Posthallucinogen-Like Visual Illusions (Palinopsia) with Risperidone in a Patient without Previous Hallucinogen Exposure: Possible Relation to Serotonin 5HT2a Receptor Blockade

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Background: Previous reports document visual illusions resembling hallucinogen persisting perception disorder (HPPD) after risperidone treatment in patients with histories of previous LSD exposure. **Methods:** We report a case with visual disturbances resembling HPPD after each of three consecutive risperidone dose increases. **Results:** Contrasting with previous reports, our patient lacked any history of substance abuse, particularly hallucinogen exposure. She lacked neurologic or other contributory illnesses. Illusions generally remitted within 48 hours each time. Coadministration of trazodone and clonazepam may have contributed to these phenomena, although clonazepam has been used to treat this condition. She had been unusually sensitive to the side-effects of many psychotropics. **Conclusions:** This case is unique due to the absence of substance abuse. This and another report note heightened sensitivity to medication side-effects. Visual phenomena resembling HPPD evidently can occur with risperidone and, possibly, other atypical antipsychotics and certain antidepressants regardless of previous hallucinogen use. Several lines of evidence implicate reduced 5HT2a serotonin receptor stimulation rather than increased 5HT2c stimulation.

Introduction

Visual perceptual disturbances in users of lysergic acid diethylamide (LSD) have been reported with the serotonin 5-HT2/dopamine D2 antagonist risperidone (*Abraham* and *Mamen*, 1996). We encountered a patient lacking any history of substance abuse who complained of visual perceptual disturbances following each of three distinct dose increases of risperidone. Review of a MEDLINE search revealed no identifiable previous reports of such phenomena in patients treated with risperidone in the absence of previous hallucinogen exposure.

Case Report

A 55 year-old white female with a sixteen year history of bipolar disorder presented as an outpatient in a nonpsychotic manic relapse. Her symptoms included euphoria, grandiosity, increased energy, decreased need for sleep, hyperactivity, flight of ideas and poor judgment, all of which had gradually increased over several weeks. Over the past sixteen years the patient had averaged one to two bipolar episodes yearly (totalling four depressive and ten manic lifetime episodes). She was fully functional when euthymic, maintaining a full-time job. She had been a responsible, disciplined woman who enjoyed working as a secretary. She denied any history of alcohol or substance abuse (including caffeinism). She was followed by one of the authors (ECL) for the previous 9 years and had always been a highly reliable patient. She did not drink alcohol or use substances and previous urine drug screens had always been negative. She had a normal childhood and developmental history. She got along well with her parents and siblings and had been a compliant child and adolescent. MRI studies of the brain showed no abnormalities. Other laboratory investigation, including thyroid studies, were unremarkable except for a mild chronic elevation of creatinine.

The patient had an extensive history of severe and disabling side-effects with most standard biological therapies for bipolar disorder. After 6 years of lithium, she developed mild chronic renal insufficiency, with an average creatinine of 1.6, and her nephrologist recommended she discontinue lithium. Valproate produced a severe rash, and carbamazepine resulted in marked leukopenia. She was unusually sensitive to the parkinsonian side-effects of neuroleptics. Even chronic administration of risperidone at doses as low as 1 mg daily eventually led to parkinsonism. She developed substantial urinary retention with edema when anticholinergics were added to the regimen. The patient became ataxic on low doses of clonazepam (0.25 – 0.5 mg/day) as well as other benzodiazepines at dose-equivalent amounts. She could not tolerate antihistamines or barbiturates either.

In light of these intolerances, a conservative regimen had been employed. The patient was maintained on trazodone 150 mg and risperidone 0.5 mg at bedtime while euthymic. After 30 days on this regimen, her mother became ill and the patient developed symptoms of nonpsychotic manic relapse. Clonazepam was therefore added, however the symptoms of mania progressed over the next 6 days. Risperidone was then increased to 1 mg at bedtime. Thus, the patient was now on a low dose regimen of trazodone 150 mg, risperidone 1 mg, and clonazepam 0.25 mg, each at bedtime. In the early morning after the second night of this regimen (i. e., after the second dose

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of risperidone 1 mg), while fully awake, the patient noticed a "flesh-colored membranous" halo of light surrounding her hand. As she moved her hand, the light would follow as a trail, which the patient called "a streamer". She also reported a vivid after-image of a dim light upon closing her eyes. These phenomena remitted the next day, but her mania escalated, and she was hospitalized on a psychiatric ward at a general hospital.

