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Chapter 6
The Role of 9-OH-Risperidone in inducing Prolactin Elevation

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Summary

The atypical antipsychotic risperidone significantly increases plasma prolactin levels in patients, whereas clozapine, olanzapine and quetiapine do not. The difference in neuro-endocrine response can not readily be explained by their affinity for the dopamine D$_2$ receptor, but may be connected to their metabolism. To gain insight in the contributory role of risperidone’s active metabolite 9-OH risperidone, we measured the plasma concentrations of risperidone, 9-OH risperidone and prolactin.

Blood samples were taken from twenty-five patients with a psychotic disorder (14 male, 11 female; mean age 25± 7 yr (range 17-52)), after risperidone treatment for at least 4-6 weeks. Risperidone was given at a dose ranging from 1-6 mg/day (mean dose: 3 mg/day). Mean plasma concentrations for risperidone was 4.6 (range 1.0 - 36.2 µg/l) and for 9-OH risperidone 19.4 (range 1.0 -75.0 µg/l). Mean prolactin concentrations were 985.5 (SD 721.7, range 106-3700 ME/L).

Dosages of risperidone (in mg/day) correlated significantly with plasma concentrations of risperidone, 9-OH risperidone, active moiety and prolactin. Statistical analysis did not reveal a correlation between plasma levels of risperidone and plasma prolactin concentrations. Yet, plasma concentrations of 9-OH-risperidone showed a positive correlation with prolactin concentration. Pearson correlation 0.516, p=0.008. These data support an active role of 9-OH-risperidone in risperidone’s high tendency to elevate prolactin levels. In addition, 9-OH risperidone must be taken into account when monitoring levels for drug compliance.
Chapter 6

Introduction

The atypical antipsychotics are characterized by a low propensity to induce extra-pyramidal side effects (EPS). They differ, however, as regards weight gain, insulin resistance and the induction of prolactin elevation.

Most classical antipsychotics are potent dopamine 2 (D2) antagonists and they inevitably induce Hyperprolactinemia. In contrast, the atypical antipsychotics olanzapine, quetiapine and clozapine induce only mild, transient prolactin elevations. Surprisingly, the atypical agent risperidone produces profound and lasting increases in plasma prolactin levels, that are similar or even greater than those seen with haloperidol or other classical antipsychotics (Knegtering et al. 2000). This is an unexpected finding since risperidone is a considerably less potent D2 receptor antagonist than haloperidol (Leysen 1981; Leysen et al. 1992; Leysen et al. 1994).

Several ideas have been advanced to explain the differences between atypical and typical antipsychotics with regard to their EPS liability (for review see Westerink 2002). Most important theories are:

1) A higher affinity for the 5HT \textsubscript{2} receptor compared to the dopamine D\textsubscript{2} receptor
2) A lower dopamine D\textsubscript{2} receptor occupancy
3) Surmountable binding to dopamine receptors

These theories on atypicality do not, or only partly, explain the lack of significant prolactin elevation by clozapine, quetiapine and olanzapine. Recently, Kapur et al., proposed a poorer penetrability of the blood-brain barrier of risperidone to explain its higher tendency for Hyperprolactinemia as compared to olanzapine and quetiapine (Kapur et al. 2001; Kapur et al. 2002).

All fore-mentioned theories have focused on the interaction of the antipsychotic agents \textit{per se} with dopamine neurotransmission at the level of the various dopamine-D\textsubscript{2} receptors. Relatively little attention has been directed to the pharmacokinetic differences between the compounds with respect to their active metabolites to account for their endocrinological profiles. Indeed, for most antipsychotics the contribution of their metabolites is generally considered to be of only minor importance (Baldessarini et al. 1993). An exception is risperidone. This drug is extensively metabolised in the liver to 9-hydroxy-risperidone, an active metabolite with similar receptor binding profile as risperidone (Beijsterfeldt van et al. 1994). Presumably, 9-OH-risperidone contributes to risperidone’s pharmacological action (Aravagiri et al. 1998). Table 6.1 shows the major metabolic pathways of risperidone discussed in this article.
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Figure 6.1. Pharmacokinetics and dynamics of risperidone after oral administration

In this study, we propose that 9-OH risperidone considerably contributes to risperidone's higher tendency to prolactin elevation. To test this hypothesis we have measured the plasma levels of risperidone, 9-OH risperidone and prolactin from patients with schizophrenia, treated long-term with risperidone. In addition, we have investigated whether measurement of 9-OH risperidone plasma levels should be included when monitoring for compliance.

