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THERAPEUTIC DRUG MONITORING IS USEFUL WHEN PHARMACOGENETIC ASSESSMENT IS UNAVAILABLE: CASE REPORT OF DELUSIONAL DISORDER

LA MONITORIZACIÓN TERAPÉUTICA DE FÁRMACOS ES ÚTIL CUANDO LA EVALUACIÓN FARMACOGENÉTICA NO ESTÁ DISPONIBLE: CASO CLÍNICO DE TRASTORNO DELIRANTE

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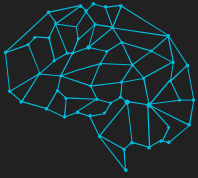
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RESUMEN

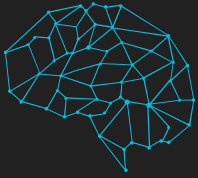
Los niveles plasmáticos de antipsicóticos han sido extensamente utilizados para la evaluación de la pobre respuesta terapéutica, la falta de adherencia y los eventos adversos en pacientes con trastorno delirante. No han sido frecuentemente utilizados como indicadores del estado metabólico, para determinar si un paciente con trastorno delirante es metabolizador pobre, intermedio o metabolizador ultra-rápido de antipsicóticos. Los tests de farmacogenética son, por supuesto, el método más idóneo para la última tarea, pero no son fáciles de obtener para su uso clínico. Reportamos el caso de una mujer de 46 años de edad con trastorno delirante que ha desarrollado efectos adversos inesperados con el tratamiento a dosis bajas de risperidona, y una pobre respuesta clínica. La monitorización de niveles plasmáticos indicó niveles elevados de risperidona y una ratio elevada concentración-dosis, que sugirió acumulación de risperidona no adecuadamente metabolizada. Paradójicamente, los efectos secundarios se incrementaron, cuando al reducir la dosis de risperidona, se añadió aripiprazol 5mg/día. Por ello, se realizó un cambio a olanzapina 5 mg/día. Se añadió sertralina 150 mg/día posteriormente para el tratamiento de síntomas depresivos comórbidos. Se alcanzó una respuesta clínica completa. A pesar de que otros factores pudieran haber contribuido a ello, la secuencia de eventos sugiere que la paciente pudiera ser metabolizadora lenta del CYP2D6, que metaboliza risperidona y aripiprazol. En caso de no disponibilidad de tests farmacogenéticos, la monitorización de niveles plasmáticos, ayudó a los clínicos a decidir el manejo apropiado del paciente.

Palabras clave: Trastorno delirante; niveles plasmáticos; Monitorización terapéutica de fármacos; CYP450.

ABSTRACT

Antipsychotic plasma levels have been extensively used in the assessment of poor treatment response, lack of adherence and adverse events in delusional disorder. It has not been used as an indicator of metabolizer status, to determine whether a delusional disorder patient is a poor, intermediate, or ultra-rapid metabolizer of antipsychotics. Pharmacogenetic probes are, of course, the right method for the latter task, but they are not readily available for clinical use. We report the case of a 46-year-old woman with delusional disorder who developed unexpected adverse effects to treatment with relatively low dose risperidone and poor symptomatic response. Blood level monitoring indicated high levels of risperidone and a high concentration-to-dose ratio, which suggested accumulation of unmetabolized risperidone. Paradoxically, extrapyramidal side effects increased when, after reducing the risperidone dose, 5 mg/day of aripiprazole was added. Consequently, the patient was switched to olanzapine 5 mg/day. Sertraline 150 mg/day was later added for comorbid depression. A complete symptomatic response was achieved. Although other factors may well have been at play, this sequence of events suggests that the patient was a slow metabolizer of CYP2D6, which metabolizes both risperidone and aripiprazole. With pharmacogenetic assessment not available, therapeutic drug monitoring helped clinicians decide on appropriate management.

Keywords: Delusional disorder; Plasma levels; Therapeutic drug monitoring; CYP450.