Over the course of several days, her risperidone was advanced to 5 mg b.i.d. Trazodone and clonazepam were maintained at the previous doses. After this risperidone dose increase, she reported seeing "streams of light" projecting from the metallic beads on her blouse while awake and fully alert. She described these "streamers" as "3 inch long lines of light", the same metallic color as the beads, in rays shining downward and forward at right angles. These visual illusions resolved within 48 hours. The mania eventually remitted and the patient was discharged from the hospital on trazodone 150 mg h.s., risperidone 5 mg bid, and clonazepam 0.25 mg h.s., without further visual events. She gradually developed oversedation and a parkinsonian resting tremor over the next 3 months. Consequently, trazodone was reduced to 50 mg h.s., risperidone to 2 mg b.i.d., and clonazepam was increased to 0.5 mg h.s. The visual illusion did not recur.

Five months later (8 months after the previous hospital discharge), the patient was readmitted for a new hypomanic episode. She had continued on risperidone 2 mg b.i.d., trazodone 50 mg h.s., and clonazepam 0.5 mg h.s. Risperidone was then increased to 3 mg b.i.d. and trazodone was increased to 300 mg h.s. The following day, the same visual phenomena of the previous hospitalization reappeared while she was awake and fully alert. The "streamers" resolved a few days after discontinuing risperidone.

In summary, the visual phenomena appeared after 3 consecutive dose increases of risperidone. The doses of trazodone and clonazepam remained without change during the first two increases in risperidone whereas the third risperidone increase was accompanied by an increase in trazodone. Prior to the addition of risperidone, the patient denied any similar phenomena despite dose increases of trazodone to 450 mg h.s. and clonazepam to 3 mg h.s. Although neuroopthalmological examination was not undertaken, visual fields had been full to confrontation. Risperidone was discontinued several months following the third episode of visual illusions and the patient has not suffered recurrent visual illusions in the 30 months subsequent to this third episode.

Discussion

Ophthalmologists refer to these drug-induced visual illusions as palinopsia, despite the absence of structural posterior cerebral hemispheric lesions (*Hughes* and *Lessell*, 1990; *Kawasaki* and *Purvin*, 1996). Although similar perceptual disturbances have been reported in psychosis (*Abraham*, 1983), our patient was not psychotic. Moreover, she denied experiencing these phenomena ever before. The phenomena had never been present during any previous episode of mania or depression despite intensive evaluations over the preceding 9 years. Neither has the patient suffered a recurrence over the past several years since risperidone was discontinued. There has been no evidence of diseases causing transient palinopsia in our patient. Rather, the patient complained of these phenomena immediately following 3 consecutive dose increases in risperidone. This is consistent with rapid binding of risperidone to cortical 5HT2 receptors within several hours of administration (*Nyberg* et al., 1993). Resolution of the palinoptic visual illusions several days following their onset cannot be explained but may relate to habituation, physiological accommodation, or some other mechanism.

The visual illusions experienced by our patient may, therefore, relate to serotonin 5HT2a receptor blockade. These illusions strikingly resemble the phenomena of hallucinogen persisting perception disorder. Hallucinogens such as LSD act as serotonin 5HT2a and 5HT2c receptor agonists (*Sanders-Bush* et al., 1988; *Glennon*, 1990). Relatively reduced 5HT2a and 5HT2c receptor stimulation after ceasing hallucinogen use is therefore likely, possibly relating to post-hallucinogen perceptual phenomena. Recently, similar visual perceptual disturbances after risperidone administration have been reported in several patients with histories of LSD use (*Abraham* and *Mamen*, 1996). These cases comport with a deficient 5HT2a receptor stimulation hypothesis since risperidone blocks this receptor (*Schotte* et al., 1996).

Although a history of hallucinogen exposure was absent in our patient, acute increases in 5HT2a receptor blockade after the three consecutive dose increases of risperidone may nevertheless have led to these visual phenomena. Moreover, "visual trails" have been reported with trazodone (*Hughes* and *Lessell*, 1990) as well as nefazodone (*Kraus*, 1996; *Schwartz*, 1997), antidepressants with 5HT2a antagonist properties (*Giannangeli* et al., 1999; *Hedges* et al., 1996). These cases were not associated with previous LSD exposure. Thus, there is reason to believe that 5HT2a blockade by risperidone can lead to visual illusions even without previous LSD use. Furthermore, although visual illusions corresponded to risperidone dose increases, trazodone may have augmented the phenomena in our patient by further enhancing 5HT2a blockade since both risperidone and trazodone block this receptor.

