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Expected clinical benefits of paliperidone extended-release formulation when compared with risperidone immediate-release

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Background: The development of paliperidone extended release (ER) may represent a new strategy to improve the pharmacological treatment of schizophrenia. The drug maintains the atypical antipsychotic profile of its parent compound risperidone, but it is associated with an innovative delivery system (OROS technology) that offers the possibility to obtain smooth drug plasma levels using an oral antipsychotic. Clinical trials confirmed that paliperidone ER is efficacious in the management of schizophrenia and well tolerated, however no direct clinical comparisons between paliperidone ER and immediate-release formulations of risperidone have been conducted to date. *Objective*: The present study evaluates possible differences between paliperidone ER and immediate-release formulations of risperidone due to structural/molecular and delivery system diversities, providing an estimation of their significance in the context of clinical results. *Methods*: A search of Medline and EMBASE was performed using the keywords 'Risperidone', 'Paliperidone' and 'OROS technology'. *Results/conclusion*: The analysis suggests that the chemical structure and pharmacokinetic profile of paliperidone ER might provide clinical benefits in terms of efficacy, tolerability and more consistent drug response among patients, when compared with the parent compound risperidone in its immediate release formulations. The relevance of these differences is discussed, taking into account several clinical aspects involved in the drug therapy of schizophrenia.

Keywords: 9-OH-risperidone, OROS technology, paliperidone, pharmacokinetic, risperidone

Expert Opin. Drug Deliv. (2009) 6(3):319-331

1. Introduction

After more than a decade of clinical superiority, atypical antipsychotic agents are now the first choice in the treatment of schizophrenia. The so-called second generation antipsychotics have been demonstrated to provide clinical advantages over conventional medications since their improved therapeutic properties differentiate them in terms of overall positive symptom control [1-6] and amelioration of negative and cognitive symptoms [7,8]. Furthermore, certain atypical antipsychotics have been shown to be more effective in reducing relapse rates when compared with conventional antipsychotics [9,10], thus not only affirming their overall clinical superiority, but also advocating their use for the contentment of costs in the long-term therapy of psychosis [9].

Interestingly, however, not all atypical antipsychotics are equal to one other. A recent meta-analysis of randomized controlled trials reported that only some of the atypical antipsychotics tested (risperidone, olanzapine, amisulpride and

10.1517/17425240902780158 ISSN 1742-5247

clozapine) were more efficacious than conventional medications, suggesting that – consistently with their heterogeneous pharmacology – atypical antipsychotic agents are a clinically dis-homogeneous group [11]. Further studies indicated that atypical antipsychotic drugs appear to be superior to conventional antipsychotics with regard to cognitive function, however different effects in specific cognitive functions (attention, verbal fluency, visual learning and working memory) were reported depending on the atypical antipsychotic administered [12].

With respect to safety, the atypical antipsychotic agents have represented clear progress in their lower liability to cause reversible and irreversible movement disorders, including tardive dyskinesia [13-15]. However, the tolerability and safety profiles of new generation antipsychotics are dissimilar and the relative safeness of some new antipsychotics in the area of movement disorders is often associated with an increased risk of inducing significant sedation and weight gain, as well as to negatively alter glucose and lipid metabolism [16-18].

The different pharmacological efficacy and safety characteristics among second generation antipsychotics highlight the evident possibility to develop additional and superior treatment options for schizophrenia. From this point of view, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) have confirmed the medical need of individualized pharmacotherapy for psychosis, stressing the availability of diversified treatment options to allow wise clinical balancing between benefits and risks [19,20].

Variability in the clinical response to antipsychotic therapy should not be regarded as surprising, since at least two major clusters influence the pharmacological treatment of schizophrenia. On one side, the heterogeneous phenotypes of schizophrenia are probably the result of multiple genetic and environmental interactions. In contrast, currently available antipsychotic agents vary greatly in their chemical and structural composition, in their receptor-binding affinities and in their delivery mechanisms (i.e., pharmaceutical formulations) [21]. As a result, this multicluster-coupled variability often leads to differential effects of pharmacotherapy on the symptoms of schizophrenia and overall treatment outcomes.

Other factors such as disease and concomitant medication intake might also contribute to determining the clinical outcome of antipsychotic therapy, altering the efficacy and tolerability of antipsychotic drugs and limiting the choice of possible pharmacological interventions. Furthermore, partial and non-adherence to therapy is still widely diffused among patients treated with antipsychotic drugs, often resulting to high rates of treatment discontinuation [19]. Thus an advance in pharmacological therapy of schizophrenia is required, focussing on several practical problems that still affect or limit the success of antipsychotic therapy.

A new oral antipsychotic drug, paliperidone ER, has recently been developed which might represent an innovative approach in the treatment of schizophrenia. The delivery system of paliperidone ER (Osmotic-controlled Release Oral-delivery System [OROS] technology) provides constant drug release over 24 h, so reducing the drug plasma fluctuations that characterize the immediate release formulations of oral antipsychotics [22]. Although paliperidone possesses a pharmacological profile very similar to the parent compound (paliperidone is the 9-OH metabolite of risperidone), it is a unique drug, as confirmed by the World Health Organization (WHO), in its Anatomical, Therapeutic and Chemical classification (ATC), which classifies drugs based on their anatomical area of therapeutic action and on pharmacological and chemical therapeutic characteristics. Every drug has an alphanumerical code that indicates five levels in sequence, namely the principal anatomical group, the therapeutic subgroup, the pharmacological subgroup, the chemical subgroup and the active ingredient. In confirmation of the structural and pharmacological differences, paliperidone and risperidone have been assigned different ATC codes, namely N05AX13 (N = nervous system; 05 = psycholeptic; A = antipsychotics; X = other antipsychotics; 13 = paliperidone) for paliperidone and N05AX08 for risperidone, which did not happen in the evolution from risperidone to risperidone long-acting [23].

