

Efficacy and safety of risperidone long-acting injection in elderly people with schizophrenia

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Abstract: Antipsychotic medication is the mainstay of treatment in elderly patients with psychosis. In recent years, second generation antipsychotics have come to be preferred. Long-acting risperidone is the first such antipsychotic available for use in this vulnerable group of patients and offers an attractive alternative to traditional medications. The available literature revealed that long-acting risperidone is generally well tolerated and is effective in treating both the positive and negative symptoms of schizophrenia. Despite a lack of randomized trials and head-to-head studies, it appears to be a useful addition to the treatment armory for patients with chronic psychosis who require a depot preparation. Further research into its endocrine and metabolic side effects is needed.

Keywords: risperidone, long-acting injection, old age, efficacy, safety

Introduction

The key feature of psychosis is the misinterpretation of reality as shown by altered perceptions, false beliefs, and disorganized patterns of speech and behavior. In the elderly, psychotic symptoms arise in a number of conditions: schizophrenia, schizoaffective disorder, delusional disorder, mood disorder, delirium secondary to medical conditions, and neurodegenerative conditions including Alzheimer's disease, vascular dementia, dementia with Lewy bodies and Parkinson's disease. Social isolation, sensory deficits, and polypharmacy are additional risk factors.¹

Approximately 15% of all patients with schizophrenia have an onset of symptoms after the age of 40 years, 7% after the age of 50 and 3% thereafter.² Hallucinations and persecutory delusions are common and generally follow a chronic course.³ In people with Alzheimer's disease, the prevalence of psychotic symptoms ranges from 30% to 50%.⁴ In dementia with Lewy bodies, visual hallucinations occur in 80% of cases while auditory hallucinations and paranoid delusions have a prevalence of 20% and 65%, respectively.⁵ Between 20% and 60% of people with Parkinson's disease develop psychotic symptoms.⁶ Psychotic symptoms can be associated with aggressive or disruptive behavior, are a source of distress to caregivers, and often result in institutionalization.⁷

Antipsychotic medications form the mainstay of treatment of psychotic symptoms. In recent years, second generation antipsychotics like risperidone, olanzapine, and clozapine have been preferred over older drugs like haloperidol because of their lower incidence of extrapyramidal, anticholinergic and cardiac side effects and a possible greater efficacy in reducing negative and neurocognitive symptoms.⁸

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Treatment nonadherence is one of the greatest challenges facing prescribers with 20% to 50% of all patients failing to comply fully with medical recommendations.⁹ Rates of nonadherence to antipsychotic prescriptions are even higher. In the large, prospective CATIE Schizophrenia Study on the effectiveness of antipsychotics, for example, 75% of patients discontinued treatment within 18 months.¹⁰ Risk factors for nonadherence include ongoing psychosis, limited insight, adverse reactions, stigma, and poor rapport with the treating clinician.¹¹ In addition, older people may have difficulty taking medications correctly because of sensory impairment, cognitive deficits, medical co-morbidity, polypharmacy, and heightened sensitivity to adverse effects.¹²

For patients with psychosis who will not or cannot take oral medication on a regular basis a long-acting injectable antipsychotic may offer a solution. Until recently choice was limited to first generation preparations such as haloperidol decanoate and flupenthixol decanoate, all of which can provoke parkinsonism, unsteadiness, and falls to which the elderly are vulnerable. Long-acting risperidone injection is the first "atypical" or second generation antipsychotic freely available for the treatment of psychosis.

This paper focuses on this treatment formulation and its use in the older patients with schizophrenia and related psychoses. Suitable papers were identified by means of an electronic search of MEDLINE, EMBASE, Scopus, PsycINFO and CINAHL databases using combinations of the key terms "risperidone", "antipsychotic agents", "therapeutic use", "adverse effects", and "aged".

Pharmacology of risperidone long-acting injection

Both risperidone and its active metabolite 9-hydroxy risperidone are thought to have antipsychotic potency.¹³ Long-acting risperidone injection is an extended release microsphere formulation of risperidone encapsulated in polyglactin for intramuscular injection. Traditional antipsychotic depot preparations are esterified and delivered in an oil-based suspension. Because of its lack of a hydroxyl group, risperidone cannot be esterified, but its encapsulation in biodegradable polymer microspheres makes possible its delivery in a water-based vehicle. The polymer dissolves into water and carbon end products, providing a steady release of medication.

After a single intramuscular injection, less than 1% of the dose is released followed by a lag of three weeks, which makes it necessary to prescribe an oral antipsychotic during this time. From that point on, release occurs steadily

between weeks 4 to 6 and subsides by week 7. Thereafter, twice-weekly injections result in sustained therapeutic plasma concentrations that persist for four to six weeks after the last injection. The elimination phase is complete at seven to eight weeks following microsphere breakdown.

