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Risperidone

A Review of its Pharmacology and Therapeutic Potential in the Treatment of Schizophrenia

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Synopsis

Risperidone, a benzisoxazol derivative, is a novel antipsychotic agent which combines potent serotonin (5-hydroxytryptamine) 5-HT$_2$ and dopamine D$_2$ receptor antagonism. Development of the drug was stimulated by reports that the selective serotonin 5-HT$_2$ antagonist ritanserin improved the negative symptoms of schizophrenia and decreased extrapyramidal symptoms when combined with haloperidol. The relatively low incidence of extrapyramidal symptoms with risperidone may reflect a preferential action on mesolimbic rather than nigrostriatal dopaminergic pathways.

Recent clinical investigation suggests that risperidone is of at least comparable efficacy to haloperidol and perphenazine in improving the symptoms of acute and chronic schizophrenia on short term administration. Advantages offered by risperidone over haloperidol include a faster onset of antipsychotic action, a lower incidence of extrapyramidal effects and possibly greater efficacy against the negative symptoms of schizophrenia. If these benefits prove to be maintained during long term therapy, risperidone is likely to make a significant contribution to the treatment of schizophrenia.

Pharmacodynamic Properties

Risperidone shows high affinity for central serotonin 5-HT$_2$, adrenergic-α_1 and -α_2, histamine H$_1$, and dopamine D$_2$ receptors *in vitro* and for serotonin 5-HT$_2$, adrenergic-α_1 and dopamine D$_2$ receptors *in vivo*. In the rat, risperidone increased dopamine turnover in the striatum, nucleus accumbens, olfactory tubercle and frontal cortex at doses in excess of those required for 50% occupancy of central dopamine D$_2$ receptors *ex vivo*, suggesting possible modulation of dopamine turnover by serotonin 5-HT$_2$ receptor blockade.

Risperidone exhibits central serotonin 5-HT$_2$ and neostriatal dopamine D$_2$ antagonistic activity, but is devoid of anticholinergic activity, in several *in vivo* animal models. It is also effective in animal behavioural models considered predictive of antipsychotic activity (e.g. suppression of apomorphine- and amphetamine-induced stereotypy and conditioned avoidance behaviour). In healthy volunteers, risperidone produced an alteration in sleep architecture similar to that seen with the selective serotonin 5-HT$_2$ antagonist ritanserin, while in patients with chronic schizophrenia risperidone 5 to 10 mg/day restored sleep patterns and improved sleep efficiency, showing a more pronounced ameliorative effect than haloperidol. Following multiple dose (4-week) administration, risperidone produced marked and sustained increases in serum prolactin levels in schizophrenic patients; there was no evidence of tolerance to this effect. The cardiovascular effects of risperidone reflect its α-adrenergic antagonistic activity, comprising a dose-related decrease in blood pressure and reflex tachycardia on single, but not

multiple, dose administration. Patients with schizophrenia appear to be more tolerant of the hypotensive effect of risperidone than healthy volunteers.

Pharmacokinetic Properties

Risperidone undergoes extensive metabolism (hydroxylation and oxidative N-dealkylation), and its major metabolite, 9-hydroxy-risperidone, displays similar pharmacological activity to the parent compound. Oxidative metabolism of risperidone is subject to genetic polymorphism. The oral bioavailability of risperidone varies from 66% (extensive metabolisers) to 82% (slow metabolisers). Peak plasma risperidone concentrations of 3 to 8 μg/L were achieved within 2 hours of single oral dose administration of risperidone 1mg to extensive metabolisers. Plasma concentrations of risperidone, 9-hydroxy-risperidone and the active moiety (risperidone + 9-hydroxy-risperidone) were linearly related to dosage (≤ 25 mg/day) in schizophrenic patients.

Risperidone and its metabolites are extensively distributed throughout the body. Plasma protein binding of risperidone is approximately 90% and the volume of distribution is 1.2 L/kg. Risperidone is primarily excreted via the urinary route, with approximately 70% of the administered dose being recovered in the urine and 15% in the faeces over a 1-week period postdose. Plasma elimination half-lives ($t_{1/2}\beta$) of risperidone and 9-hydroxy-risperidone in extensive metabolisers are 2.8 and 20.5 hours, respectively, with a $t_{1/2}\beta$ for the active moiety of approximately 24 hours. In poor metabolisers $t_{1/2}\beta$ of risperidone is extended to approximately 16 hours, whereas that of the active moiety is unchanged. Renal clearance of risperidone is reduced in patients with impaired renal function.

Therapeutic Use

Short term (4 to 8 weeks) noncomparative studies in patients with chronic schizophrenia have demonstrated marked improvements in general symptoms [Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions (CGI) scale] with risperidone ≤ 25 mg/day, and a reduced incidence of extrapyramidal symptoms and antiparkinson drug requirements in comparison with prior antipsychotic therapy. These effects appeared to be maintained on long term (≤ 12 months) follow-up. Addition of risperidone 2 to 6 mg/day to existing antipsychotic therapy tended to produce a greater improvement in negative symptoms [Scale for Assessment of Negative Symptoms (SANS)] than the addition of placebo.

Recent findings from several short term (8 weeks) multicentre studies in patients with predominantly chronic schizophrenia suggest that risperidone 4 to 8 mg/day is of at least comparable efficacy to haloperidol 10 to 20 mg/day in alleviating the positive symptoms of the disease, and that it may confer the advantage over haloperidol of a faster onset of antipsychotic action, a lower incidence of extrapyramidal effects, and possibly greater efficacy against the negative symptoms of schizophrenia. Risperidone 5 to 15 mg/day has demonstrated similar antipsychotic efficacy to perphenazine 16 to 48 mg/day on short term administration to patients with acute exacerbation of chronic schizophrenia.

Tolerability

The more commonly reported adverse effects of risperidone in recent clinical trials included sedation (30% of patients), insomnia (26%), agitation (22%), extrapyramidal symptoms (17%), dizziness (14%), anxiety (12%) and rhinitis (10%).

The incidence of extrapyramidal symptoms is linearly related to dosage (1 to 16 mg/day); at therapeutic dosages of 4 to 8 mg/day the incidence is comparable to that seen with placebo and significantly less than that associated with haloper-

idol 10 or 20 mg/day. Tardive dyskinesia has rarely been reported on long term (≥12 months) risperidone therapy.

Risperidone produces α-adrenergically mediated hypotension; however, the use of conservative dose titration schedules and divided doses minimises the risk of clinically important hypotension. Significant and dose-related weight gain (1.2 to 2.2 kg over 8 weeks) has been reported with risperidone 2 to 16 mg/day.

Dosage and Administration

Titration of risperidone dosage is recommended, starting at 1mg orally twice daily, and increasing to 3mg twice daily over 3 days; the dosage may then be individualised. The optimum therapeutic dosage is 4 to 8 mg/day; dosages above 10 mg/day do not appear to confer greater clinical efficacy but are associated with a higher incidence of extrapyramidal symptoms.

For elderly patients and those with impaired renal function a starting dosage of 0.5mg twice daily, increased in 0.5mg aliquots to a total dosage of 1 or 2mg twice daily, is recommended.

1. Pharmacodynamic Properties

While the diagnostic symptoms of schizophrenia are now well established, the aetiology and pathophysiology of the disease remain unclear. Although overactivity of central dopaminergic pathways has been implicated in the development of schizophrenia (the so-called 'dopamine hypothesis' of schizophrenia),[1-4] there is little evidence to indicate that this is the primary neurochemical abnormality. Rather, there is emerging evidence for specific neuronal deficits in schizophrenia[5] which may result in secondary dysfunction of central neurotransmitter systems including, among others, dopamine and serotonin (5-hydroxytryptamine; 5-HT).[6-8] Thus, while the clinical potency of typical antipsychotics is closely correlated with their *in vitro* affinity for the dopamine D_2 receptor,[9] serotonin 5-HT_2 antagonistic activity has been associated with efficacy against the negative symptoms of schizophrenia (e.g. blunted affect, anergia and motor retardation) and a low propensity to cause extrapyramidal symptoms.[8,10]

Risperidone, a benzisoxazol derivative (fig. 1), was selected for evaluation in patients with schizophrenia because it combines potent serotonin 5-HT_2 and dopamine D_2 receptor antagonism. The therapeutic value of this combination was suggested by earlier studies of the selective serotonin 5-HT_2 receptor antagonist ritanserin added to standard neuroleptic therapy in patients with schizophrenia.[11,12] Studies in standard animal behaviour models demonstrate a very useful pharmacodynamic profile for risperidone. Clinical experience appears to confirm the value of this pharmacological approach to the treatment of schizophrenia.