Recently completed trials assessing recurrence prevention have shown encouraging longer term effects of paliperidone ER, with respect to both efficacy and tolerability [24-25], so confirming the previous findings of 6-week studies [26-28], showing that paliperidone ER is effective in rapidly controlling a broad range of schizophrenia symptoms and has a favourable tolerability profile as an atypical antipsychotic.

To date however, no direct comparisons have been carried out to compare the effects of paliperidone ER with those of the immediate release (IR) formulations of risperidone. As paliperidone is the most active chemical derivate of risperidone, and considering the different delivery systems, similarities and differences between the two drugs are expected. This analysis of the existing data intends to address whether or not a clinical superiority of paliperidone ER over risperidone IR could be established and explained in terms of structural–molecular differences and/or innovative delivery system.

2. Comparison between paliperidone ER and risperidone IR

2.1 Methods

A literature review was performed using the keywords 'Risperidone', 'Paliperidone' and 'OROS technology'. Additional articles were included based on the authors' knowledge of the literature and after reviewing the reference lists of retrieved articles. Abstract books from congresses of the last three years were also reviewed.

2.2 Differences due to structural (molecular) diversity

2.2.1 Interactions with biomembrane and neurotransmitter receptors

Chemically, paliperidone differs from the older antipsychotic risperidone because of a hydroxyl group in position 9 (**Figure 1**).

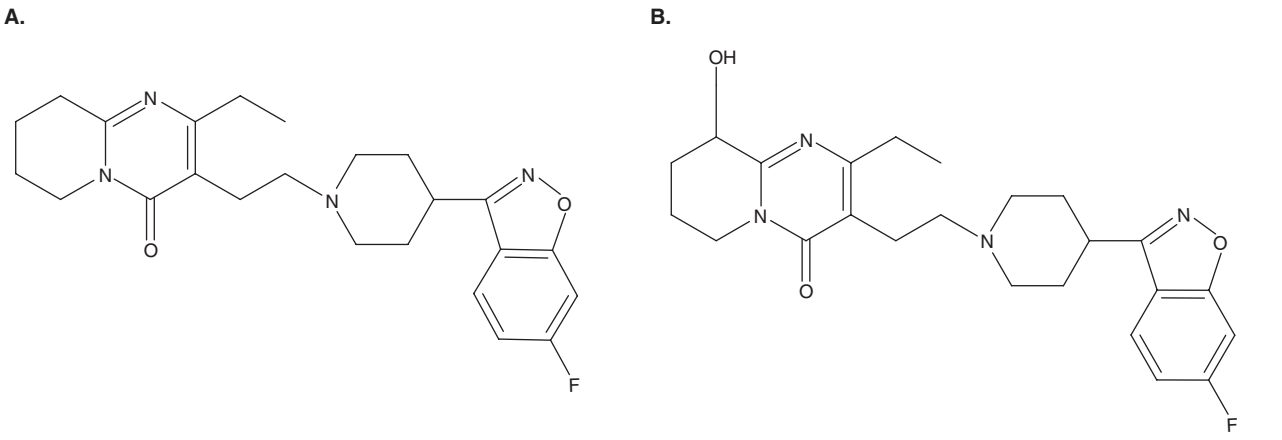

Figure 1. Chemical structures of risperidone (A) and paliperidone (B).

The presence of a hydroxyl group has significant effects on the structure and pharmacological action of central nervous system (CNS) active compounds. The addition of a hydroxyl group to the monoamine dopamine in position beta transforms it into noradrenaline (**Figure 2**), a completely different neurotransmitter in terms of receptor binding, uptake mechanisms, neuronal pathways and physiopathology. It is therefore conceivable that risperidone and paliperidone could also diverge on some of their chemical and clinical features.

Indeed, it has been recently shown that the hydroxyl group confers a significantly different polarity for risperidone and paliperidone [29]. It is well established that antipsychotic drugs, because of their amphipathic or amphiphilic properties, may posses a different ability to interact with bio-membranes. When a model membrane made of lipid from biological sources was used to test the ability of several antipsychotic drugs to modify biological membrane properties, the two compounds sharing the strongest chemical similarity among the antipsychotics tested (risperidone and paliperidone) showed striking differences in their mode of molecular intercalation with the lipid bilayer [29]. This implies that these drugs interact differently with membrane lipid organization, modifying lipid dynamics and possibly inducing subsequent modifications in their interactions with cell membrane proteins [29]. Antipsychotic membrane intercalation may thus modulate the efficacy and tolerability profile of compounds and it can be hypothesized that the activity of antipsychotic medications may result from a combination of drug–receptor plus drug–membrane interactions [30].

Although risperidone and paliperidone showed comparable high affinity for D_2, $5HT_{2A}$, $alpha_1$ and $alpha_2$-adrenergic receptors when the drugs were compared *in vitro*, moderate differences could be observed when receptor occupancies of the two drugs are analysed *ex vivo* [31-33]. Such differences are not reflected in the ability of the two drugs to treat schizophrenia symptoms, since alterations of plasma risperidone/paliperidone ratio due to CYP2D6 polymorphisms did not produce a different clinical efficacy in risperidone-treated patients [34]. However, recent results showed that risperidone and paliperidone differently alter the firing of serotonergic and noradrenergic neurons following selective serotonin reuptake inhibitor (SSRI) administration, suggesting that paliperidone may be effective in clinical conditions such as SSRI-resistant depression, while risperidone may not be [35].

