Plasma levels of oral risperidone during enteral nutrition in a pregnant schizophrenic patient

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Introduction

Antipsychotic (AP) medication in pregnant women has always been a complex and controversial clinical challenge. On the one hand, this is due to possible adverse pregnancy outcomes for both the mother and child, that is, premature births, poor neonatal adaptation signs and higher rates of congenital malformation [Sadowski *et al.* 2013]. On the other hand, composite pharmacological interactions related to physiological changes that occur during pregnancy increase the difficulties in drug management. The augmentation of plasmatic volume, the reduction in albumin concentration, the increase of glomerular filtration and the modifications in hepatic metabolism are some of the factors that affect the pharmacokinetics of APs in pregnant women [Anderson, 2005]. Furthermore, the route of administration of a drug is a well-known factor that affects its absorption and distribution with direct consequences on plasmatic concentration and therapeutic effects. Among these latter effects, drug administration by nasogastric tube (NGT) is of particular interest in clinical pharmacology. Enteral feeding is a common condition among patients receiving long-term care as well as among psychiatric patients with rejection of food intake. Inappropriate prescribing behaviour together with incorrect procedures for drug delivery may result in significant harm to patients [Zhu and Zhou, 2013]. Unfortunately, there are virtually no data available on the pharmacokinetics of APs, such as risperidone, administered by NGT. Therefore, we believe it is important to share our findings in order to better address the management of APs during pregnancy and give impulse to further research on pharmacokinetics when administered by NGT.

Case report

The patient was a 28-year-old woman who was diagnosed with paranoid schizophrenia in 2009 according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* diagnostic criteria. During her first episode, characterized by thought-content disorder, she had been treated with paliperidone extended release 6 mg once a day with complete remission of the symptoms, following maintenance treatment throughout 2.5 years with 3 mg once a day. The treatment was stopped when she realized she was in her 8th week of pregnancy. Around the 24th week, the family reported behavioural changes, suspicious attitudes and an increasingly irritable mood.

She was first hospitalized during the 36th week on the 3rd day of pregnancy due to delusion of reference, thought broadcasting and intrusive mental images of her son's violent death. She also presented delusion of biomorphism (the conviction that organic dead matter such as food or water are living beings) with a secondary total rejection of food intake and hydration. On admission, a gynaecological ultrasound was realized, showing physiological parameters of foetal well-being. Furthermore, a general blood test was performed, showing malnutrition. Thus, enteral nutrition by NGT was begun. A polyurethane tube (Flexiflo Abbott; length 91 cm, diameter 4 mm) was placed according to standard procedures. The feeding phase began at 09:00 hours with a pattern of 400 ml in bolus four times a day, with forced hydration of 100 ml of water every 2 hours. The subject was fed with a polymeric hyperproteic formula (Nutrison Protein Plus Multifibre). Cyclic control of stomach emptying was carried out before the administration of a new bolus (Figure 1). Antipsychotic treatment

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Figure 1. Daily enteral nutrition delivered by nasogastric tube. A bolus of 400 ml of enteral nutrition (red rectangle) was delivered in 2 hours (200 ml/h). Before passing each bolus, a gastric aspiration with a 10 ml syringe was carried out (*) to check gastric retention. If gastric retention was confirmed, the process was interrupted for 1 hour after which a new control was realized. The 4 mg oral solution of risperidone (blue triangle) was administered half an hour before the bolus delivery.

consisting of risperidone oral solution titrated up to 4 mg twice a day was administered. The oral solution was dispensed by tube 30 minutes before the enteral bolus. The tube was rinsed with physiological solution before and after drug administration. On account of the absence of any sort of psychopathological response and the high risk to the foetus, on the 8th day of treatment, predosis serum levels of risperidone (i.e. 1 hour before the drug administration) and its active metabolite 9-hydroxy-risperidone were measured by means of high performance liquid chromatography (HPLC) testing. They resulted in low, nontherapeutic levels (Figure 2). After 16 days of hospitalization, an elective Caesarean delivery was carried out on the 5th day of pregnancy during the 38th week with good obstetrical outcomes (boy, 3.3 kg of weight, Apgar score of 9 at the 1st minute and 10 on the 5th minute).