The pharmacokinetics of long-acting risperidone is linear in the dose range of 25 to 50 mg. Following extensive first-pass metabolism of risperidone by the liver, 90% is bound in plasma to albumin and alpha-1 acid glycoprotein prior to elimination via the kidneys. Plasma levels are normal in patients with hepatic insufficiency, but may be raised by 60% in patients with renal impairment.¹⁴

Since aging is associated with decreased rates of renal blood flow, glomerular filtration and renal clearance as well as reduced levels of synthesis and activity of hepatic microsomal enzymes, caution is required in older patients with renal or hepatic impairment. An age-related fall in total body water results in higher plasma concentrations of this water-based medication, increasing both its activity and the potential for adverse effects. Reduced cerebrovascular perfusion and the increased sensitivity of alpha-1 adrenergic receptors also make the elderly more susceptible to orthostatic hypotension, dizziness and falls. With age, the loss of ascending dopaminergic neurones and postsynaptic dopamine receptors can halve the levels of striatal dopamine by age 65 years, resulting in parkinsonism and tardive dyskinesia given risperidone's high affinity for dopaminergic D2 receptors.^{12,15}

Risperidone must be used with caution with other centrally acting medicines. It antagonizes the effects of levodopa and other dopamine agonists and potentiates the orthostatic effects of tricyclic antidepressants and antihypertensives. Caution is advised when combining risperidone with drugs known to prolong the QT interval because of the risk of cardiac arrhythmias. Risperidone levels are increased by cytochrome 450 2D6 inhibitors such as paroxetine and fluoxetine and decreased by cytochrome 450 3A4 inducers like carbamazepine, corticosteroids, and barbiturates.

Efficacy

Long-acting risperidone proved effective, safe, and tolerable in a large, 12-week randomized, controlled trial in younger adults with schizophrenia. Positive and negative symptoms of schizophrenia improved significantly; adverse reactions were infrequent at low doses, and most patients rated injection pain as low.¹⁶ There were also improvements in positive and negative symptoms, extrapyramidal side-effects and patient satisfaction in a six-month open label study of patients with

schizophrenia and other psychoses as they transitioned to long-acting risperidone from other antipsychotics.¹⁷ In a retrospective case-note audit of patients prescribed long-acting risperidone over a 35-month period, total inpatient days fell from 4,550 to 2,188 following treatment initiation.¹⁸

In a secondary analysis of findings from an open-label, 50-week trial of long-acting risperidone injection, 57 older patients (mean age 71 years) with clinically stable schizophrenia or schizoaffective disorder received 25 mg to 75 mg every two weeks.¹⁹ Oral risperidone was prescribed two weeks before and three weeks after the first injection. Dosing was guided by clinical judgment. Thirteen of the 57 patients terminated treatment early, mostly because of withdrawal of consent. Clinical improvement, defined as a fall of 20% or more in scores on the Positive and Negative Symptom Scale, occurred in 42% and 62% of those in the 25 mg and 50 mg groups, respectively. Scores on the Clinical Global Improvement scale fell by at least one point in 37% and 76%, respectively. Too few patients took 75 mg to provide meaningful results. Improvements were also noted on each of the 10 sub-scales of the 36-item Medical Outcomes Short-Form (SF-36) quality of life scale.

Similar findings emerged from another secondary analysis of data from the six-month, open-label Switch to Risperidone Microspheres (StoRMi) study concerning 52 older patients (mean age 71 years) with clinically stable schizophrenia or schizoaffective disorder.²⁰ Doses at study end were 25 mg (60%), 37.5 mg (26%), and 50 mg (14%) every two weeks. There were 10 discontinuations, mostly due to adverse events. At study end, 47% of patients had an improvement of 20% or more in Positive and Negative Symptom Scale scores. There were also statistically significant improvements in scores on the Clinical Global Improvement scale, Extrapyramidal Symptom Rating Scale, SF-36 scale, and patient satisfaction scale.

Case series were typically small. In a review of six patients (mean age 72 years) treated with fortnightly doses of either 25 mg or 37.5 mg long-acting risperidone, two demonstrated long-term clinical improvement.²¹ Of the 18 patients (mean age 71 years) in another series, 12 required 37.5 mg per fortnight, three were given 50 mg, and one was given 75 mg. All experienced some symptomatic improvement and four became free of all positive and negative symptoms.²² Finally, in a retrospective chart review of 48 elderly patients with schizophrenia, 60% of 25 patients treated with 25 to 50 mg long-acting risperidone achieved strictly defined symptomatic remission after six months. The majority (72%) were rated as improved or much improved on

the CGI scale, and all but six persisted with treatment over this period. Unspecified side effects were rated as moderate in five cases and severe in two others.²³