2.2.2 Interactions with proteins regulating drug pharmacokinetics

2.2.2.1 p-glycoprotein (P-gp) transporter

The hydroxyl group of paliperidone may alter the ability of the two drugs to cross the brain barrier. *In vitro* studies indicated that the IC(50) values of risperidone for inhibiting p-glycoprotein (P-gp) mediated transport of rodamine-123 and doxorubicin were 63.26 and 15.78μM, respectively, while paliperidone showed IC(50) values higher than 100μM [36]. P-gp is a transmembrane active efflux carrier, encoded by a gene member of the highly conserved superfamily of ATP-binding cassette (ABC) transporter proteins [37], expressed at the blood–brain barrier level that regulates intra-cerebral concentrations and, by extension, may affect the clinical response of CNS-targeting drugs that are substrates of this transporter. Consistently, recently it was demonstrated that ABCB1 gene variants coding for P-gp predict the treatment course and outcome in those patients treated with antidepressants that are substrates of P-pg-transporter [38]. Recent recommendations for future research that will aid clarification of the association between ABCB1 genotypes and factors related to P-gp activity have also been published [39], highlighting the importance of P-gp affinity for the clinical effect of CNS penetrating drugs such as antipsychotics.

According to a possible involvement of P-gp activity in the regulation of risperidone-induced effects, pre-clinical studies indicated that brain concentrations of risperidone active moiety were 10-fold higher in P-gp knockout mice than in wild-type animals and, consistently with these

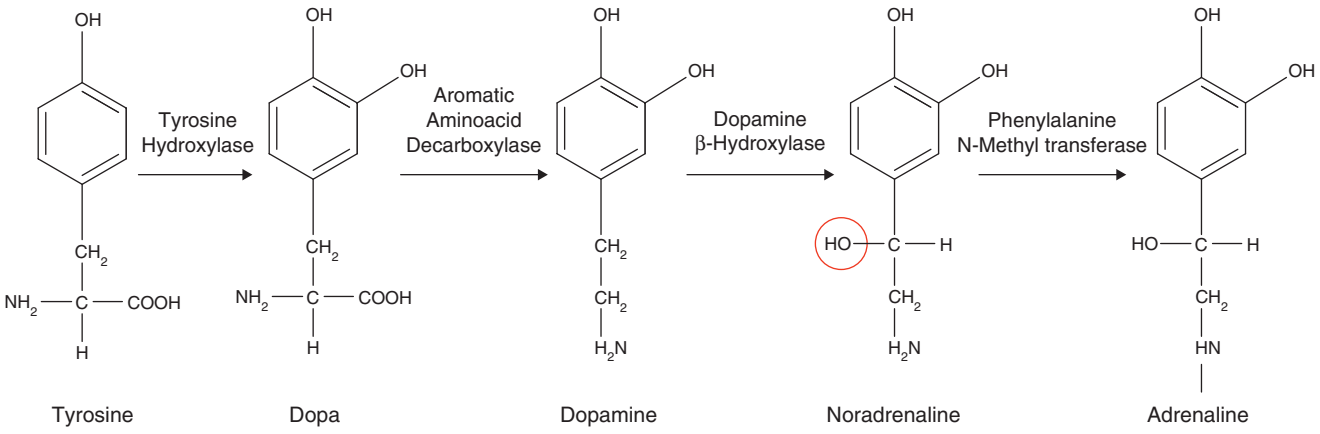

Figure 2. Schematic representation of adrenaline bio-synthesis. Dopamine and noradrenaline differ for a hydroxyl group.

pharmacokinetic analyses, the administration of 0.3 mg/kg of risperidone in knockout animals was as effective as the 3 mg/kg dose in wild-type mice [40]. Furthermore, a clinical analysis of association tests between genotypes and improvement in total Brief Psychiatric Rating Scale (BPRS) scores of 130 schizophrenia patients undergoing risperidone treatment, indicated that genotyping ABCB1 may help to predict the efficacy of risperidone treatment, providing further evidence that risperidone and P-gp interaction has an impact on the clinical effects of the atypical antipsychotic [41].

Risperidone, a stronger P-gp inhibitor than paliperidone, may be particularly sensitive to concomitant administration of other P-gp-dependent drugs. In a study designed to examine the *in vitro* effects of the two compounds on P-gp mediated transport, paliperidone was found to have less potential than risperidone to influence the pharmacokinetics of co-administered drugs [36]. Moreover, the comparison of plasma concentrations of the two antipsychotics with their relative potency as inhibitors of P-gp substrate suggested that risperidone but not paliperidone may inhibit P-gp activity *in vivo* [42].

Drug–drug interaction at P-gp level was analysed in 12 healthy male volunteers treated with risperidone, showing that the bioavailability of risperidone was increased by verapamil [43]. Compared with placebo, verapamil co-treatment increased the peak plasma concentration of risperidone by 1.8-fold, furthermore the area under the plasma concentration–time curve (AUC) from 0 to 24 h of risperidone was 2.0-fold higher following verapamil administration. The AUC from 0 to 24 h of paliperidone was less increased during verapamil treatment (1.46-fold), while paliperidone peak plasma concentration was not affected [43].

Further analyses are warranted to better clarify the clinical benefits that might come from a reduced interaction with the multidrug resistance transporter P-gp, however, the possibility to obtain more consistent pharmacokinetic profiles among patients seems to constitute one of the main advantages coming from the paliperidone molecular structure when compared with risperidone.