After the delivery, an aggravation of the patient's symptoms was observed, showing general worsening of negativism. Thus, 6 days later, after the achievement of the informed consent, electroconvulsive therapy (ECT) was initiated. After the second session, the patient started to accept food intake and consequently oral medication, presenting a progressive remission of her psychotic symptoms. Later on, a second analysis of the predosis serum levels of risperidone was conducted, resulting in increased and therapeutic levels (risperidone 8.3 ng/ml, 9-hydroxy-risperidone 64.6 ng/ml). No secondary effects such as extrapyramidal signs were detected. Ten days later, after the 6th session of ECT, the patient was discharged due to her clinical improvement and a complete insight of her illness, following normal and complete nutrition. The same day, a new pre-dosis analysis of risperidone and its active metabolite serum levels was carried out, giving a result of

25.0 and 48.2 ng/ml, respectively. The presence of mild bradykinesia with facial hypomimia and mild upper limb joint rigidity was identified, without other extrapyramidal signs nor other secondary effects. During the ambulatory follow-up, risperidone was progressively titrated down as the patient presented an episode of akathisia and to reduce the mentioned extrapyramidal effects. ECT was stopped during the 9th session when the patient showed psychopathological stability with the possibility of developing a normal bond with her son.

Discussion

In spite of keeping the administered dose stable, the risperidone serum levels measured during the different periods of the patient's hospitalization presented great differences (Figure 2). Many things are happening at once (pregnancy, enteral feeding, ECT), and we believe it is important to address the possible causes of this variability and to figure out to what extent the NGT administration of risperidone can affect blood concentration and therapeutic effects.

The augmentation of plasmatic volume and the changes in protein binding could increase the apparent volume of distribution, resulting in a decrease in initial concentrations achieved after a loading dose, and a decrease in peak of plasma concentrations after multiple-dose administration. There is also a progressive increase in the glomerular filtration rate that can affect the clearance of drugs eliminated by kidneys [Frederiksen, 2001], as the case of risperidone and its active metabolite which are eliminated via kidney (~70%). Moreover, the well-known modifications in drug-metabolizing hepatic enzymes affect the steady-state concentration of drugs. Risperidone

Figure 2. Risperidone and 9-hydroxy-risperidone serum levels (expressed in ng/ml) during administration by nasogastric tube and by oral route. The first blood sample extraction coincides with the 38th week and 5th day of pregnancy, and with the 8th day of treatment with risperidone administered by nasogastric tube. The second and the third extraction coincide respectively with the 8th and the 19th day after delivery, that is, 2 days and 13 days after continuous risperidone oral administration.

is metabolized by the liver to 9-hydroxy-risperidone, mostly via the CYP2D6 enzymatic pathway. CYP2D6 exhibits a high degree of interindividual variability because of its more than 80 alleles variants, with possible consequences in serum level concentration and in clinical response [Cartwright *et al.* 2013]. Furthermore, its activity seems to increase during the third trimester of pregnancy [Anderson, 2005]. In order to exclude the presence of poor metabolizer polymorphisms in our patient and to better direct our findings, a pharmacogenetic analysis of CYP2D6 polymorphisms was carried out, showing that the subject is a conventional metabolizer.