1.1 Effects on Central Neurotransmitter Systems

1.1.1 Receptor Binding Properties

Nanomolar concentrations of risperidone inhibit specific *in vitro* ligand binding at serotonin 5-HT_2, α_1- and α_2-adrenergic, histamine H_1, and dopamine D_2 receptors in rat brain[13][table I]. The equilibrium dissociation constant (K_i) for risperidone at the dopamine D_2 receptor (3 nmol/L) is comparable to that for haloperidol (1.55 nmol/L). In contrast to this classic neuroleptic, but in com-

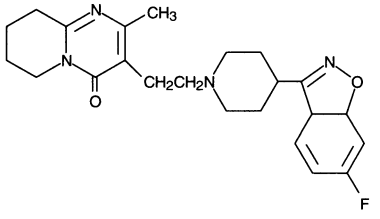

Fig. 1. Structural formula of risperidone.

mon with the atypical neuroleptic clozapine, risperidone has a high affinity for the serotonin 5-HT_2 receptor (K_i = 0.12 nmol/L), α_1-adrenoceptor (K_i = 0.8 nmol/L) and α_2-adrenoceptor (K_i = 7.3 nmol/L).[13] Risperidone displays considerably lower *in vitro* affinity for the serotonin 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1A} and dopamine D_1 receptor subtypes (K_i = 47, 52, 270 and 620 nmol/L, respectively) and negligible affinity for serotonin 5-HT_{1B} and 5-HT_3, β-adrenergic, muscarinic and peptidergic receptors, and ligand binding sites on membrane sodium, chloride, and calcium channels,[13,15] and is only a weak inhibitor of synaptosomal monoamine neurotransmitter uptake.[13]

In vivo, subcutaneous risperidone inhibited labelling by intravenous [^{3}H]spiperone of serotonin 5-HT_2 receptors in the frontal cortex and dopamine D_2 receptors in the striatum and nucleus accumbens of the rat [dose required for 50% inhibition of 5-HT_2 and D_2 receptor occupancy (ED_{50}) = 0.03 and ≈ 1.0 mg/kg, respectively].[13] *Ex vivo* autoradiographic studies of rat brain indicated that risperidone produced 50% occupancy of serotonin 5-HT_2, α_1-adrenergic and dopamine D_2 receptors at subcutaneous doses of 0.0075, 0.32 and 2.5 mg/kg, respectively,[16] maintaining the selectivity for the serotonin 5-HT_2 receptor shown *in vitro*. Positron emission tomography in healthy volunteers indicated that risperidone occupied ≈ 60% of the serotonin 5-HT_2 receptors in the frontal cortex and ≈ 50% of the dopamine D_2 receptors in the striatum after a single subtherapeutic dose (1mg).[17] Similarly, a high level of *in vivo* dopamine D_2 receptor occupancy in the basal ganglia and frontal cortex was revealed by single photon emission computerised tomography (SPECT) in a schizophrenic patient receiving risperidone 12 mg/day.[18]

1.1.2 Effects on Dopamine Turnover

Central dopamine D_2 receptor blockade induces a feedback increase in the activity of nigrostriatal and mesolimbic dopaminergic neurons, reflected acutely in an increase in dopamine metabolism in the striatum, nucleus accumbens and olfactory tubercle,[19] and this effect is acutely potentiated by serotonin 5-HT_2 receptor antagonists.[20] In the presence of incomplete dopamine D_2 receptor blockade, this enhancement of nigrostriatal activity might be expected to partially counteract the effects of dopamine D_2 receptor blockade, thereby reducing the initial likelihood of extrapyramidal effects. However, serotonin 5-HT_2 receptor antagonism is unlikely to account for the low incidence of extrapyramidal effects seen with risperidone on long term therapy: in contrast to the acute situation, serotonin 5-HT_2 receptor blockade does not influence the decrease in dopamine metabolism associated with chronic dopamine D_2 receptor blockade.[21]

Table I. *In vitro* receptor binding profile of risperidone in rat brain membrane preparations[13,14]

Radioligand	Receptor	Mean dissociation constant [K_i (nmol/L)]
[^{3}H]ketanserin	serotonin 5-HT_2	0.12
[^{3}H]haloperidol	dopamine D_2	3.0
[^{3}H]pyrilamine	histamine H_1	2.1
[H^3]WB4101	α_1-adrenergic	0.8
[H^3]clonidine	α_2-adrenergic	7.3

In the rat, subcutaneous risperidone at doses of up to 10 mg/kg produced dose-related increases in homovanillic acid (HVA) and dihydroxyphenylacetic acid (DOPAC) levels in the striatum, nucleus accumbens and, to a lesser extent, the olfactory tubercle and frontal cortex.[13] The maximal effect was seen with risperidone doses 2- to 10-fold higher than those required to produce 50% occupancy of dopamine D_2 receptors *ex vivo*, possibly reflecting modulation of dopamine turnover by serotonin 5-HT_2 receptor blockade.

1.2 Central Nervous System Effects

1.2.1 In Vivo Effects in Animal Models

In the rat, parenterally administered risperidone inhibited 5-hydroxytryptophan- and mescaline-induced head twitch activity (ED_{50} = 0.016 and 0.037 mg/kg, respectively),[22] tryptamine-induced bilateral clonic seizures of the forepaws and coarse body tremors (ED_{50} = 0.014 and 0.049 mg/kg, respectively),[23] and the m-chlorophenylpiperazine-

stimulated hind limb flexor reflex,[24] thereby demonstrating central serotonin 5-HT_2 antagonistic activity. The ability of drugs to ameliorate changes in stereotyped animal behaviour induced by apomorphine or amphetamine is a standard test of potential antipsychotic efficacy.[25,26] In the rat, subcutaneous risperidone inhibited apomorphine-induced agitation and stereotypy (gnawing, grooming, sniffing and reduced locomotion) [ED_{50} = 0.15 mg/kg],[23] amphetamine-induced agitation (ED_{50} = 0.056 mg/kg)[23] and amphetamine-induced stereotypy.[27] Risperidone was approximately 4 to 10 times less potent than haloperidol against these behavioural expressions of central dopaminergic overactivity; however, in distinction to haloperidol, risperidone displayed antagonistic activity over a wide dose range (0.011 to 0.93 mg/kg).[27] Subcutaneous risperidone additionally inhibited apomorphine-induced emesis in the dog (ED_{50} = 0.006 mg/kg), exhibiting a potency 2 to 4 times greater than that of haloperidol.[23] Catalepsy, which is a characteristic response to neostriatal dopamine receptor antagonism,[1] and may therefore be considered predictive of extrapyramidal actions, was induced in the rat by relatively high doses of risperidone (ED_{50} = 3 mg/kg subcutaneously or 6.3 mg/kg orally).[23,28]

In drug discrimination tests in the rat, risperidone 0.3 to 2.5 mg/kg produced potent antagonism of the discriminative stimulus properties of lysergide (serotonin 5-HT_2-mediated) and *d*-amphetamine (dopamine D_2-mediated).[29,30] In this respect, risperidone resembles the other centrally acting combined serotonin 5-HT_2 and dopamine D_2 receptor antagonists pirenperone and setoperone, although it is more potent and longer acting.

Drug-induced suppression of conditioned avoidance behaviour, which is considered predictive of antipsychotic activity,[31] has been demonstrated during acute risperidone administration in the monkey,[32] dog[33] and rat.[23,28] Inhibition of schedule-controlled behaviours in the rat was seen with risperidone at doses 4 to 14 times higher than the corresponding doses of haloperidol.[23]

The xylazine-induced loss of the righting reflex in the rat was inhibited by subcutaneous risperidone (ED_{50} = 2.35 mg/kg), indicating central α_2-adrenergic activity.[23] Risperidone was devoid of anticholinergic, narcotic analgesic, and anticonvulsant effects *in vivo*.[23]

Risperidone (0.025 to 0.25 mg/kg intramuscularly), in contrast to clozapine (1 to 25 mg/kg), produced dose-related acute dystonia in the cebus monkey, displaying similar dystonic potency/liability to haloperidol.[33] This would suggest that, contrary to previous suggestions,[34] pronounced serotonin 5-HT_2 antagonism in relation to dopamine D_2 antagonism does not offer protection against extrapyramidal syndromes, at least in the nonhuman primate.