CASE

A 46-year-old woman with no previous psychiatric history was first admitted to our inpatient unit two years ago. On admission, she reported delusional ideas of several months' duration. The ideas focused mainly on her neighbours and relatives who, she was convinced, were spreading nasty rumours about her. She also harboured suspicions of jealousy against her husband, which had led her to verbally assault him. The patient was diagnosed with delusional disorder (DD), mixed type, with ideas of reference and persecution, as well as delusional jealousy. She was prescribed risperidone 4 mg daily. The response was poor and she developed extrapyramidal symptoms, namely rigidity, bradykinesia and masked facies. Following her inpatient stay, she was referred to day hospital but side effects (sedation, increased rigidity) worsened and she began to show symptoms of depression and anxiety. Risperidone and 9-OH-risperidone plasma levels were determined, and the active moiety (risperidone + 9-OH-risperidone) and concentration-to-dose ratio (C/D) were calculated, with the following results: risperidone: 10.1 ng/ml [normal: 2.8-9 ng/mL], 9-OH-risperidone: 98 ng/mL, risperidone +9-OH-risperidone: 109.1 ng/mL [normal: 10-120 ng/mL], C/D: 27.025 (accumulation of risperidone) (de Leon et al., 2010). Because active moiety plasma levels were high and the patient refused to continue the regimen because of extrapyramidal effects, risperidone was reduced to 2 mg/day and combined with aripiprazole 5 mg/day. However, several weeks later, adverse effects (rigidity, bradykinesia and akathisia) increased again. We hypothesized, at this point, that she was a poor metabolizer for CYP2D6. Her regimen was changed to olanzapine 5 mg/day. Good response to olanzapine was rapid and this improvement was maintained. Both psychotic and mood symptoms improved and side effects decreased. Plasma levels of olanzapine were in the normal low range: 21 ng/mL (normal: 20-80 ng/mL). During the follow-up period, mild depressive symptoms appeared, so sertraline 150 mg daily was added to the olanzapine. A complete response to this drug combination was achieved within 3 weeks. The patient was not available to give consent to publish this report so all identifiable personal details have been omitted or changed to make identification impossible.

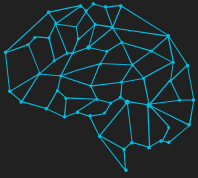
DISCUSSION

Standard treatment of DD involves both pharmacotherapy and psychotherapy as required (APA, 2013; Muñoz-Negro et al., 2020). Pharmacotherapy in most instances means an-

tipsychotics and, historically (Munro, 1978), pimozide was thought to be the drug of choice. More recently, however, comparative studies between first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA) have not shown superior effectiveness for pimozide but, instead, underscored the risk of cardiac side effects (e.g. QT prolongation) with this drug (Muñoz-Negro & Cervilla, 2016; Peralta & Cuesta, 2019). Currently, given the significant side effects and poor adherence to most FGA, SGA are usually seen as the more appropriate and safer option (Mews & Quante, 2013; González-Rodríguez et al., 2018). Regarding dose, some studies have reported that doses for DD patients need not be as high as those for schizophrenia (Liu et al., 2018). Other studies have found no dose difference requirements between the two disorders (González-Rodríguez et al., 2016). Our patient ultimately needed only olanzapine 5 mg/day.

Aside from the often knotty issues of adherence, the relatively poor response to antipsychotics in DD may have several explanations. As was the case for our patient, DD is often co-morbid with depression. Even when depression is not evident, some have hypothesized that serotonergic dysfunction is a characteristic of DD (Dimopoulos et al., 2008). The use of tricyclics and selective serotonin reuptake inhibitors (SSRIs), have reportedly been found helpful, especially in the somatic type of DD (Hayashi et al., 2004) and, of course, in DD patients with co-morbid depression (Kulkarni et al., 2018). De Portugal and colleagues identified an affective phenotype in a subgroup of patients with DD in their DELIREMP study (de Portugal et al., 2013). In our patient too, the combination of an antipsychotic and an antidepressant, olanzapine and sertraline, worked well.