2.2.2.2 *CYP2D6 hepatic enzyme*

Preclinical and clinical studies demonstrate that paliperidone does not undergo significant hepatic metabolism and the drug is predominantly (59%) excreted by the kidney as unchanged drug [44]. It is then unlikely that clinically relevant hepatic drug–drug interactions might occur in patients when paliperidone is co-administered with drugs that are metabolized by the liver. Conversely, risperidone is extensively metabolized by CYP2D6 hepatic enzyme, which catalyses the hydroxylation of risperidone to paliperidone [34].

The activity of CYP2D6 is dependent on genetic factors (CYP2D6 polymorphisms) and hepatic function and it is also subject to significant inhibition or activation by several drugs that could be co-prescribed during antipsychotic therapy such as antidepressants, anti-epileptics, mood stabilizers and anti-arrhythmic drugs [45-47].

In a drug–drug interaction study, the antidepressant and CYP2D6 substrates fluoxetine (20mg) and paroxetine (20mg) have been shown to significantly increase the plasma concentration of risperidone [48,49]. However, fluoxetine did not affect the plasma concentration of paliperidone [49] and paroxetine produced a slight but not significant reduction of paliperidone [48], indicating that paliperidone plasma concentrations are less affected by the concomitant drug intake.

The variations of risperidone pharmacokinetic parameters, however, might be more complex when the effect of CYP2D6 is evaluated in an individual showing different metabolic activity. Generally extensive and poor metabolizers have different risperidone/paliperidone ratio in plasma but share similar concentrations of the active moiety, consequently no major differences in the clinical efficacy of risperidone could be observed between the two genetic groups [34]. Such therapeutic bioequivalence of risperidone between extensive and poor metabolizers, however, might be unexpectedly

altered when the antipsychotic drug is co-administered with CYP2D6 interacting drugs.

A study investigating the effect of fluoxetine (20 mg/day) administration on risperidone plasma levels in poor and extensive metabolizers showed that the AUC of risperidone increased from 83.1 ± 46.8 ng.h/ml (monotherapy) to 345.1 ± 158.0 (combination therapy) in extensive metabolizers and from 398.3 ± 33.2 ng.h/ml (monotherapy) to 514.0 ± 144.2 ng.h/ml (combination therapy) in poor metabolizers [50]. The AUC of paliperidone was unchanged in extensive metabolizers following fluoxetine administration (monotherapy vs combination therapy: 386.8 ± 153.0 ng.h/ml vs 317.7 ± 125.2 ng.h/ml,), but a significant increase of paliperidone plasma concentration could be observed in poor metabolizers (monotherapy 178.3 ± 23.5 ng.h/ml; combined therapy 274.0 ± 55.1 ng.h/ml) [50], indicating that risperidone pharmacokinetic parameters (risperidone, paliperidone and active moiety plasma concentration) might be differently affected in the two genetic groups when the drug is co-administered with a CYP2D6 substrate such as fluoxetine.

Further studies are needed to evaluate the effect of co-administration of paliperidone or risperidone with known CYP2D6 enzyme inducers, since it is was found that carbamazepine significantly reduced plasma concentrations of both risperidone and paliperidone in patients receiving risperidone [51]. However, it is expected that paliperidone, avoiding liver metabolism, may reduce the risk of under- or over-dosage due to drug–drug interactions or to CYP2D6 genetic variability.

Accordingly, a study investigating the influence of the CYP2D6 polymorphism on plasma concentrations of risperidone and paliperidone in 37 schizophrenic patients (three ultra-rapid metabolizers, 16 homozygous and 15 heterozygous extensive metabolizers and three poor metabolizers) maintained on risperidone 4 – 8 mg/day, demonstrated that the steady state plasma concentrations of paliperidone were not related to genotype [52]. The pharmacokinetic of paliperidone was also analyzed in a small number of CYP2D6 poor (n = 2) and extensive (n = 3) metabolizers treated with paliperidone liquid solution (an IR formulation of paliperidone) and no differences could be observed between the two genetic groups in the plasma concentration of paliperidone [44]. Finally, a clinical study comparing paliperidone ER (1mg) pharmacokinetic parameters in 10 subjects suffering from moderate hepatic impairment with 10 matched controls, showed that the time to maximum plasma drug concentration and terminal half-life was similar in the two groups, suggesting that the requirement of dose adjustment might be avoided in patients with mild hepatic impairment [44].

2.3 Differences due to drug delivery technology

2.3.1 Fluctuations of drug plasma levels

Oral risperidone is available as a conventional tablet and as a solution, furthermore a recent fast-disintegrating oral tablet formulation has been developed. The different formulations of risperidone share similar bioequivalence and are characterized by a rapid and complete absorption [53]. In a study of 23 female inpatients assuming repeated administration of 2mg of risperidone twice a day, risperidone concentration quickly reached a peak (Tmax 1.6 h) and half-life in plasma was very short (3.2 h) paliperidone was rapidly metabolized from the parent compound, showing a peak concentration after 2.5 h and longer half-life than risperidone [54]. A pharmacokinetic profile showing significant peaks and troughs during the day was also observed following administration of a single dose (1 mg) of [^{14}C]-paliperidone oral solution in healthy male subjects. This immediate release formulation of paliperidone induced a rapid rise of paliperidone plasma concentration (Tmax 1.5 h) followed by a significant decline of the drug in the plasma [44]. Both the molecules of risperidone and paliperidone are then associated to significant fluctuation of drug plasma levels when administered as oral immediate release formulations.