1.2.2 Effects on Sleep

Sleep abnormalities similar to those associated with depression, including impaired sleep continuity, reduced rapid eye movement (REM) sleep latency, and diminished slow-wave sleep, have been reported in schizophrenia.[35] Ganguli and coworkers[36] observed a significant inverse correlation, which was independent of the presence of depression, between slow-wave sleep and negative symptoms in non-medicated patients with schizophrenia. Experience with the selective serotonin 5-HT_2 antagonist ritanserin indicates that serotonin 5-HT_2 receptor blockade promotes slow-wave sleep;[37] indeed, ritanserin has demonstrated efficacy in patients with dysthymic disorders.[38]

In rats, low doses of risperidone (0.01 to 0.06 mg/kg intraperitoneally) significantly increased slow-wave sleep and decreased wakefulness; doses in excess of 0.63 mg/kg had the opposite effect, probably as a result of increasing dopaminergic blockade.[39] In healthy volunteers, single oral dose administration of risperidone 2mg did not appear to affect slow-wave sleep, although computerised analysis of electroencephalographic delta waves suggested a change in sleep architecture similar to that seen with ritanserin.[40] A dose- and duration-dependent restoration of sleep patterns and improved sleep efficiency were reported in 10 chronic schizophrenic patients treated with risperidone 5 to 10 mg/day

for 2-week periods.[41] Similarly, 3 of 4 patient-rated sleep parameters (quality, latency, and maintenance of sleep) improved more with risperidone (mean dosage 12 mg/day) than with haloperidol (mean dosage 10 mg/day) in 44 patients with chronic schizophrenia.[42]

1.3 Neuroendocrine Effects

Dopamine secreted into the portal hypophyseal circulation is believed to be the major modulator of prolactin release from the anterior pituitary. Antagonism of dopamine D_2 receptors in the tuberoinfundibular tract blocks tonic inhibitory control of prolactin secretion from the pituitary, resulting in increased plasma prolactin levels.[43] Consequently, hyperprolactinaemia is a recognised response to typical antipsychotics.

In keeping with its lower striatal dopamine D_2 receptor binding affinity, risperidone was one-third as potent as haloperidol in reversing dopamine-induced suppression of prolactin release from rat anterior pituitary cells *in vitro*.[44] *In vivo*, however, risperidone was 3 to 5 times more potent than haloperidol in elevating plasma prolactin levels in the rat; this apparent enhancement of the drug's stimulatory effect on prolactin release was attributed to the high plasma concentrations of risperidone and its active metabolite, 9-hydroxy-risperidone.[44]

After single oral (≤ 4mg) or intramuscular (≤ 1mg) dose administration of risperidone to healthy volunteers prolactin levels increased 5- to 10-fold within 1 to 4 hours before returning to basal levels after 5 to 24 hours[45] (data on file, Janssen Pharmaceutica). In patients with schizophrenic disorders, sustained increases in plasma prolactin levels of similar magnitude were observed during short term (4 weeks) administration of risperidone 2 to 25 mg/day and were reversed upon treatment withdrawal.[46,47] Elevation of plasma prolactin can be associated with galactorrhoea, disruption of the ovulatory cycle or frank amenorrhoea.

At therapeutic doses, risperidone had no significant effect on plasma levels of triiodothyronine, thyroid stimulating hormone, growth hormone, follicle stimulating hormone, luteinising hormone, testosterone, progesterone, or cortisol).[42,47,48]

1.4 Haemodynamic Effects

The cardiovascular effects of risperidone reflect its α-adrenergic blocking activity. A dose-proportional decrease in blood pressure with reflex tachycardia was observed in healthy volunteers following single oral dose administration of risperidone 1 to 4mg, and orthostatic hypotension occurred at the highest dose (data on file, Janssen Pharmaceutica). However, physiological adaptation to α-adrenoceptor antagonism is rapid, and repeated administration of risperidone 1 mg/day to healthy volunteers for 1 to 3 weeks was not associated with significant haemodynamic changes (data on file, Janssen Pharmaceutica).

Patients with schizophrenia appear to be more tolerant to the hypotensive effects of risperidone than healthy volunteers, and clinically significant hypotension has not been observed during clinical trials with this drug.[42,49,50]

Electrocardiographic studies did not reveal any clinically significant abnormalities of cardiac conductance during repeated administration of risperidone.[46-48]

2. Pharmacokinetic Properties

The pharmacokinetics of risperidone have been investigated by the manufacturer in healthy volunteers and in a limited number of patients with schizophrenic disorders, and the following information, unless otherwise indicated, refers to unpublished findings (data on file, Janssen Pharmaceutica).

Plasma concentrations of risperidone and the active moiety (risperidone plus 9-hydroxy-risperidone) have been determined predominantly by radioimmunoassay (detection limit 0.1 to 0.2 μg/L)[51] or high performance liquid chromatography (detection limit 1 to 2 μg/L).[52,53]

Risperidone is extensively metabolised and its major metabolite, 9-hydroxy-risperidone, displays similar pharmacological activity to the parent drug.[44] Oxidative metabolism of risperidone is

subject to genetic polymorphism of the debrisoquine-type, mediated by cytochrome CYP2D6 (cytochrome P450-IID6). Thus, some individuals are extensive metabolisers (approximately 90% of the Caucasian and 99% of the Oriental populations), while others are intermediate or poor metabolisers of risperidone. The therapeutically active moiety is essentially represented by the sum of risperidone plus 9-hydroxy-risperidone. Pharmacokinetic parameters for both compounds are summarised in table II.

2.1 Absorption and Plasma Concentrations

Orally administered risperidone is well absorbed, reaching peak plasma concentrations within 2 hours. The absolute oral bioavailability of risperidone in extensive metabolisers is approximately 66%, reflecting moderate first-pass metabolism, while the corresponding figure in poor metabolisers is 82%.[45] Irrespective of metabolic status, the absolute oral bioavailability of the active moiety is 100%.[45] Oral absorption of the drug is not affected by food.[54]

Plasma concentrations of risperidone, 9-hydroxy-risperidone, and the active moiety were linearly related to dosage (≤ 25 mg/day) in 17 psychiatric patients. The mean steady-state trough concentration of risperidone was 0.46 μg/L per mg dose; the corresponding value for the active moiety was 6.64 μg/L per mg dose.

2.2 Distribution

Risperidone and its metabolites are rapidly and extensively distributed within the body. Tissue radioactivity levels in rat liver, gastrointestinal tissues, pituitary and kidney are 5 to 10 times higher than plasma levels following administration of [^{14}C]risperidone. In the rat brain risperidone and 9-hydroxy-risperidone showed a preferential distribution to the frontal cortex and striatum, and the elimination half-lives of both compounds from these brain areas were 3 to 5 times longer than from plasma.[55]

Plasma protein (predominantly albumin and α_1-acid glycoprotein) binding of risperidone and 9-hydroxy-risperidone is 90 and 77%, respectively, at plasma concentrations ranging from 0.5 to 200 μg/L.[56] The apparent volume of distribution of risperidone at steady-state is approximately 1.1 L/kg, independent of metabolic status.[45]

Placental transfer of risperidone and 9-hydroxy-risperidone is very low in rats, but both compounds appear in breast milk of dogs at concentrations equal to or greater than plasma levels. Information on the placental transfer and mammary excretion of risperidone in humans is currently lacking.