Methodology

The present study is part of a large survey at the University Hospital Groningen into antipsychotic-induced Hyperprolactinemia and sexual dysfunctions. Inclusion criteria for this subset included: age between 18 and 45 years, having a diagnosis within the schizophrenic spectrum or other psychotic disorders and having received risperidone treatment for at least 4 weeks. Informed consent was obtained from all participating patients. The study was approved by the local ethical committee. From each individual patient blood samples were taken simultaneously for determination of risperidone, 9-OH-risperidone and prolactin concentrations. Blood samples were collected between 8.30 - 9.00 a.m. Reversed phase HPLC with UV-detection was used to determine plasma risperidone and 9-OH-risperidone concentrations in the blood samples. With this method plasma concentrations down to 2µg/L for risperidone and 1µg/L for 9-OH-risperidone can be measured. To determine prolactin levels the MAIA clone kit was used. With this method prolactin concentrations over the range of 6.0-10,000 ME/L can be measured. Samples are
reacted with a mixture of monoclonal antibodies to prolactin. By measuring the bound fraction (Separation Reagent pellet) of the sample in a gamma counter calibrated to detect 125-Iodine, the concentration of prolactin in the sample can be determined.

For statistical analysis the Pearson correlation coefficient for non parametric variables was used. Prolactin levels, serum levels of risperidone and active moiety were normalized by converting them to their natural logarithm. For all analyses, the effects were tested at the 2-sided $\alpha$ level of 0.05.

Results

Twenty-five patients treated with risperidone (14 male, 11 female; mean age 25 years, range 17-52, SD 7 years) had plasma assessments available of the three compounds under study. All these patients had a psychotic disorder according to DSM-IV criteria (20 with a diagnosis within the schizophrenic spectrum and 5 with other psychotic disorders). Subjects received risperidone treatment for a minimum of four weeks, with a mean risperidone dosage of 3 mg/day (range 1-6 mg/day). Mean prolactin concentrations were 985.5 (range 106-3700 ME/L). Plasma concentrations of risperidone, 9-OH-risperidone, the active moiety of both and serum prolactin are listed in table 6.1.

Table 6.1. plasma concentrations during 4 to 6 weeks treatment with risperidone mean dosage 3 mg/day (range 1-6 mg)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean plasma concentrations(± SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>4.6 (± 7.4) µg/l</td>
<td>1.0 to 36.2 µg/l</td>
</tr>
<tr>
<td>9-OH-risperidone</td>
<td>19.4 (± 16.7) µg/l</td>
<td>1.0 to 75.0 µg/l</td>
</tr>
<tr>
<td>Active moiety</td>
<td>24.0 (± 18.7) µg/l</td>
<td>2.0 to 77.0 µg/l</td>
</tr>
<tr>
<td>Prolactin concentration</td>
<td>985.5 (±721.7) mE/L*</td>
<td>106-3700 mE/L*</td>
</tr>
</tbody>
</table>

\* 1ng/ml = 20 ME/L

In figure 6.2 the (Pearson) correlation coefficients are presented between the oral daily risperidone dosage, plasma levels of risperidone, 9-OH risperidone and serum prolactin. Oral risperidone dosage is significantly correlated with plasma risperidone levels ($r=0.521; p=0.008$) as well as plasma 9-OH risperidone levels ($r=0.571; p=0.003$) and plasma prolactin levels ($r=0.445; p=0.026$). In contrast to plasma risperidone, only 9-OH risperidone correlates significantly with plasma prolactin levels ($r=0.516; p=0.008$). No significant correlations were found between plasma risperidone levels and plasma prolactin levels ($r=0.234, p=0.260$) nor between plasma risperidone levels and 9-OH risperidone levels ($r=0.293, p=0.155$).
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Figure 6.2. Correlations between daily oral risperidone dosage, plasma risperidone, plasma 9-OH risperidone and plasma prolactin

In figure 6.3 plasma risperidone and 9-OH risperidone are presented together as their active moiety. Oral risperidone dosage correlates significantly with the active moiety of risperidone \((r=0.764; p=0.000)\) and plasma prolactin levels \((r=0.445; p=0.026)\). The active moiety correlates significantly with plasma prolactin levels \((r=0.519; p=0.008)\).
Figure 6.3. Correlations between daily oral risperidone dosage, the active moiety (of plasma risperidone and 9-OH risperidone) and plasma prolactin

- $r=0.445$  
  $p=0.026$

- $r=0.764$  
  $p=0.000$

- $r=0.519$  
  $p=0.008$

$P$ = Pearson correlation coefficient,
Active moiety is sum of plasma levels of risperidone and 9-OH risperidone

**Discussion**

In this study treatment with risperidone at therapeutic doses was associated with profound Hyperprolactinemia. In addition, assessment of risperidone and its major metabolite 9-OH-risperidone revealed plasma levels of 9-OH-risperidone approximately 4 times higher than those of the parent compound. Risperidone levels and that of its metabolite correlated significantly with the risperidone dosage. In addition, a statistically significant correlation was found between the daily dosage of risperidone and 9-OH-risperidone with plasma prolactin. No correlation was found between plasma risperidone and plasma prolactin levels.