The development of novel delivery systems, however, demonstrated that it is possible to produce significant changes in the pharmacokinetic profile of a drug. One of the innovative mechanisms to control drug delivery is provided by the Osmotic-controlled Release Oral-delivery System (OROS), developed by ALZA Corporation, CA, USA. The OROS tablet delivers the drugs by acting as a osmotic pump. It contains a semi-permeable membrane designed to release the drug through a laser-drilled orifice. In the gastrointestinal tract, the osmotic pressure gradient induces the passage of the water into the tablet through the semi-permeable membrane leading to a constant release of the drug through the drilled orifice [55]. Recently, innovative two- and multilayer tablets have been also developed to improve the control and flexibility of drug release. These formulations contain one or several drug layers and a push compartment. All layers of these tablets absorb water from the gastrointestinal tract, so promoting drug release; furthermore, the polymer contained in the push layer expands providing additional force to deliver the drug through the orifice (**Figure 3**) [55].

Several therapeutic areas employ OROS technology for drug delivery, including cardiovascular endocrinology and urology [55]. The calcium channel blocker nifedipine utilizes OROS technology for the treatment of hypertension [56], as well as glipizide in the therapy of type 2 diabetes [57]. OROS technology is also associated to oxybutynin in the drug therapy of urinary incontinence [58] and to doxazosin to improve the treatment of benign prostatic hyperplasia [59]. The use of OROS technology is associated to more stable drug concentrations, uniform drug effects and to improved safety [55]. Generally the OROS system is well tolerated and drug delivery is independent of the concomitant ingestion of food [60,61].

Recently, OROS technology was applied to improve the efficacy of CNS active compounds, such as methylphenidate, paliperidone and hydromorphone [55]. Paliperidone ER is the

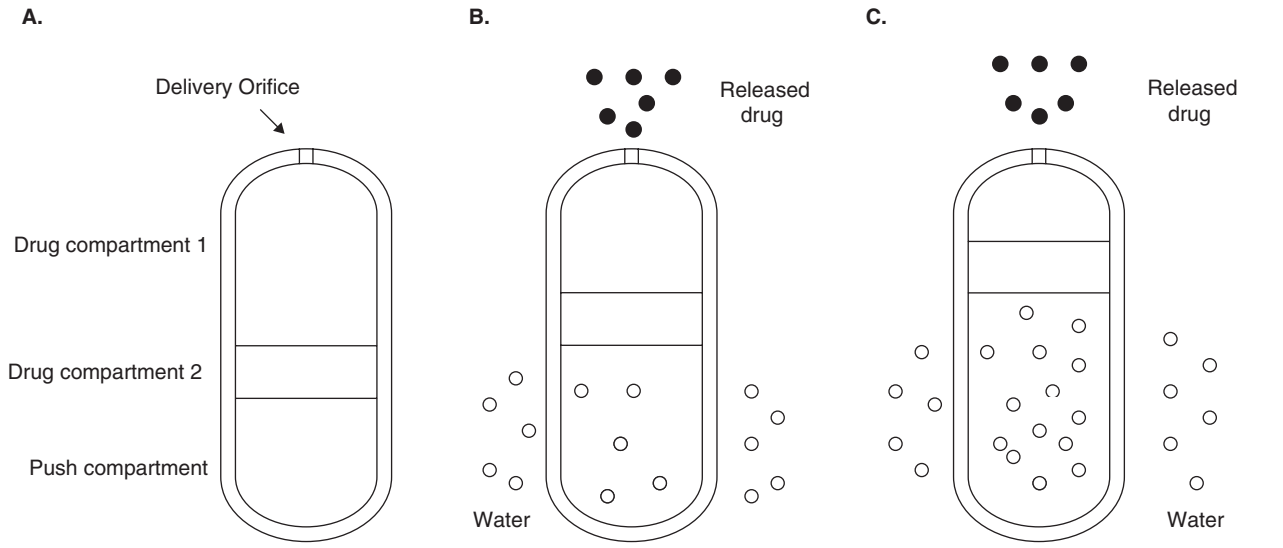

Figure 3. Schematic representation of an OROS triple-layer extended-release tablet (A). The osmotic gradient determines the passage of the water into the compartments (**B**), producing a constant gradual release of the drug (**C**).

first oral atypical antipsychotic that has been associated with OROS technology. The extended release system is constituted of a triple-layer cylindrical extended release tablet (**Figure 3**) that minimizes the fluctuations in the release of the active compound. The constant release of paliperidone allows a gradual increase in plasma drug concentrations until the maximum plasma concentration is reached (C_{max} 24 h), providing relatively stable plasma drug concentrations during the day and avoiding the rapid rise and fall in plasma drug concentrations that are characteristic of oral IR formulations [22].

The OROS technology of paliperidone ER is then associated with a pharmacokinetic profile that is completely different from that of IR formulations of risperidone. The smooth fluctuations of drug–plasma levels might provide peculiar pharmacological properties to paliperidone ER, possibly preventing over-dosages and/or under-dosages during the day.

2.3.2 *Fluctuations of dopamine D_2 receptor occupancy*

As pointed out by recent brain imaging studies, a large number of antipsychotic drugs currently used in clinical practice (risperidone included) induce a proper therapeutic efficacy when a D_2-receptor occupancy greater than 65% is reached in basal ganglia [62]. Furthermore, it was observed that an increased incidence of extra-pyramidal symptoms occurred when the striatal D_2-receptor occupancy exceeded 80 – 85% [62], indicating that the possibility to obtain an optimal therapeutic effect is strongly limited by a narrow 'D_2 -receptor occupancy window' (65 – 85%).