2.3 Metabolism and Excretion

The main metabolic pathways of risperidone in humans are hydroxylation and oxidative N-dealkylation (fig. 2). After single oral dose administration of [^{14}C]risperidone to healthy volunteers, unchanged drug and 9-hydroxy-risperidone represent 10 and 70% of plasma radioactivity, respectively, in extensive metabolisers as compared with 71% for risperidone and negligible quantities for the metabolite in poor metabolisers.[57]

The primary route of excretion of 9-hydroxy-risperidone is urinary. Over a 1-week period following oral risperidone administration about 70% of the administered dose was recovered in the urine and 15% in the faeces.[57] In extensive metabolisers 9-hydroxy-risperidone was the dominant urinary species, accounting for 31% of the administered dose, followed by acid metabolites of risperidone and 9-hydroxy-risperidone, 7-hydroxy-risperidone and unchanged risperidone (each accounting for ≈ 5%), and glucuronide metabolites (≈ 3%).[57]

The mean total body clearance of orally administered risperidone in healthy young volunteers was 7-fold higher among extensive metabolisers than among poor metabolisers (394 *vs* 54 ml/min), reflecting the large contribution made by metabolic (nonrenal) clearance in the former group.[45] However, the more efficient clearance of risperidone in extensive metabolisers is compensated by the appearance of 9-hydroxy-risperidone, which, with its predominantly renal pattern of excretion, shows a clearance similar to that of risperidone in poor metabolisers.[45] Consequently, the pharmacokinetics

Table II. Pharmacokinetic parameters of risperidone (R) and 9-hydroxy-risperidone (9HR) in different populations after administration of a single 1mg oral dose of risperidone

Reference	Subjects (no.)	Drug/ metabolite	t_{max} (h)	C_{max} (μg/L)	$t_{1/2\beta}$ (h)	$AUC_{0-\infty}$ (μg.h/L)	CL_R (L/h/1.73m^2)
Ishigooka et al.[48]	Young volunteers (6)	R	4.3	2.9	4.0	19.0	
		9HR	10.0	2.8	15.5	74.1	
Huang et al.[45]	Young volunteers:						
	extensive metabolisers (9)	R	0.8	7.9	2.8	32.0	0.45[a]
		9HR	3.2	6.5	20.5	161	2.4[a]
	poor metabolisers (2)	R	1.3	16.5	16.2	386	0.9[a]
		9HR	3.6	1.0	24.6	42.6	3.0[a]
Data on file, Janssen Pharmaceutica	Young volunteers (8)	R	1.0	5.3	2.9	23.5	1.58
		9HR	3.0	4.3	16.5	98.7	3.64
	Elderly volunteers (12)	R	1.0	6.4	3.3	26.2	1.14
		9HR	2.0	5.0	23.4*	150*	2.99
	Liver disease (8)	R	1.0	8.2	4.0	35.9	1.88
		9HR	6.5*	2.4*	17.9	88.2	4.06
	Moderate renal insufficiency[b] (7)	R	1.0	9.6*	5.1	65.8*	0.97
		9HR	5.0	5.2	27.2*	220*	1.02*
	Severe renal insufficiency[c] (7)	R	1.0	9.7	3.2	48.6	0.33*
		9HR	5.0	5.6	33.6*	257*	0.67*

a Renal clearance expressed in L/h.

b Creatinine clearance 30-60 ml/min/1.73m^2.

c Creatinine clearance 10-29 ml/min/1.73m^2.

Abbreviations and symbols: AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration; CL_R = renal clearance; t_{max} = time to C_{max}; $t_{1/2\beta}$ = plasma elimination half-life; * $p < 0.05$ compared with young healthy controls.

of the active moiety is largely independent of metabolic status.[45]

The mean plasma elimination half-lives ($t_{1/2\beta}$) of risperidone and 9-hydroxy-risperidone are 2.8 and 20.5 hours, respectively, in extensive metabolisers,[45] while that of the active moiety (based on the decline in plasma radioactivity after oral administration of [^{14}C]risperidone) is approximately 24 hours.[57] Although the mean $t_{1/2\beta}$ of risperidone is prolonged to 16 hours in poor metabolisers,[45] the $t_{1/2\beta}$ of the active moiety remains virtually unchanged at 22 hours.[57]

2.4 Effects of Age and Disease States

The pharmacokinetics of risperidone in healthy elderly volunteers and in patients with moderate or severe renal insufficiency or liver disease have been compared with those in healthy young volunteers (data on file, Janssen Pharmaceutica) [table II]. The renal clearances of 9-hydroxy-risperidone and the active moiety were reduced by ≈ 70 to 80% in patients with impaired renal function, while oral clearance of the active moiety was reduced by ≈ 30% in the elderly and by ≈ 55% in renally impaired patients. As a consequence, the mean plasma elimination half-life of the active moiety was extended from 18.7 hours in healthy young volunteers to 24.3 hours in the elderly and 25.3 and 29 hours, respectively, in patients with moderate and severe renal impairment. The pharmacokinetics of risperidone in patients with liver disease were similar to those in healthy individuals, although the free fraction of risperidone in plasma was increased in the former group as a result of decreased levels of albumin and α_1-acid glycoprotein.[56] These results suggest that it may be appropriate to reduce risperidone dosage in the elderly and in those with renal impairment. Dosage reduction may also be prudent in patients with hepatic dysfunction until more extensive experience with risperidone in this population is acquired.

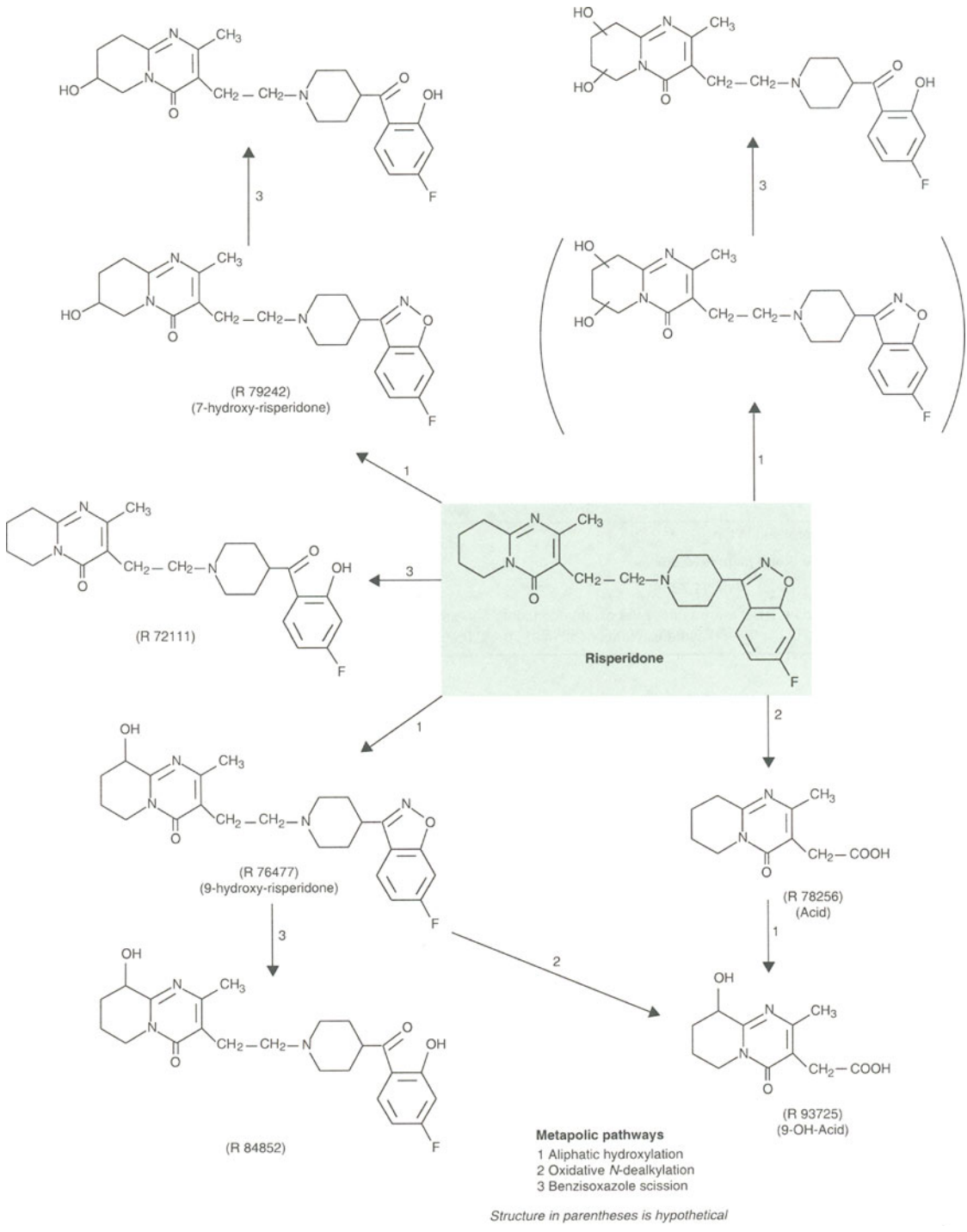

Fig. 2. Metabolic pathways of risperidone in humans.[57]

2.5 Drug Interactions

Several drugs evaluated *in vitro* show potential to interfere with the metabolism of risperidone because they compete for or bind to cytochrome CYP2D6. Limited observations *in vivo* indicate that patients co-medicated with thioridazine, amitriptyline, desipramine, thiethylperazine or metoprolol, which are substrates of cytochrome CYP2D6,[58] behave as if they were slow metabolisers of risperidone. The clinical significance of these findings is probably minimal, however, since the changes in concentration of risperidone and its equiactive metabolite are inversely proportional and there is little net effect on the concentration of the active moiety.