Another possibility is that trazodone or clonazepam produced palinoptic illusions in our patient through 5HT2c receptor stimulation. Trazodone itself reduces serotonin reuptake and thereby enhances the availability of serotonin to receptors, including 5HT2c. Furthermore, the trazodone metabolite, meta-chlorophenylpiperazine, acts as a 5HT2c agonist and its effects are mimicked by LSD in rats (*Callahan* and *Cunningham*, 1994). The effects of clonazepam resemble those observed with 5HT2c agonists in a murine dorsolateral periacqueductal gray stimulation model of panic anxiety (*Jenck* et al., 1998). Clonazepam also potentiates serotonin agonist-mediated head twitches in mice (*Moser* and *Redfern*, 1988), a behavior thought to be mediated by 5HT2a/2c stimulation (*Takeuchi* et al., 1997). However, 5HT2c stimulation seems a less likely mechanism in our patient. Clonazepam reduces the synaptic availability of serotonin (*Wagner* et al., 1986; *Lima* et al., 1993, 1995), reducing serotonin availability to the 5HT2c receptor.

Trazodone, taken by our patient, actually antagonizes 5HT2a/2c head twitches in mice (*Takeuchi* et al., 1997). Moreover, risperidone also is a 5HT2c antagonist (*Canton* et al., 1994), and the palinopsia correlated with dose increases of risper-

idone rather than trazodone or clonazepam. A Medline literature search disclosed no reported drug interactions between risperidone and trazodone or clonazepam, suggesting that the illusions represent a risperidone effect, rather than an unidentified, secondary, risperidone induced, pharmacokinetic or pharmacodynamic enhancement of effect of either trazodone or clonazepam. In the latter event, it is also more likely that the palinopsia would increase over several days as plasma levels continued to rise, rather than the actually observed decrease. Furthermore, palinoptic illusions have been reported with nefazodone (*Kraus*, 1996; *Schwartz*, 1997), a drug with 5HT2a and 5HT2c antagonist properties (*Hedges* et al., 1996). Nefazodone is metabolized to the 5HT2c agonist metachlorophenylpiperazine, but much less so than is trazodone (*Hedges* et al., 1996). Further still, LSD is considered to exert its psychic affects primarily through the 5HT2a receptor rather than through 5HT2c (*Aghajanian*, 1994; *Almaula* et al., 1996; *Newton* et al., 1996). Finally, it has been proposed that LSD destroys cortical GABAergic interneurons, thereby reducing GABAergic inhibition on visual circuits and presumably leading to palinopsia (*Abraham*, 1993; *Kawasaki* and *Purvin*, 1996). Both 5HT2a (*Marek* and *Aghajanian*, 1996) and 5HT2c (*Green* and *Grant*, 1998) agonists exhibit effects consistent with enhanced GABA release. Whereas 5HT2c stimulation in our patient should therefore increase GABAergic visual circuit inhibition, 5HT2a blockade would antagonize excitation of cortical GABAergic interneurons (*Marek* and *Aghajanian*, 1996) and predispose to the visual circuit disinhibition proposed in palinopsia. Consequently, the palinopsia observed in our patient probably relates to 5HT2a blockade rather than 5HT2c stimulation, although the latter is not impossible.

Analogous to 5HT2a antagonism, reduced 5HT2a stimulation due to disrupted serotonin tracts may underlie complex visual phenomena reported after midbrain lesions (*Geller* and *Bellur*, 1987; *Kolmel*, 1991; *Lauterbach* and *Spears*, 1997). We recently treated such a patient with paroxetine, leading to resolution of visual after-images which were refractory to carbamazepine, tricyclic antidepressants, ondansetron, buspirone, and benzodiazepines (*Lauterbach* and *Spears*, 1997). Paroxetine, a serotonin reuptake inhibitor, would be expected to increase serotonin availability to postsynaptic receptors and ameliorate conditions attributable to reduced 5HT2a stimulation, but it would likely aggravate conditions attributable to increased 5HT2c stimulation. Consequently, this additional line of evidence supports the concept of reduced 5HT2a stimulation in mediating palinopsia.

Heightened sensitivity to side-effects was noted in our case and another (*Morehead*, 1997). While an exact mechanism for these phenomena remains to be defined, it will be of interest to determine if similar visual phenomena are consistently noted in patients treated with 5HT2a antagonizing atypical antipsychotics and antidepressants regardless of previous hallucinogen exposure.

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