The Hyperprolactinemia found after 6 weeks of risperidone treatment is in accordance with our previous findings, as well as with the data of large clinical trials, showing prolactin levels higher than with classical neuroleptic-treatment (Knegtering et al. 1998; Kleinberg et al. 1999; Knegtering et al. 2000; Knegtering et al. 2003). Clearly, risperidone contrasts with most of the other atypical antipsychotics, which produce only transient prolactin elevation (Kapur et al. 2001; Kapur et al. 2002; Kim et al. 2002). This difference in endocrine response has not been fully clarified so far. There is however one important distinction between EPS induction and prolactin elevation. The induction of EPS is mediated through blockade of central dopamine D$_2$ receptors in the striatum. Conversely, antipsychotic-induced prolactin elevation is due to blockade of peripheral dopamine D$_2$ receptors, located in the anterior pituary outside the blood brain barrier (Kapur et al. 2002). Here, the tonic inhibitory effect of dopamine on the release on
prolactin is overruled by a blockade of the postsynaptic D2 receptors, resulting in Hyperprolactinemia. To explain the high levels of prolactin associated with chronic risperidone treatment, several mechanisms may be called upon. Drugs with a poor penetration of the blood brain barrier, are more active at the peripheral D2 receptors as compared to the central D2 receptors. In an experimental study, Kapur and coworkers, have compared the effects of antipsychotics on peripheral D2 receptors in the tubero-infundibular tract and the central D2 receptors in the striatum (Kapur et al. 2002). They thus calculated the “central to peripheral ratio of D2 occupancy”. Risperidone displayed a higher peripheral potency at a given level of functional central antagonism as compared to quetiapine and olanzapine. In other words, risperidone’s central activity (i.e. antipsychotic action) is paralleled by a relatively higher peripheral activity (i.e. a higher prolactin elevation).

Although clozapine, olanzapine and quetiapine are not associated with prolonged prolactin elevation, Turrone et al., demonstrated that they do produce a short transient prolactin increase immediately after dose administration (Turrone et al. 2002). In contrast, risperidone demonstrated a much higher transient increase of prolactin, superimposed on a sustained elevation (Turrone et al. 2002). Since the release of prolactin with the so-called prolactin sparing antipsychotics is of short duration, accumulation does not come about with subsequent dosing of these antipsychotics (Kapur and Seeman 2001). Indeed a drug must exert a prolonged action to account for accumulation. Given the short half-life of risperidone (2-4 hr), we therefore propose that the active metabolite 9-hydroxy risperidone (9-OH-risperidone) is a relevant factor in cumulating prolactin elevation over time (Heykants et al. 1994).

Risperidone is preferentially metabolized to 9-OH risperidone by the P450 liver enzyme CPY2D6 to 9-OH risperidone. This is the major active metabolite in humans with a half-life of 20 hour (Caccia 2000). Notably, 9-OH risperidone displays receptor affinities for the D2 and 5HT2 receptors similar to risperidone (Beijsterveldt van et al. 1994). From a receptor occupancy study in healthy subjects it was concluded that, 9-OH risperidone will substantially contribute to the overall antipsychotic effect of risperidone (Nyberg et al. 1995). Moreover, 9-OH risperidone counterbalanced the variability in the disposition of risperidone (Nyberg et al. 1995). Importantly, early in vitro experiments have demonstrated a comparable potency of risperidone and 9-OH-risperidone to stimulate prolactin release (Bowden et al. 1992). Since both compounds have similar pharmacological actions, the combination of risperidone and its active metabolite 9-OH risperidone together are often referred to as the ‘active moiety’. There are however important differences between risperidone and 9-OH-risperidone, with regard to their distribution within the peripheral and central compartments, plasma and brain respectively.