3. Therapeutic Use in Schizophrenia

Clinical evaluation of risperidone has proceeded through nonblind noncomparative trials, including 1 published long term study, to double-blind comparisons with both typical and atypical neuroleptics. The general schizophrenic population (diagnostic criteria DSM-IIIR of the American Psychiatric Association) is represented in these trials, as well as patients with schizodepressive disorder and psychotic major depression. Several trials involved patients with acute exacerbation of psychotic symptoms, but the largest trials evaluated risperidone predominantly in patients with chronic illness. A number of these patients were undergoing *de novo* antipsychotic treatment with risperidone, while others had residual symptoms unresponsive to available antipsychotic agents and/or were intolerant of current neuroleptics. Demonstration of antipsychotic efficacy in this latter group of patients addresses two important limitations of current therapies, namely the relative lack of effect on negative symptoms and induction of extrapyramidal symptoms.

Risperidone therapy was uniformly preceded by a short (generally 1-week) placebo washout period, during which previous antipsychotic treatment (predominantly phenothiazines, butyrophenones and thioxanthenes, where specified) was withdrawn. During trials of risperidone, patients were generally permitted use of short-acting benzodiazepines for sedation and anticholinergics (usually benzatropine, ethybenztropine, orphenadrine or dexetimide) for control of extrapyramidal symptoms. Clinical response was evaluated using several rating scales designed to score specific psychiatric items or to grade global response, including the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impressions (CGI) scale, the Scale for Assessment of Negative Symptoms (SANS), and the Positive and Negative Syndrome Scale for Schizophrenia (PANSS). The Simpson and Angus Rating Scale (SARS) and the Extrapyramidal Symptom Rating Scale (ESRS) were commonly employed to evaluate extrapyramidal symptoms.

Risperidone shows evidence of a curvilinear ('inverted-U') dose-response relationship over the range 1 to 16 mg/day, with maximum antipsychotic activity apparently occurring at dosages of 4 to 8 mg/day.[59-61] Studies incorporating individualised dose titration regimens support this finding, although the relative absence of adverse reactions to risperidone during the initial titration phase of these trials has tended to encourage escalation toward the upper end of this range.[42,62,63] Sedation and extrapyramidal symptoms appear to be more prevalent at these higher dosages and may, thus, adversely influence the scoring of negative symptoms such as anergia.[42,47]

3.1 Noncomparative Studies

Short term (4 to 8 weeks) oral monotherapy with risperidone at maintenance dosages generally within the range of 2 to 10 mg/day (although extending as high as 20 or 25 mg/day in isolated studies) produced a steady improvement in weekly total BPRS score, resulting at final evaluation in a decrease of 14 to 37% in total BPRS score compared with baseline.[46,47,49,50,64-68] Caution is nevertheless required in interpreting these findings, as statistically significant reductions of similar magnitude (20 to 30%), particularly with respect to negative symptoms of schizophrenia, are regularly seen in response to placebo.[69,70] Significant im-

provements in CGI scores,[49,50,66,71] SANS global and subscale scores[46] and PANSS subscale scores[65] were also noted with risperidone from week 1 or 2 onwards. Improvement was seen in all types of symptom clusters, including the BPRS factors anergia, thought disturbance, anxiety-depression, activation and hostility,[46,47,50,65] as well as depressive symptoms in combined acute psychotic and depressive syndrome.[72]

Follow-up of patients with chronic schizophrenia (n = 111) who received risperidone monotherapy for up to 12 months indicated that the initial reduction in total BPRS score observed during the first 4 weeks of treatment was subsequently maintained (fig. 3),[67] although the absence of a control group precludes assessment of the drug's long term efficacy in this spontaneously remitting condition.

Despite the withdrawal of antiparkinsonian medication prior to initiation of risperidone therapy, a significant decrease in SARS score was reported in several studies,[49,50] while others reported a lower incidence of extrapyramidal symptoms and a decreased need for antiparkinsonian medication as compared with prior neuroleptic treatments.[64,66,67]

3.2 Comparisons with Placebo

A single-blind 4-week crossover comparison of risperidone 2 to 6 mg/day and placebo in patients with chronic schizophrenia and tardive dyskinesia (n = 10) who were concomitantly maintained on their pre-existing neuroleptic therapy (predominantly haloperidol or chlorpromazine) noted significant improvements in total BPRS and Hamilton Depression Rating Scale (HDRS) scores on addition of risperidone, and a tendency for a greater decrease in SANS and State Trait Anxiety Inventory-X1 (STAI-X1) scores with risperidone than with placebo.[73] Similarly, risperidone 2 to 10 mg/day (mean 9.7 mg/day) produced a significantly greater reduction in total BPRS and CGI scores than placebo at treatment end-point in a 6-week study in patients with acute exacerbation of chronic schizophrenia (n = 12).[62]

Confirmation of these preliminary findings is provided by the results of a recent large scale North American comparative investigation employing fixed doses of risperidone and placebo in schizophrenic patients (n = 523). The US component of this study, involving 388 patients with either acute or chronic schizophrenia, demonstrated significant superiority of risperidone 6 to 16 mg/day over placebo on total PANSS, PANSS positive symptom, PANSS-derived BPRS and CGI scores, and of risperidone 6 and 16 mg/day on PANSS negative symptom score, after 8 weeks' treatment.[60] As a result, the proportion of patients showing a clinical improvement (defined as a $\geq 20\%$ reduction in total PANSS score) at treatment end-point was significantly higher with risperidone 6 mg/day (57%), 10 mg/day (40%) and 16 mg/day (51%) than with placebo (22%). The rate of premature treatment discontinuation because of lack of efficacy was accordingly lower in recipients of risperidone 6 mg/day (17%) than in placebo recipients (62%). These findings closely mirror those of the Canadian arm of this study (n = 135), which found risperidone, at the optimal dosage of 6 mg/day, to be significantly more effective than placebo on all outcome measures employed, including total PANSS, PANSS positive, negative and general psychopathology subscales, PANSS-derived BPRS, CGI-Improvement and CGI-Severity of Illness scores.[59]

3.3 Comparisons with Other Antipsychotics

Although limited by brief washout periods and short treatment durations, comparative therapeutic studies in patients with schizophrenia suggest that risperidone is at least as effective as established antipsychotic agents (table III), and that it may offer advantages in terms of its rapidity of onset of action, possible efficacy against negative symptoms, and relative absence of extrapyramidal effects.