Classical oral IR antipsychotics are generally associated with rapid increases in drug plasma concentration followed by a significant decline of drug plasma levels. Considering that the D_2 occupancy is related to drug plasma concentration, it is possible that the D_2 occupancy level might exceed the extra-pyramidal symptoms threshold (80 – 85%) during the rapid rise of drug plasma concentration that follows drug intake. Conversely, the D_2 receptor occupancy might fall below the therapeutic threshold when drug concentration reaches minimal levels in plasma. It has been then hypothesized that antipsychotic plasma level fluctuations might lead to an increased extra-pyramidal symptoms incidence and to a discontinued efficacy on symptoms control [63].

The gradual and continuous drug release of paliperidone allows achieving and sustaining D_2-receptor occupancy levels in the brain that are sufficient for proper antipsychotic efficacy over a 24 h period. Consistently, brain imaging studies have predicted that paliperidone ER (6 – 9mg) should induce D_2-receptor occupation levels in the striatum ranging between 70 and 80% [64]. Furthermore, it was estimated that paliperidone ER administration should produce sixfold less fluctuation compared with an IR formulation [22]. Starting from the 'D_2-receptor occupancy threshold' concept, it is then expected that the increased possibility to achieve stable D_2-receptor occupancies above the therapeutic threshold – and below the extra-pyramidal threshold – should confer to paliperidone ER an improved therapeutic efficacy and reduced extra-pyramidal symptoms liability than oral formulations of risperidone.

2.4 Expected differences in the clinical outcomes

Paliperidone and risperidone share similar affinities for D_2 and 5-HT_{2A} receptors, indicating that the two drugs should possess comparable therapeutic properties as atypical antipsychotics [31-33]. A similar antipsychotic efficacy was indeed observed in patients treated with risperidone, showing a different risperidone/paliperidone ratio in plasma, confirming the hypotheses that the two molecules may posses comparable

potency in contrasting schizophrenia symptoms [31,34]. Furthermore, the 'atypical' therapeutic properties of paliperidone ER have been recently ascertained in several clinical trials, showing that the antipsychotic is effective in reducing both positive and negative symptoms of schizophrenia with a reduced incidence of extra-pyramidal side effects. Accordingly, a recent analysis pooling three 6-week studies demonstrated that paliperidone ER induces significant improvements in all of the five symptomatic domains (PANSS factor scores) of schizophrenia: positive symptoms, negative symptoms, depression/anxiety, uncontrolled hostility/excitement and disorganized thoughts [65]. Furthermore, an analysis of 207 patients established the efficacy of paliperidone ER in relapse prevention of schizophrenia symptomatology, showing that a longer time to recurrence could be observed in paliperidone ER-treated patients than in the placebo-treated group [25].

Although both risperidone and paliperidone behave as atypical antipsychotics, the different pharmacokinetic profiles of the two drugs might differentiate some of their therapeutic properties. The pharmacokinetic of paliperidone ER is characterized by smooth fluctuations of plasma drug concentrations [22] and potentially by a reduced liability to cause unexpected over- or under-dosages due to CYP2D6 genetic variability, hepatic impairment and or drug–drug interactions [44]. These pharmacokinetic properties might have a profound impact in clinical practice, since stable and predictable drug plasma concentrations might provide a constant therapeutic efficacy associated with a reduced frequency of side effects.

To date no head-to-head clinical comparisons of paliperidone ER and oral risperidone have been conducted to compare the efficacy and tolerability of paliperidone ER versus oral risperidone in the treatment of schizophrenia. However, a 'virtual' comparison of the two drugs was carried out collecting data obtained from previous randomized and placebo-controlled studies of adults with schizophrenia (18 – 65 years) treated for six weeks with risperidone (2 – 6 mg/day) or paliperidone ER (6 – 12 mg/day) or placebo [66]. The results of the computational analysis showed that paliperidone might possess a significantly higher therapeutic efficacy than risperidone as indicated by PANSS score (mean PANSS score reduction at end point -4.6 for placebo, -11.4 for risperidone and-19.0 for paliperidone) [66]. Furthermore, paliperidone showed an improved tolerability when compared to risperidone [66].

These 'virtual' results must be interpreted with caution since comparisons were made by matching data coming from different study designs, however, other recent clinical findings seem to support the hypothesis that smooth plasma levels provided by paliperidone ER might lead to an improved therapeutic efficacy and a low incidence of extra-pyramidal symptoms.

In clinical trials evaluating the efficacy of paliperidone ER (6 – 12mg) on schizophrenia symptom control [26], it was observed that clinical improvements occurred very rapidly following paliperidone treatment initiation (as early as day 4) and that a strong symptom control was induced by paliperidone ER in individuals achieving a proper clinical response [26,27]. Conversely, the time to onset of the therapeutic activity of IR antipsychotics varies across trials, with some studies registering a rapid response while in others substantial improvements were observed only after 2 – 3 weeks of antipsychotic administration [67,68].

Rapid symptom control is a clear therapeutic benefit in the treatment of schizophrenia. In contrast to oral risperidone formulations, paliperidone ER treatment can be started directly at the recommended dosage and this might accelerate the appearance of the therapeutic effects.

The possibility to avoid titration is due to the pharmacokinetic profile of paliperidone that improves the tolerability of the drug. Accordingly, recent studies demonstrate that paliperidone ER was generally well tolerated and the incidence of extra-pyramidal symptoms was similar to placebo when the antipsychotic was administered at the dose of 6 mg [26,27]. The frequency of movement disorders increased following administration of higher dosages of paliperidone ER, which might induce a small enhancement in SAS and AIMS scale scores compared with placebo, although the analysis of BARS global clinical rating score did not highlight any significant differences between placebo and paliperidone ER treated individuals [65]. This positive tolerability profile was also confirmed in a multicenter study involving elderly schizophrenic patients treated with paliperidone ER (3 – 12mg), showing that the discontinuation rate due to adverse events as well as the incidence of treatment-emergent adverse events were similar in placebo and paliperidone ER treated patients [69].

