP 2D6 to a major active metabolite, 9-hydroxyrisperidone, which 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 likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. The hydroxylation of risperidone is dependent upon debrisoquine 4-hydroxylase, i.e., the metabolism of risperidone is sensitive to the debrisoquine hydroxylation type genetic polymorphism. Consequently, the concentrations of parent drug and active metabolite differ substantially in extensive and poor metabolizers. However, the concentration of risperidone and 9-hydroxyrisperidone combined did not differ substantially between extensive and poor metabolizers, and elimination half-lives were similar in all subjects (approximately 20 to 24 hours) [18].
- **Excretion:** One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxyrisperidone represents 35–45% of the dose. The remainder is inactive metabolites. The results indicate that a 1 mg dose of risperidone produced modest pharmacokinetic changes in elderly subjects, including reduced clearance of the active antipsychotic fraction by about 30%. In patients with impaired liver function, the unbound fraction of risperidone was increased by about 35% due to diminished concentrations of both α1-AGP and albumin. In patients with impaired renal function, the changes were substantial; C max and AUC of risperidone and 9-hydroxyrisperidone combined were increased by about 40% and 160% respectively, half-life was prolonged by about 60% and clearance decreased by about 60%. The plasma levels of risperidone and its major metabolite, 9-hydroxyrisperidone, were determined at steady state. Blood samples were obtained from 85% of all trial patients receiving risperidone. Blood samples were drawn prior to the morning dose [19,20].

Use of risperidone in the treatment of schizophrenia [21]

	Parameter	Result
Efficacy	Acute therapy	Equally or more effective than conventional antipsychotics
	Long-term treatment	More effective in relapse prevention than conventional antipsychotics and may be more effective than other atypical antipsychotics. Further improvement is probable with long-acting injectable risperidone use even in stable patients in remission
	Positive symptoms	Equally or more effective than conventional antipsychotics
	Negative symptoms	Reduction of negative symptoms; direct effect is probable
	Anxiety/ depression	Reduction of anxiety and depression even after short-term Treatment
	Cognition	Improvement in attention, cognitive and motor speed, verbal fluency, secondary memory and executive
		Functioning
Tolerability	EPS	Dose-dependent potential for inducing EPS at doses V 6 mg/day; comparable to placebo
	Weight gain	Moderate potential for inducing weight gain; average weight gain 2 – 2.5 kg/year
	Diabetes mellitus	Potential for inducing diabetes mellitus type 2 comparable to that of conventional
		Antipsychotics
	Prolactin	Dose-dependent potential for inducing hyperprolactinemia but very low risk of inducing prolactin associated side effects
Dose	Acute therapy	4 – 6 mg/day
Recommendations		
	Long-term treatment	3 – 4 mg/day
	Elder patients	2 – 4 mg/day

Table b

Indications and clinical use

Adults

Schizophrenia

Risperidone is indicated for the acute treatment and maintenance treatment of schizophrenia and related psychotic disorders. In controlled clinical trials, risperidone was found to improve both positive and negative symptoms of schizophrenia. It has been shown to be effective in maintaining clinical improvement during long term therapy (1 year).

Severe Dementia - Symptomatic management of inappropriate behaviour

Risperidone may be useful in severe dementia for the short-term symptomatic management of inappropriate behaviour due to aggression and/or psychosis. Other behavioural disturbances seen in this patient population as well as disease stage remained unaffected by risperidone treatment.

Bipolar Disorder - Mania

Risperidone is indicated as monotherapy for the acute management of manic episodes associated with Bipolar I disorder. The efficacy of risperidone in the treatment of acute bipolar mania was established in three 3- week, placebo-controlled trials. The safety and effectiveness of risperidone for long-term use, and for prophylactic use in bipolar disorder have not been evaluated. Physicians who elect to use risperidone for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient

Geriatrics (> 65 years of age)

Geriatric patients generally have decreased renal, hepatic and cardiac function, and an increased tendency to postural hypotension. Therefore, lower starting doses, lower rates of dose adjustment and lower maximal doses are recommended in these patients.

Risperidone is substantially excreted by the kidneys. Thus, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, caution should be taken in dose selection and titration. It may also be useful to monitor renal function in these patients [14,22].

Potential effect on cognitive and motor performance

Since risperidone may cause somnolence, patients should be cautioned against driving a car or operating hazardous machinery until they are reasonably certain that risperidone does not affect them adversely.

Psychiatric

Suicide

The possibility of suicide or attempted suicide is inherent in psychosis and bipolar mania, and thus, close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Renal

The pharmacokinetics of risperidone were significantly altered in patients with renal disease. In patients with moderate to severe renal disease, clearance of risperidone and its active metabolite 9-hydroxyrisperidone, combined, decreased by 60%, compared to young, healthy subjects.

Therefore, lower starting doses and lower maximal doses of risperidone are recommended in patients with any degree of renal impairment. It may also be useful to monitor renal function in these patients [23].

Marketed formulations of risperidone

- Risperidone tablets: It is available in various dosage strengths of 0.25, 0.5, 1, 2, 3 and 4 mg tablets.
- Risperidone oral solution: It is available as 1 mg/ml oral solution.
- Risperidone rapidly or mouth dissolving tablets: This is the latest advancement for managing acute psychosis. Risperidone is available as M-Tab. It is especially designed for children and elderly patients, who have swallowing problems. The disintegration time for M-tab is approximately 29 seconds. It is available as 0.5, 1, 2, 3 and 4 mg tablets [24].
- Long acting parenteral risperidone: USFDA has recently approved Risperdal® ConstaTM, a microsphere preparation designed to be administered Intramuscularly (IM). It is available in high dose of 25 to 50 mg for IM gluteal injection. It suffers from the drawback that an initial oral dose should be provided along with this injection. To maintain the steady state plasma levels (for 4-6 weeks) it should be administered biweekly. Usually steady state can be achieved after 4th injection of risperidone [25,26]. Risperidone formulation is available as injection, powder for suspension, extended release 12.5mg, 25mg, 37.5mg and 50mg [27].

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