3.3.1 Haloperidol

Several small scale comparative trials of 6 to 12 weeks' duration, employing flexible dose-titration regimens, have demonstrated improvements in BPRS, CGI, PANSS, and Schedule for Affective

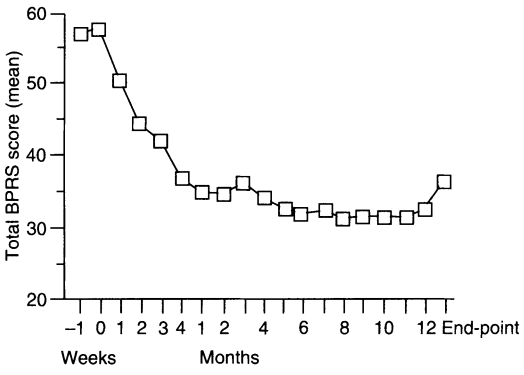

Fig. 3. Change in total Brief Psychiatric Rating Scale (BPRS) score during long term (≤ 12 months) nonblind therapy with risperidone 0.5 to 22.5 mg/day (mean maintenance dosage 8.2 mg/day) in schizophrenic patients (n = 111).[67]

Disorders and Schizophrenia - Change Version (SADS-C) scores with risperidone 2 to 20 mg/day in patients with chronic schizophrenia[42,63,75] or acute exacerbation of chronic schizophrenia.[62,74] In the study by Claus and colleagues,[42] patients treated with haloperidol 2 to 20 mg/day (mean maintenance dosage 10.3 mg/day) showed no significant improvement on any of the rating scales employed [CGI, PANSS, SADS-C, Nurses' Observation Scale for Inpatient Evaluation (NOSIE-30)], suggesting that the study population was treatment-resistant at this dosage level of haloperidol, whereas those treated with risperidone 2 to 20 mg/day (mean maintenance dosage 12 mg/day) displayed a modest but statistically significant improvement at end-point evaluation on all but the PANSS negative symptom subscale. The improvement in total SADS-C score was significantly greater in risperidone than in haloperidol recipients, whereas the changes in PANSS (total, positive, negative and general psychopathology subscale scores) and NOSIE-30 scores did not differ significantly between the 2 treatment groups. The BPRS factors of thought disturbance (representative of positive symptoms) and anergia (representative of negative symptoms) improved markedly during the first 4 weeks of dosage titration with risperidone 2 to 20 mg/day in patients with chronic schizophrenia; after 8 weeks of treatment the improvements were similar with risperidone and haloperidol 2 to 20 mg/day.[63]

In patients with acute exacerbation of chronic schizophrenia, sustained and significant reductions in total BPRS score were obtained during 6 and 8 weeks' treatment with risperidone 2 to 20 mg/day (mean maintenance dosage 9.7 mg/day; mean maximal dosage 9.5 mg/day) and haloperidol 2 to 20 mg/day (mean maintenance dosage 18.0 mg/day; mean maximal dosage 9.9 mg/day).[62,74] The time course of the reduction in total BPRS score was similar with the 2 treatments, although a significant reduction in this parameter occurred earlier with risperidone (after 1 week) than with haloperidol (after 3 weeks) in one of the studies.[62] Patient response rates [i.e. those achieving complete remission[74] or a ≥ 20% reduction in total BPRS score[62] at treatment end-point] were either identical with the 2 treatments (45%)[74] or tended to be higher with risperidone than with haloperidol (57 *vs* 25%).[62] However, neither risperidone nor haloperidol had a significant effect on negative symptoms, as measured on the SANS scale.[62] Analysis of the response of individual BPRS items to short term antipsychotic therapy indicated that haloperidol 2 to 20 mg/day was effective against all items, whereas risperidone 2 to 20 mg/day was ineffective against items of grandiosity, motor retardation, excitability and disorientation.[74] Despite similar reductions in total BPRS score with risperidone and haloperidol, haloperidol had a significantly greater effect on the BPRS anxiety-depression factor and the BPRS items of anxiety and guilt feelings.[74]

Comparisons of risperidone and haloperidol additionally include 2 multicentre double-blind North American and European studies employing fixed-dose regimens in 523 and 1362 patients with predominantly chronic schizophrenia.[59-61] The results of these studies should, however, be interpreted with caution, since each study compared multiple doses of risperidone with only a single dose of haloperidol. In addition, the choice of a relatively high haloperidol dose (20mg) for the North

Table III. Summary of randomised, double-blind, comparative clinical studies of risperidone (RIS) in patients with schizophrenia

Reference	Schizophrenia status	No of patients	Daily dose (mg)	Duration (weeks)	Results			
					rating scale	overall efficacy	rating scale	extrapyramidal effects
Haloperidol (HAL)								
Borison et al.[62]a	acute-on-chronic	36	RIS 2-10 HAL 4-20	6	BPRS, CGI, SANS	RIS ≥ HAL	ESRS, AIMS	RIS < HAL
Češková & Švestka[74]	acute-on-chronic	62	RIS 2-20 HAL 2-20	8	BPRS	RIS ≡ HAL		RIS ≤ HAL
Chouinard et al.[59]b	chronic	135	RIS 2 RIS 6 RIS 10 RIS 16 HAL 20	8	PANSS, CGI, BPRS	RIS ≡ HAL RIS > HAL RIS ≡ HAL RIS ≡ HAL	ESRS	RIS < HAL RIS < HAL RIS ≡ HAL RIS < HAL
Claus et al.[42]	chronic	44	RIS 2-20 HAL 2-20	12	PANSS, SADS-C, CGI, NOSIE-30	RIS ≥ HAL	ESRS	RIS ≡ HAL
De Cuyper[63]	chronic	43	RIS 2-20 HAL 2-20	8	BPRS, CGI, NOSIE-30	RIS ≡ HAL	ESRS	RIS < HAL
Marder & Meibach[60]b	acute/chronic	388	RIS 2 RIS 6 RIS 10 RIS 16 HAL 20	8	PANSS, CGI, BPRS	RIS ≡ HAL RIS > HAL RIS ≡ HAL RIS > HAL	ESRS	RIS ≤ HAL RIS ≤ HAL RIS ≤ HAL RIS ≤ HAL
Min et al.[75]	chronic	35	RIS 5-10 HAL 5-10	8	PANSS, CGI, BPRS	RIS ≤ HAL	ESRS,UKU	RIS ≤ HAL
Perphenazine (PPZ)								
Høyberg et al.[76]	acute-on-chronic	107	RIS 5-15 PPZ 16-48	8	PANSS, BPRS, CGI	RIS ≥ PPZ	ESRS, UKU	RIS ≡ PPZ
Clozapine (CLZ)								
Heinrich et al.[77]c	acute-on-chronic	59	RIS 4 or 8 CLZ 400	4	BPRS, CGI	RIS ≡ CLZ	SARS	RIS ≡ CLZ

a Three-arm study including 2 active treatment groups and 1 placebo group.

b Six-arm study including 5 active treatment groups and 1 placebo group.

c Patients were not specified as having been selected on the basis of established treatment-resistance to classic antipsychotics.

Abbreviations and symbols: AIMS = Abnormal Involuntary Movement Scale; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions scale; ESRS = Extrapyramidal Symptom Rating Scale; NOSIE-30 = Nurses' Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Syndrome Scale; SADS-C = Schedule for Affective Disorders and Schizophrenia - Change Version; SANS = Scale for Assessment of Negative Symptoms; SARS = Simpson and Angus Rating Scale; UKU = UKU Side Effect Rating Scale; ≡ indicates similar effect; ≤ indicates tendency towards lesser effect; < indicates statistically significant lesser effect ($p < 0.05$); ≥ indicates tendency towards greater effect; > indicates statistically significant greater effect ($p < 0.05$).

American study can be criticised on the grounds that this may have inadvertently introduced bias in favour of risperidone, since the parkinsonian symptoms associated with high dose antipsychotics are readily mistaken for negative symptoms such as blunted affect, emotional withdrawal and lack of spontaneity.

Recently published findings from the US arm of the North American study, in which hospitalised patients (n = 388) were randomised to treatment with placebo, risperidone 2, 6, 10 or 16 mg/day, or haloperidol 20 mg/day for 8 weeks, indicated that risperidone 6 mg/day (the dosage producing the greatest improvement in positive and negative symptoms) was significantly superior to haloperidol 20 mg/day with respect to the improvement in total PANSS score (17 *vs* 4% reduction) and PANSS-derived BPRS score (18 *vs* 6% reduction), and tended

to be superior on PANSS positive and negative symptom and CGI scores.[60] Clinical improvement (defined as a ≥ 20% reduction in total PANSS score) was achieved in a significantly higher proportion of risperidone recipients (57% receiving 6 mg/day and 51% receiving 16 mg/day) than haloperidol recipients (30%) at treatment end-point. Furthermore, the improvement in total PANSS score tended to occur earlier with risperidone 6 or 16 mg/day (after 1 week) than with haloperidol (after ≈ 4 weeks).