Extra-pyramidal symptoms are not, however, the only side effects that might occur during long-term antipsychotic therapy. Cardiovascular and metabolic side effects, such as weight gain and disturbances in glucose and lipid metabolism, often compromise the clinical outcome of patients treated with atypical antipsychotics [70,71]. Risperidone and paliperidone induce alfa$_1$ adrenergic antagonism that was associated with cardiovascular and metabolic side effects induced by antipsychotic drugs [72,73]. Moreover, risperidone and paliperidone interact *in vitro* with H_1 histaminergic receptors that may cause sedation and weight gain in maintenance antipsychotic therapy [71].

Although longer term studies are required to fully evaluate the effect of paliperidone ER on body weight and metabolic parameters, the results of the 6-week trials are encouraging, since only moderate weight gain (0.2 – 0.9 kg) was observed in patients receiving paliperidone ER [65]. Furthermore, the increase of body weight induced by paliperidone ER compares favourably with that observed in placebo-controlled 10-week trials of atypical antipsychotic agents [70-71].

Ex vivo studies indicated that paliperidone injections induce relatively smaller H_1 occupancy levels in the brain of

laboratory animals when compared to similar dosages of risperidone [32,33]; furthermore, low peaks of H_1 receptor occupancy are expected when the paliperidone is administered as an ER formulation. It is then feasible that a reduced involvement of H_1 receptors might account for a reduced weight gain liability of paliperidone ER. This hypothesis is also supported by a recent study showing that paliperidone ER (9 mg) did not exacerbate daytime somnolence compared with placebo [74], suggesting that the drug might be less prone to induce the H_1-mediated effects that have been described for risperidone [75].

Other factors, however, might also contribute to explaining the low weight gain liability of paliperidone ER. A previous study which aimed to simultaneously analyze the effect of several candidate genes and environment factors on body weight in patients treated with risperidone, indicated that CYP2D6 genotype significantly influenced body weight during the antipsychotic treatment [76]. A similar relationship between CYP2D6 polymorphisms and weight gain was also observed in 11 subjects receiving olanzapine, supporting the hypothesis that variants of CYP2D6 enzymes may play a role in weight changes observed following antipsychotic therapy, possibly due to unexpected increases in drug concentrations [77].

Paliperidone is poorly metabolized by CYP2D6 enzyme and similar drug plasma concentrations were found in extensive and poor metabolizers, accordingly a reduced incidence of weight gain due to unpredictable over-dosages are expected following paliperidone ER administration.

This property might also possibly account for the low incidence of QTc lengthening observed during treatment with paliperidone ER. Indeed, a study pooling data from three 6-week trials indicated that no relevant differences could be detected when the proportion of individuals with abnormal corrected QT intervals was analyzed in placebo and paliperidone ER treated patients [65], suggesting paliperidone ER has a low propensity to enhance QT-related cardiac risks. Conversely, an enhancement of corrected QT interval lengthening was observed in patients treated with risperidone and was related to the CYP2D6 genotype [78].

It is still debated whether risperidone and paliperidone might differently regulate prolactin release. Starting from the biochemical profile, the two compounds should induce a similar blockade of pituitary D_2 receptors transmission that can be associated with a comparable propensity to increase plasma prolactin levels. However, pharmacokinetic related factors should be also considered in evaluating the expected hyper-prolactinemia liability of the two drugs.

Recent studies indicated that the different effects of atypical antipsychotics on prolactin elevation is related to their differential blood–brain disposition [79]. Preclinical analyses showed that, following risperidone administration, the brain/blood ratios of risperidone and paliperidone were 0.22 and 0.04, respectively [80], suggesting that blood–brain barrier may be preferentially penetrable by risperidone, while paliperidone is accumulated outside of the blood–brain barrier. Accordingly, a previous study of 20 patients indicated that paliperidone might be the main contributor to the rise of prolactin serum levels observed following risperidone administration [81].

However, the concentrations of paliperidone measured in the brain following paliperidone (1 – 6 mg/kg/day) administration were different from those of risperidone+paliperidone observed after risperidone (1 – 6 mg/kg/day) treatment, suggesting that the presence of risperidone might alter the pharmacokinetics of paliperidone [80] and possibly the propensity of paliperidone to induce hyper-prolactinemia.

This hypothesis is supported by a large clinical study evaluating the role of CYP2D6 polymorphism on prolactin induction in 118 schizophrenia patients (40 males, 78 females, aged 15 – 60 years) showing different risperidone/paliperidone ratios in plasma. The results of this analysis established that the concentrations of paliperidone cannot be significantly correlated with the increase of serum prolactin and that paliperidone may not play a predominant role in rise of serum prolactin level observed in risperidone-treated patients [82].

Although an analysis of randomized double-blind studies of risperidone found that prolactin level did not correlate with the incidence of clinically detected prolactin-related adverse effects [83], further studies are needed to evaluate whether paliperidone ER and IR formulations of risperidone might posses a different propensity to induce hyperprolactinemia. Starting from the molecular and pharmacokinetic properties of the two drugs, at least a reduced variability of hyperprolactinemia incidence among patients is expected following paliperidone ER administration. It should be evaluated whether more consistent pharmacokinetic profiles may facilitate pharmacological interventions against hyper-prolactinemia.