Safety and tolerability

Risperidone is a selective monoaminergic antagonist with a high affinity with serotonergic 5-HT₂ and dopaminergic D₂ receptors. It also binds to alpha-1 adrenergic receptors and, to a lesser extent, to H₁ histaminergic and alpha-2 adrenergic receptors. It has no affinity with cholinergic receptors and therefore has no anticholinergic side effects.¹³ Problems with sedation, orthostatic hypotension and rhinitis may be related to its alpha-1 antagonistic properties.¹³ Risperidone is associated with less weight gain than other second generation antipsychotics, presumably because of its lower affinity with histamine-1 receptors.^{13,19,22} Because of its greater blockade of nigrostriatal dopaminergic D₂ receptors than other atypical antipsychotics, it can lead to extrapyramidal side effects, especially at higher doses.^{12,13}

In the secondary analysis described above of 57 elderly patients receiving long-acting risperidone, 74% of all patients reported adverse effects.¹⁹ Events reported by more than 10% were insomnia (14%), constipation (12%), bronchitis (12%), psychosis (11%), and rhinitis (11%). A death due to myocardial infarction was judged not to be related to treatment. Scores on the Extrapyramidal Symptom Rating Scale (ESRS) fell by 30%; there were no new cases of tardive dyskinesia, and no significant changes in electrocardiogram parameters. An increase in weight of more than 7% was seen in none of those taking 25 mg and in 29% and 89% of those taking 50 mg and 75 mg doses respectively. After the first injection, five patients reported mild pain and five reported moderate pain. On a visual analogue scale ranging from zero to 100, pain ratings fell from 8 initially to 2 at study end.

In the other secondary analysis outlined previously concerning 52 elderly patients, the adverse effects of long-acting risperidone were monitored at baseline and then one, three, and six months later.²⁰ Adverse events occurring in more than 5% of cases were as follows: parkinsonism (15%), other extrapyramidal disorders (15%), tremor (8%), depression (6%), diarrhoea (6%), dizziness (6%), and insomnia (6%).²⁰ Events leading to discontinuation included one case each of worsened psychosis, parkinsonism, other extrapyramidal disorder, depression, a suicide attempt and urinary tract infection. Most adverse events were considered mild (53%) or moderate (34%). One patient developed tardive dyskinesia and another diabetes but there were no cerebrovascular or prolactin-related events and no significant change in weight.

Extrapyramidal side effects (tremor, tardive dyskinesia with bradykinesia, and bradykinesia with rigidity) were the reasons given for discontinuation in three patients in a case series of six treated with long-acting risperidone injection.²¹ In another case series of 18 patients, adverse effects were uncommon with only two patients stopping treatment because of extrapyramidal symptoms.²² Treatment was continued despite one report each of sedation, modest weight gain, and a transient ischemic attack.²²

Specific concerns

No evidence has emerged from the studies cited above of increased cerebrovascular events though the number of patients was relatively small and few were very old. This is an important matter given the concerns that second generation antipsychotics might be responsible for increased cerebrovascular events and mortality in patients with dementia. The Committee on Safety of Medications in the United Kingdom, having reviewed the literature on the use of risperidone and olanzapine for the treatment of behavioral and psychological symptoms of dementia, concluded that each was associated with at least a two-fold increase in the risk of stroke and therefore should not be prescribed in dementia.²⁴ Subsequently, a meta-analysis of mortality in 17 placebo-controlled trials of four atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) found a pooled incidence of mortality of 3.5% versus 2.3% for placebo, a small but statistically significant difference.²⁵ These findings were not replicated, however, in a population linkage study of stroke in older people prescribed risperidone or olanzapine.²⁶

None of the studies considered here addressed concerns regarding prolactin. Risperidone and conventional antipsychotics raise prolactin levels by blocking dopamine in the tuberoinfundibular pathway.²⁷ The short-term effects of raised prolactin include sexual dysfunction and loss of libido while longer-term problems include decreased bone density and osteoporosis to which patients with schizophrenia may be predisposed by risk factors such as sedentary lifestyle, smoking and poor nutrition.^{27,28} Further research of this matter in vulnerable aged patients is clearly necessary.

Conclusions

On balance, long-acting risperidone injection is effective, generally well tolerated and safe in late-life psychosis and is a useful treatment modality for patients who find it difficult to take tablets. Based on published case series, the manufacturers' recommended dose of 25 mg fortnightly can be safely doubled in some cases. The commonest dose in two series was 37.5 mg.^{21,22}

It seems reasonable to start depot treatment at a dose of 25 mg fortnightly after a period of treatment with oral risperidone (0.5 to 3 mg daily) to confirm tolerability. Oral supplementation is required for three weeks after the first injection.¹⁴ Extrapyramidal side effects do occur and should be monitored regularly. There is no evidence to date of an increase in cerebrovascular events but raised prolactin levels with consequent osteoporosis warrant further study as do glucose control and lipid function in genuinely old people.¹⁹ Further controlled trials and case series are required to fill these gaps in knowledge.

Disclosures

The authors have no conflicts of interest to declare.

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