Subgroup analysis of total PANSS scores indicated that, in contrast to haloperidol, which was effective (*vs* placebo) only in recently (≤ 1 month) hospitalised patients, risperidone 6 mg/day was effective across all categories, including those hospitalised long term (≥ 6 months).[60] Insofar as long term hospitalised patients are often unresponsive to conventional antipsychotics (a premise supported in this case by the lack of response to haloperidol), this finding raises the possibility that risperidone might be of benefit in treatment-resistant schizophrenia.

A parallel evaluation of the results of the Canadian contingent of this study, comprising 135 patients who were considered to be poorly responsive to standard antipsychotic therapy, is also available.[59] Risperidone 6 mg/day proved significantly superior to haloperidol 20 mg/day on most efficacy parameters, including total PANSS, PANSS general psychopathology, PANSS-derived BPRS, and CGI-Improvement and Global Evaluation scores, and tended to be superior on the PANSS positive and negative symptom scores (fig. 4). The response rate (percentage of patients showing ≥ 20% reduction in total PANSS score) also tended to be higher with risperidone 6 mg/day (73%) than with haloperidol 20 mg/day (48%) at treatment end-point. Moreover, the clinical improvement in patients treated with risperidone 6 mg/day was evident from the first week onwards, whereas that with haloperidol was delayed until the end of the second week.

In the larger 15-nation European trial, in which patients with chronic schizophrenia (n = 1362) were randomised to treatment with risperidone 1, 4, 8, 12 or 16 mg/day, or haloperidol 10 mg/day for 8 weeks, risperidone 4 and 8 mg/day proved to be the optimal therapeutic dosages, producing the greatest improvements in total PANSS score.[61] Patient response rates (≥ 20% reduction in total PANSS score) were similar with risperidone 4 and 8 mg/day (63 to 66%) and haloperidol 10 mg/day (58%) [data on file, Janssen Pharmaceutica]. Among the subset of patients with prominent anxiety and depression (BPRS anxiety/depression cluster score ≥ 10), risperidone 4 and 8 mg/day demonstrated significant superiority over haloperidol 10 mg/day with respect to the improvement in total PANSS, PANSS general psychopathology, total BPRS, and BPRS activity and anxiety/depression scores.[61]

3.3.2 Perphenazine

A recent double-blind 8-week Scandinavian study indicated that risperidone 5 to 15 mg/day (mean maintenance dosage 8.5 mg/day) was at least as effective as perphenazine 16 to 48 mg/day (mean maintenance dosage 28 mg/day) in the treatment of patients with acute exacerbation of chronic schizophrenia (n = 107).[76] While the two drugs produced comparable improvements in total PANSS, PANSS subscale (positive, negative and general psychopathology), PANSS-derived BPRS, BPRS factor (activity, anergia, anxiety/depression and thought disturbances) and CGI scores, the proportion of patients showing a ≥ 20% reduction in total BPRS score was significantly higher with risperidone than with perphenazine (78 *vs* 59%). Risperidone also showed a significant advantage over perphenazine in terms of the improvement in BPRS anxiety factor score. Among the subgroup of patients with predominantly negative symptoms (n = 76), risperidone was significantly superior to perphenazine with respect to the proportion of patients showing clinical improvement (defined as a ≥ 20% reduction in total BPRS score or total PANSS score) [76 or 78% *vs* 53%].

3.3.3 Clozapine

Risperidone and clozapine have been compared under randomised double-blind conditions, albeit

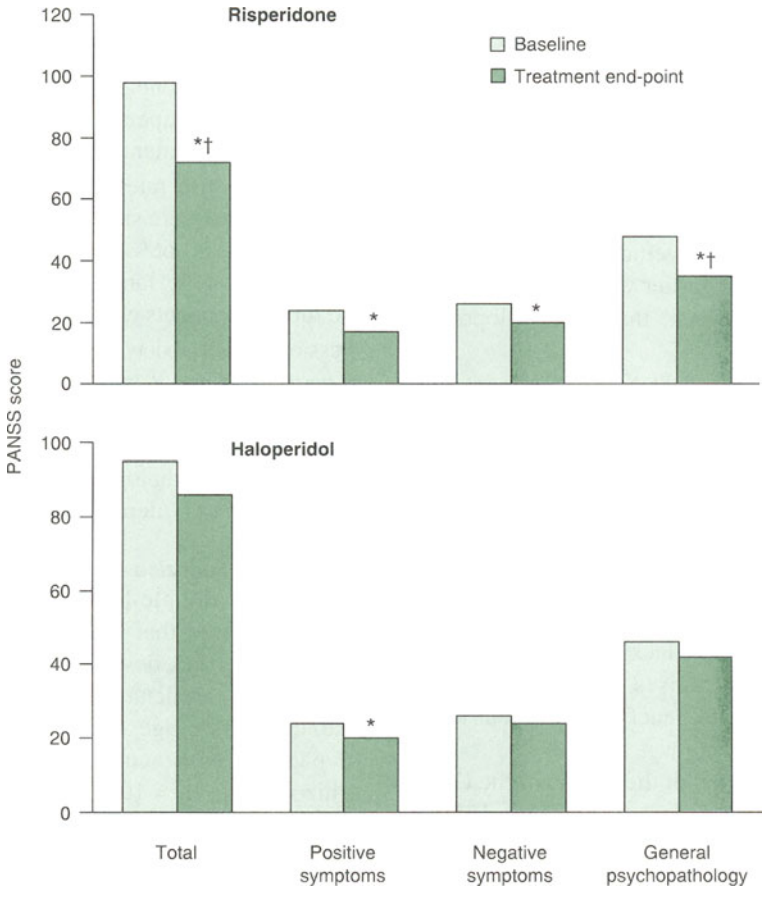

Fig. 4. Therapeutic responses to risperidone 6 mg/day (n = 22) and haloperidol 20 mg/day (n = 21) during a randomised double-blind comparative trial in chronic schizophrenia. Responses are expressed in terms of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score and subscale scores at baseline and at treatment end-point; * $p < 0.01$ *vs* placebo, † $p < 0.05$ *vs* haloperidol.[59]

in a population which was not known to be unresponsive to conventional antipsychotics. Since use of clozapine is currently restricted to treatment-resistant schizophrenia, the clinical relevance of this comparison is questionable. Clozapine 400 mg/day and risperidone 4 or 8 mg/day were of comparable therapeutic efficacy in patients with acute schizophrenia and prominent paranoid features (n = 59), producing similar decreases in total BPRS and BPRS subscale scores after 4 weeks' double-blind treatment.[77] At treatment endpoint, identical proportions of risperidone (4 mg/day) and clozapine recipients (60%) exhibited a moderate or marked clinical improvement (assessed in terms of CGI rating).

4. Tolerability

The adverse effect profile of risperidone reflects its known activity at central adrenergic, histaminergic, serotonergic and dopaminergic receptors. Overall the drug is well tolerated and has a low propensity to induce extrapyramidal symptoms. The more common adverse events reported among risperidone (≤ 10 mg/day) recipients in North

American comparative trials included insomnia (26% of patients), agitation (22%), extrapyramidal symptoms (17%), dizziness (14%), anxiety (12%) and rhinitis (10%) [data on file, Janssen Pharmaceutica] (table IV). In addition, sedation has been documented in up to 30% of risperidone recipients in clinical trials. It should be emphasised that several of these symptoms are commonly encountered in schizophrenic patients and are therefore difficult to ascribe to risperidone. In the US arm of the North American study, patient-elicited symptoms of fatigue, sedation, ocular disturbances, orthostatic dizziness, palpitations, weight gain, diminished sexual desire and erectile dysfunction were positively and significantly related to risperidone dose.[60] Adverse events serious enough to necessitate drug withdrawal occurred in 8% of 1294 inpatients with chronic schizophrenia treated with risperidone 1 to 16 mg/day (data on file, Janssen Pharmaceutica).