3. Conclusions

The comparative analysis of the pharmacological properties of risperidone IR and paliperidone ER, based on structural–molecular and delivery system diversity, indicated that significant differences might be expected from the use of the two drugs in clinical practice. Although risperidone and paliperidone share a similar pharmacodynamic profile as atypical antipsychotics, the different pharmacokinetic properties of the two drugs might have a relevant effect on drug manageability and safety. Particularly, two main characteristics appear to distinguish paliperidone ER from IR formulations of risperidone: i) the possibility to avoid drug interaction with proteins that might alter the pharmacokinetic parameters (e.g., CYP2D6 and P-gp); and ii) the possibility to obtain smooth drug plasma level fluctuations.

These properties might be associated to an improved efficacy and better tolerability, since unexpected over- or under-dosages due genetic metabolism variability, drug–drug interaction or hepatic impairment should be avoided using paliperidone ER. Furthermore, the stable drug plasma levels provided by paliperidone ER should produce a rapid and constant

antipsychotic efficacy combined with a reduced incidence of side effects. These improved pharmacological properties of paliperidone ER should enlarge the pool of patients that can take advantage from the antipsychotic therapy and might improve symptom control and compliance in patients who are positive responders to risperidone IR administrations.

It should be remarked, however, that these conclusions were extrapolated from existing data coming from separate risperidone and paliperidone studies. Direct comparisons of the two drugs at pre-clinical and clinical level are needed to confirm such hypotheses.

4. Expert opinion

The clinical relevance of stable and predictable pharmacokinetic profiles has sometimes been underestimated in antipsychotic drugs development, even if directly or indirectly drug plasma levels constitute one of the main variables that determine the efficacy and safety of the therapeutic approach.

Individuals with schizophrenia are frequently affected by comorbid medical conditions (e.g., cardiovascular disease, diabetes, hepatitis or other concomitant psychiatric disorders) and these patients are more likely to have comorbid substance use disorders (e.g., alcohol, cannabis and nicotine abuse/dependence), consistently poly-pharmacy is widely practiced in the therapeutic approach to schizophrenia. Although the clinical experience and the recent progress of pharmaco-genetics may help to predict the effects of the drug treatment, the number of variables that might affect the clinical outcome of antipsychotic therapy is still elevated. In this regard, the development of new therapeutic instruments overcoming drug–drug interaction or genetic variability-related problems should be regarded as a significant improvement in antipsychotic therapy, since they might increase the chances of obtaining a proper and predictable therapeutic efficacy associated with a reduced incidence of side effects.

Symptom control and improved side effects liability, however, should be not considered the only achievable results of antipsychotic therapy. The disabilities in personal and social functioning experienced by patients suffering from schizophrenia are particularly distressing, furthermore a proper cognitive function is crucial for patients to obtain a proper quality of life [84-87] and possibly the acceptance of drug therapy [88].

Recent clinical studies highlighted the possibility that atypical antipsychotics might be the most appropriate pharmacological approach to improve social competence, quality of life and subjective well-being in patients with schizophrenia [89-90], however, it is also desirable to evaluate whether atypical antipsychotics associated with different drug delivery systems might differently improve cognitive performance and global functioning of schizophrenic individuals.

Indeed, following the administration of IR formulations of antipsychotic drugs, the activity of the several neurotransmitter systems involved in emotion, cognition and social interaction (serotonin, dopamine, noradrenaline) is largely regulated by the fluctuation of antipsychotic plasma concentrations [33,91,92], instead to be dependent from internal or external events. Although the receptor blockade induced by antipsychotic drugs is fundamental to reach a proper symptom control and relapse prevention [62], it is also important to maintain, at least in part, the physiological role of neuropsychological functions such as positive/negative reinforcement, mood and cognition, as well as to ensure their modification in relation to environmental stimuli.

The effects of paliperidone ER on personal and social functioning were evaluated in 6-week controlled clinical trials, showing significant improvements in patients as assessed by the PSP scale [65]. The short-term nature of the studies may limit the potential for assessing improvements in function, however, it is noteworthy that amelioration of social and personal functioning was associated with significant improvements in Clinical and Global Impression Scale-Severity (CGI-S) scores for patients treated with paliperidone ER, when compared with placebo [26,65]. A proper antipsychotic effect associated with well-being and improved social function perception was also observed following administration of risperidone long-acting [93]. It is thus feasible that atypical antipsychotics providing stable drug plasma levels might be advantageous in combining an efficacious relapse prevention with the improvement of patients' quality of life.

Considering the clinical benefits that might come from a proper pharmacokinetic profile, it is not surprising that drug delivery systems providing smooth drug plasma fluctuation are under investigation using several other antipsychotics. A once-daily extended release formulation of quetiapine (quetiapine fumarate) has been recently developed by AstraZeneca (AstraZeneca International, London, UK), demonstrating effectivity versus placebo in contrasting the symptoms of schizophrenia and well tolerated even when rapid dose escalation is applied [94]. Furthermore, a long-acting formulation of olanzapine (olanzapine pamoate) was recently tested for brain D_2 receptor occupancy [95]. It can be expected that research focused on possible improve-ment of pharmacokinetic profiles will provide one of the main therapeutic advances in the antipsychotic therapy of the next 5 – 10 years.

Declaration of interest

Luca Pani has participated in speakers/board meetings of Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Johnson & Johnson and GlaxoSmithKline and he is a consultant for Pharmaceutica, Janssen-Cilag, Organon Schering Plough USA, Pfizer and Sanofi-Aventis. Giorgio Marchese has nothing to declare.

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