Protein binding (mostly albumin and α-1-acid glycoprotein) of risperidone and 9-OH risperidone is 90.0 and 77.4%, respectively (Mannens et al., 1994). This would implicate a more than two times higher free fraction for 9-OH risperidone compared to the parent compound. However, logP values (logarithm of the n-octanol/water partition coefficient) for risperidone and 9-OH-risperidone are 3.04 and 2.32 respectively (Mannens et al. 1994). This indicates that the 9-OH metabolite is approximately 5 times less lipophilic than risperidone. Combining these values for
protein binding and logP with our measured plasma concentrations of risperidone and 9-OH risperidone, we would expect brain levels of the metabolite to be twice as high as those of the parent compound. This is broadly compatible with a study in rats where a single dose of risperidone resulted in brain tissue concentrations, which were comparable for the parent compound and its 9-OH metabolite (Aravagiri and Marder 2002). Moreover, it supports the notion that the 9-OH metabolite substantially contributes to the antipsychotic effect of risperidone. LogP values of risperidone and its metabolite are lower than for most other antipsychotics, indicating that risperidone and its metabolite are less lipophilic. This implies that risperidone and even more so 9-OH-risperidone do not readily enter the brain through the blood-brain barrier. Indeed, in a study comparing risperidone and 9-OH-risperidone, concentrations in different tissues in rats after 15 days of treatment with risperidone demonstrated relatively low brain/plasma ratios for risperidone and 9-OH-risperidone (Aravagiri et al. 1998). In a subsequent study, they reported equal concentration for risperidone and 9-OH-risperidone in brain tissue after a single dose of risperidone (Aravagiri and Marder 2002). However, the levels of 9-OH-risperidone were 4.5 times higher in the plasma than the risperidone levels, which is very similar to the ratio we found in our study. Although one must be careful to extrapolate experimental studies to humans, taken together, these data suggest that 9-OH-risperidone has an even lower ability to penetrate the brain than risperidone. Therefore, while both compounds presumably contribute to a similar extent to the central effects of risperidone, it can be argued that the peripheral effects on prolactin release are dominated by the much higher plasma concentrations of the 9-OH metabolite. These assumptions are supported by the findings presented here. In addition plasma 9-OH-risperidone correlated highly significantly with prolactin, where as risperidone plasma levels did not.

Clozapine, olanzapine, quetiapine and risperidone are potent serotonin receptor antagonists. Interactions with serotonin system per se clearly modulate the release of prolactin (Kar van de et al. 1996). However, a large body of clinical and preclinical evidence indicates the effect of serotonin receptor-antagonism on prolactin release is overruled by the strong concurrent D2 blockade in the pituitary (Knegtering et al. 1999). Clearly, in our patients a prolonged occupancy of D2 receptors in the pituitary is very likely, due to both the action of risperidone but even more so of its active metabolite.

There is an increasing awareness that compliance with antipsychotics is poor, and that this probably also holds for the newer atypical antipsychotics (Perkins 2002). However, monitoring risperidone blood-levels for compliance has not become clinical practice today. In our study the dose of risperidone clearly correlated with 9-OH-risperidone but not with the parent compound risperidone. Assessing risperidone levels without 9-OH-risperidone levels can easily lead to misinterpretations of patients’ compliance. Indeed, there was a wide range in the risperidone levels. The wide range or the risperidone plasma levels found in this study may relate to two factors. A methodological flaw in this study could be the variance in time between dosing and moment of blood sampling. Given the short life-time of risperidone, such variance may lead to the collection of inconsistent data. Indeed, large variations were found in plasma levels of risperidone, but also in 9-OH-risperidone and prolactin. Variations in 9-OH-risperidone and prolactin levels blood levels are probably much
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less sensitive to variations times of sampling, implying that, at least in part, this should also be attributed to individual differences in metabolism. Consequently, drug monitoring for clinical reasons should include preferable both, risperidone and 9-OH risperidone.

To conclude, we found high prolactin levels with chronic risperidone treatment. Moreover, in our study oral dosage of risperidone and plasma concentrations of 9-OH-risperidone, but not those of plasma risperidone correlated with prolactin elevation. Taken into account that the active metabolite has similar D₂ affinity, a lower brain/plasma ratio and a long half-life-time, these data are in support of a predominant role for 9-OH-risperidone in prolactin elevation, inducing prolactin elevation. This explains why, although in absence of high incidences of extra pyramidal symptoms, prolactin elevation related side effects like amenorrhea galactorrhea and sexual side effects may occur frequently. Prolactin elevation reflects peripheral D₂-antagonism of risperidone and its metabolite and therefore it is not a good index for central postsynaptic receptor occupancy by risperidone. Finally, monitoring plasma levels for compliance is valid only when it includes both risperidone and 9-OH-risperidone levels.
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