Regarding our results, the difference in risperidone serum levels observed cannot be explained just by these pregnancy-induced changes in pharmacokinetics. Considering the serum level-to-dose ratio (calculated using the following formula: risperidone serum levels (ng/ml)/risperidone daily dose (mg); [Clark *et al.* 2013]), there was an increase of 97.2% in risperidone serum levels 8 days after delivery and a 305.5% increase 19 days later. With respect to the 9-hydroxy-risperidone, the increase was of 617% and of 412.5%, respectively, showing a greater intraindividual variability. In a series of two cases of our hospital's pregnant patients treated with an oral solution of risperidone (instead of NGT administration), a pre- and post-delivery drug serum level test was carried out, showing only a moderate

augmentation of 9-hydroxy-risperidone and stable levels of risperidone in the post-delivery analysis (Table 1). Furthermore, in a case series reported by Clark and colleagues [Clark *et al.* 2013], lamotrigine serum level-to-dose ratios in pregnant women were lower during pregnancy than in the post-partum period. In detail, compared with the third trimester, lamotrigine serum concentration increased by an average of 154% within 5 weeks of delivery.

In our clinical case, two analyses of post-delivery serum levels were carried out coinciding with the 2nd and the 11th day, respectively, after the acceptance of hydration, food intake and oral medication. Thus, we consider the nasogastric route of administration as crucial in the lack of absorption of risperidone. Studies addressing this issue are scarce and there are virtually no data available on the pharmacokinetics of APs, such as risperidone, administered by NGT. The best investigated drugs are theophylline, phenytoin and antibacterial quinolones but studies have led to contradictory conclusions [Podilsky *et al.* 2009]. Trying to address plausible causes, physicochemical incompatibilities between risperidone and polyurethane tubes may represent a decisive point. A study by Kotake and colleagues [Kotake *et al.* 2006] showed that amiodarone may adhere to or be absorbed by NGT. Earlier, Bass and colleagues [Bass *et al.* 1989] found that carbamazepine in suspension may bind to PVC feeding

Table 1. Pre-delivery and post-delivery serum levels of risperidone and its active metabolite 9-hydroxy-risperidone carried out in two schizophrenic pregnant women treated in our hospital. No increase in risperidone levels were observed, whereas a total increase of 380% and of 253% was observed in 9-hydroxy-risperidone levels in the first and second patient respectively. [See Clark *et al.* [2013].].

		Daily risperidone dose	Risperidone serum levels ng/ml (ratio*)	9-hydroxy-risperidone serum levels ng/ml (ratio*)
Patient 1	39 weeks 4 days of pregnancy	1 mg/day	<0.50 [0.5]	13.50 [13.50]
	1 day post-delivery	1 mg/day	<0.50 [0.5]	4.90 [4.90]
	52 days post-delivery	1 mg/day	<0.50 [0.5]	17.30 [17.30]
Patient 2	39 weeks of pregnancy	2 mg/day	<0.50 [0.25]	6.00 [3.00]
	5 days post-delivery	3 mg/day	<0.50 [0.16]	14.0 [4.67]
	25 days post-delivery	3 mg/day	<0.50 [0.16]	16.6 [5.53]

* The ratio was calculated using the following formula: risperidone serum level (ng/ml)/risperidone daily dose (mg).

tubes and dilution with water can be used to prevent this. Despite the use of oral solution, this interaction cannot be disregarded. With the aim to reduce the potential adherence or absorption of risperidone and to wash out active material from the tube, a 10 ml rinse was made before and after drug dispensation. A study of Messaouik and colleagues [Messaouik *et al.* 2005], showed that a 20 ml rinse improves recovery of both lansoprazole and omeprazole by about 20% compared with a 10 ml rinse, making this variable significant. In addition, we believe that the effect of rinsing may be stronger than with oral solution drugs to prevent tube adherence of crushed medication. Another important aspect to bear in mind is the possible interaction between the hyperproteic enteral formula and risperidone. Moreover, the cyclic gastric aspiration carried out to check gastric content before each bolus could somehow alter the absorption of the medication.

Conclusion

Our case report sheds some light on the erratic behaviour of risperidone when administered by NGT, with possible consequences on therapeutic outcomes and secondary effects. Nasogastric administration of risperidone to treat schizophrenia is not documented in the literature. As we wait for further research, the intramuscular route of administration should be taken into account as the first option in patients with enteral nutrition.

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Conflict of interest statement

The authors declare no conflict of interest.

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