Table IV. Incidences of the more common adverse effects of risperidone ≤ 10 mg/day (mode), haloperidol ≤ 20 mg/day, and placebo in North American clinical trials (data on file, Janssen Research Foundation)

Adverse effect	Risperidone (n=324) [%]	Haloperidol (n=140) [%]	Placebo (n=142) [%]
Insomnia	26	26	19
Agitation	22	23	20
Extrapyramidal symptoms	17	39	16
Headache	14	11	12
Anxiety	12	14	9
Rhinitis	10	3	4
Constipation	7	6	3
Nausea	6	3	3
Dyspepsia	5	4	4
Vomiting	5	5	4
Dizziness	4	1	1
Abdominal pain	4	1	0
Cough	3	1	1
Tachycardia	3	1	0

4.1 Extrapyramidal Symptoms

Extrapyramidal symptoms are believed to arise from dopaminergic blockade in the striatal areas of the brain that influence motor control. Although the reported incidence of extrapyramidal symptoms is probably related to the assiduousness with which they are sought, there is no doubt that they represent a major impediment to patient compliance and clinical recovery.[78,79]

The severity of extrapyramidal symptoms in patients treated with risperidone is linearly related to daily dose over the range 1 to 16mg; at therapeutic dosages of 4 to 8 mg/day the severity is comparable to that seen with placebo[59,60,62] and clozapine 400 mg/day,[77] and significantly less than that associated with haloperidol 10 or 20 mg/day.[42,61-63] Similarly, the severity of parkinsonian symptoms, as assessed on the parkinsonism subscale of the ESRS, is linearly related to risperidone dosage over this range, and at low dosages (≤ 10 mg/day) tends to be less marked than that seen with haloperidol 20 mg/day.[59,60] Moreover, the requirement for antiparkinson medication to manage extrapyramidal symptoms is substantially less in risperidone recipients than in haloperidol-treated patients[42,59,60,62,63,74] and similar to that in perphenazine recipients.[76] Risperidone is reported to have an antidyskinetic action, as measured on the ESRS dyskinesia severity subscale.[59,62] To date there have been 2 confirmed cases of tardive dyskinesia among more than 200 schizophrenic patients treated with risperidone for periods in excess of 1 year[66] (data on file, Janssen Pharmaceutica).

4.2 Cardiovascular Effects

Risperidone is a potent α-adrenergic antagonist. Phase I trials in healthy volunteers found poor tolerance to the α-adrenergic-mediated hypotensive effect of risperidone, limiting risperidone dosage to 2 mg/day. Patients with schizophrenia frequently exhibit postural hypotension on long term antipsychotic therapy and appear capable of tolerating considerable reductions in systolic blood pressure (≥ 40mm Hg) asymptomatically.[80] These patients appear more tolerant of risperidone-mediated hypotension than healthy volunteers, and the use of conservative dose titration schedules and divided doses may be expected to minimise the risk

of clinically important hypotension, dizziness and tachycardia.

Significant QT_c interval prolongation has been described in schizophrenic patients undergoing short term (8 weeks) therapy with risperidone 5 to 10 mg/day.[75]

4.3 Other Effects

The most frequent non-extrapyramidal and non-cardiovascular adverse effects of risperidone include somnolence, fatigue, insomnia, gastrointestinal complaints, nausea, rhinitis (probably due to α-adrenoreceptor-mediated nasal congestion) and rash[59,60,66] (data on file, Janssen Pharmaceutica). Hypersalivation appears to be significantly less of a problem with risperidone than with clozapine.[77]

Menstrual disturbances were reported in 15% of female patients entered into a Japanese study using risperidone 1 to 15 mg/day for 8 weeks.[66] Risperidone-induced increases in plasma prolactin levels could potentially cause such disturbances; breast tension and galactorrhoea have also been noted. However, these effects are uncommon and appear to occur with an equal or greater frequency in patients treated with haloperidol in controlled comparative trials. Occasional reports of diminished sexual pleasure and erectile and ejaculatory dysfunction (presumably related to the drug's adrenolytic activity) were elicited by direct questioning in risperidone-treated patients. As with menstrual disorders, these effects appear to occur with comparable frequency in risperidone- and haloperidol-treated patients, and to be less frequent in perphenazine-treated patients.[76]

Significant weight gain (1.2 kg with 2 mg/day, and 2.2 kg with 16 mg/day over 8 weeks) has been reported with risperidone. The effect appears to be related to dosage and to plateau during long term administration (data on file, Janssen Pharmaceutica). The weight gain associated with the use of risperidone doses within the assumed optimal dosage range of 4 to 8 mg/day is expected to be minimal.[76]

One case of neuroleptic malignant syndrome possibly related to risperidone has been reported on coadministration with trifluoperazine and levomepromazine, both of which have been implicated in this syndrome (data on file, Janssen Pharmaceutica).

4.4 Overdosage

There is very limited experience with deliberate overdosage of risperidone. Symptoms observed after ingestion of between 20 and 300mg variously included sedation, tachycardia, hypotension, extrapyramidal symptoms, ECG abnormalities (QT_c and QRS interval prolongation) and electrolyte disturbances[81] (data on file, Janssen Pharmaceutica). In no case was the overdosage fatal and symptoms resolved after 24 hours. Gastric lavage, administration of activated charcoal, plasma expansion and general supportive care are recommended measures in the event of acute overdosage.

5. Dosage and Administration

Risperidone has a curvilinear dose-response curve, with optimal therapeutic effect seen at a daily oral dose of 4 to 8mg. It is recommended that the dosage be titrated to 3mg twice daily over 3 days, starting at 1mg twice daily, in patients with acute or chronic schizophrenia; dosage may then be individualised. However, daily dosages above 10 mg/day do not appear to confer greater clinical efficacy but are associated with a higher incidence of extrapyramidal symptoms.

For elderly patients and patients with impaired renal function a starting dosage of 0.5 mg twice daily, increased by 0.5 mg aliquots to a total dosage of 1 or 2mg twice daily is recommended. A similar dosage schedule may be advisable in patients with hepatic disease.

6. Place of Risperidone in Therapy

The treatment of schizophrenia has benefited from the recent development of selective antagonists of central serotonergic receptors. Agents such as risperidone which combine high affinity for serotonin 5-HT_2 receptors with potent dopamine D_2 receptor antagonism may be particularly useful. Unwanted dopaminergic blockade in striatal tracts

appears to be partially overcome through serotonergic mechanisms, thereby minimising the potential for extrapyramidal symptoms, whereas potent dopaminergic blockade in mesolimbic areas remains to modulate the abnormalities of thought and behaviour which are characteristic of schizophrenia. In addition, the possible antidepressant action associated with serotonin 5-HT_2 receptor antagonism may be of value in psychotic patients with prominent depressive features.

Risperidone is a broad spectrum antipsychotic agent, effective in alleviating the positive symptoms and, to a lesser extent, the negative symptoms of schizophrenia. Whether this latter effect reflects a direct action of the drug on the persistent negative symptoms of the 'deficit state' or is merely secondary to the parallel improvement in positive symptoms remains unclear. Nevertheless, significant clinical improvement (defined as a decrease in total PANSS or BPRS score of $\geq 20\%$) is seen after short term therapy in approximately 50 to 60% of patients with acute exacerbations and in patients with chronic schizophrenia. Experience in a relatively small number of patients who have received risperidone therapy for more than 1 year suggests that clinical improvement may be maintained during long term use, although this remains to be confirmed under controlled conditions. An important issue yet to be addressed is whether risperidone is effective in the subgroup of patients who are refractory or poorly responsive to treatment with the classic antipsychotics, and for whom clozapine is currently the treatment of choice.

At therapeutic dosages, risperidone appears to be at least as effective as haloperidol and perphenazine in alleviating the symptoms of schizophrenia. Risperidone confers the advantage over haloperidol of a lower incidence of extrapyramidal symptoms, a reduced requirement for antiparkinson medication, a possible antidyskinetic effect, a marginally more rapid onset of antipsychotic action and a tendency towards greater efficacy in controlling the negative symptoms of schizophrenia. These attributes might be anticipated to improve the low patient compliance rate seen with the classic antipsychotics and thereby favourably influence long term outcome. However, multidose comparisons with other antipsychotics, in particular agents such as sulpiride and thioridazine which confer a low risk of extrapyramidal effects, are required to gauge more fully the relative merits of risperidone.

If the encouraging results of recent short term trials of risperidone are replicated on longer term therapy, and the drug's potential benefit on negative symptoms is realised, risperidone may well be regarded as an appropriate first line agent for the treatment of schizophrenia. Under these circumstances, a role can be envisaged for risperidone in the treatment of patients with prominent negative symptoms who are unresponsive to conventional antipsychotics, and those with troublesome extrapyramidal symptoms.

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