The initial poor response to risperidone and the later good response to olanzapine might depend on the involvement of the serotonergic system in DD. King (1990), for instance, hypothesized that the expression of monosymptomatic hypochondriasis, a form of DD, is based on impairment of serotonin transmission and treatment may require 5-HT₂ antagonism (Guàrdia et al., 2020). In terms of the 5-HT profile, both risperidone and olanzapine are potent 5-HT_{2A} antagonists but olanzapine is also considered a potent 5-HT₆ antagonist (Meltzer & Massey, 2011). Antagonist activity at 5-HT₆ receptors has been suggested as an important factor in improving extrapyramidal effects of antipsychotic drugs (Ohno et al, 2011). Differences between risperidone and olanzapine in their actions at 5-HT receptors might, therefore, help to explain our patient's different reactions to the two drugs,



A different sort of explanation for therapeutic failures involves genetic variations in drug-metabolising enzymes. Cytochrome P450 enzymes are responsible for the biotransformation of more than 85% of existing drugs (Zanger & Schwab, 2013). The study of genetic variation in specific CYP450 genes has identified different populations: poor, intermediate, extensive or ultra-rapid metabolizers (Bertilsson, 2007). Poor metabolizers of any specific drug are more likely than others to develop adverse effects because of drug accumulation (Arranz et al., 2019). They are, as a result, treated with low doses, which may result in poor therapeutic response. This describes our patient, who was initially treated with a relatively low dose of risperidone, despite which she developed serious side effects. We knew that risperidone was metabolized by liver enzyme CYP2D6 (Suzuki et al., 2014) but we did not know the patient's metabolizer status, and genetic testing was not available to us.

Steady-state plasma levels of risperidone and the sum of risperidone and 9-OH-risperidone levels (the active moiety) were both high, suggesting an accumulation of unmetabolized drug, presumably an indication of poor metabolizing status vis a vis this enzyme (de Leon et al., 2010). The drug's active moiety and its concentration-to-dose ratio both indicated that the drug was not being appropriately metabolized and removed from the blood stream. It was, thus, accumulating and causing untoward effects. Similar findings have been reported in previous studies investigating the relationship between risperidone plasma levels and clinical outcomes and side-effect profiles (Riedel et al., 2005). This group found similar high active moiety plasma levels 49.9 (30.7) ng/ml with mean doses or risperidone of 4.3 (0.9) mg daily.

When the risperidone dose was reduced and aripiprazole (which does not, at low doses, induce extrapyramidal side-effects) added, the side-effects paradoxically, increased. This is because aripiprazole is also metabolized, in the main, by CYP2D6 (a little also by CYP3A4) (Suzuki et al., 2014). The adverse effects worsened. Olanzapine, on the other hand, is metabolized mainly by CYP1A2 (Söderberg & Dahl, 2013). When this drug was used, the patient's extrapyramidal side effects disappeared and her condition improved. Whether a person's genetic architecture makes them poor or rapid metabolizers with respect to a particular enzyme effectively predicts antipsychotic side-effects, and does so, of course, much more accurately than therapeutic drug monitoring.

However, pharmacogenetic probes are not available in most clinical settings (Arranz et al., 2019).

CONCLUSION

Despite evidence of the usefulness of therapeutic drug monitoring of antipsychotics, some have questioned its utility and it has failed to achieve uniform acceptance in the psychiatric community (Lopez & Kane, 2013). Measuring drug levels in the blood is useful in determining patients' adherence to their prescribed regimen. It is also useful in ruling out drug toxicity (de Leon, 2020). In this paper, we show how it can also serve a different purpose, namely, by indicating that a level is low or high, it can imply a person's metabolizer status with respect to the main enzyme metabolizing of the drug in question. In the presence of side effect severity and poor response, there is always an urgent clinical need to change medications. Therapeutic monitoring gives clinicians a good clue as to what drug to try next, namely one with a different metabolizing pathway.

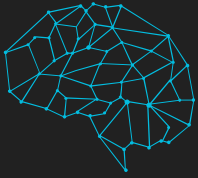
In summary, we report the case of a woman with DD who responded poorly to risperidone treatment, presenting undue extrapyramidal side effects. This was paradoxically made worse when the risperidone dose was lowered and aripiprazole added. When finally switched to olanzapine, whose metabolic pathway is different, the patient's extrapyramidal symptoms disappeared and her psychotic symptoms responded to treatment. Despite the absence of pharmacogenetic assessment, clinicians were able to make the right decision about the next antipsychotic drug to try. Therapeutic drug monitoring can serve as a useful guide to appropriate management.

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