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LETTER TO THE EDITOR

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Imipramine, methylphenidate and valproic acid-related EPS in a child: a case report

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Methylphenidate is a stimulant agent that has been used in attention deficit hyperactivity disorder (ADHD); valproic acid is an anticonvulsant and an effective mood stabilizer (Scahill and Martin, 2003) and imipramine is a tricyclic antidepressant (TCA). Some studies have reported a positive effect of imipramine on ADHD symptoms, while others reported it to be ineffective (Gundersen and Keller, 2003; Winsberg et al., 1980). Methylphenidate (CYP2D6), valproic acid (CYP2C9) and imipramine (CYP2C19, CYP2D6, CYP3A) are metabolized by several CYP enzymes. Psychotropic drug interactions are not rare in combination therapy. One drug can interact with other drugs and substances at a variety of points during distribution and metabolism. Most interactions occur at the CYP isoenzyme complex in the liver (Oesterheld and Flockhart, 2003).

Extrapyramidal symptoms (EPS) (dystonic reaction, rigidity and akathisia) occur as a result of D_2 receptor blockade (Findling et al., 2003). EPS are more common with high-potency neuroleptics (Scahill and Martin, 2003). However, it is not unusual for EPS to manifest during other psychotropic drug therapy (Ozalp et al., 2006). Moreover, younger patients appear to be at high risk of developing EPS. EPS can be controlled with a reduced dose of medication or be treated with intramuscular or oral diphenhydramine, benztropine or trihexyphenidyl administration (Findling et al., 2003).

EPS are rare adverse drug reactions to antidepressant agents. Selective serotonin reuptake inhibitors (SSRIs) have been reported to induce extrapyramidal signs and symptoms but TCAs have been less frequently reported (Lambert et al., 1998; Leo, 1996; Mamo et al., 2000; Schillevoort et al., 2002). A literature review on children and adolescents revealed only three case reports where SSRIs induced EPS (Diler et al., 2002; Horrigan and Barnhill, 1994; Sokolski et al., 2004), while only one EPS-related SSRI + TCA combination has been reported (Figueroa et al., 1998) and no EPS-related TCA alone has been reported. This may be a consequence of serotonergically mediated inhibition of the dopaminergic system, monoamine oxidase inhibitor discontinuation, comorbid Parkinson's disease and possibly deficient cytochrome P450 (CYP) isoenzyme status (Lane, 1998). Hedenmalm et al. (2006) reported that the risk of EPS with SSRIs seems to increase with advanced age and the presence of the A1 allele of the DRD2 *Taq*IA polymorphism.

EPS are very rare side-effect in valproic acid administration, particularly in children. It has been suggested that EPS may occur because of a disturbance in the GABAergic pathways inducing reversible dopamine inhibition (Ricard et al., 2005). One child (Alvarez-Gomez et al., 1993) and eight adults with epilepsy reported that they developed EPS during sodium-valproate therapy (Masmoudi et al., 2000; Ricard et al., 2005; Sasso et al., 1994). There are no EPS reports relating to stimulant usage.

In this paper, we present a case under multiple pharmacological treatment who developed EPS (oculogyric crisis) shortly after the adjunct of imipramine to a combination of methylphenidate and valproic acid, which had been administered for 1 yr.

Case report

'Y' is a 10-yr-old female who was diagnosed with ADHD and childhood bipolar disorder according to DSM-IV criteria. She was diagnosed with ADHD because of symptoms such as hyperactivity, inattention, impulsivity and oppositional behaviours. The diagnosis of childhood bipolar disorder was made because of symptoms such as insomnia, agitation, labile mood, including depressive and elevated mood. Diminished interests, psychomotor agitation, fatigue, feeling of worthlessness and thoughts of death were seen during the depressive period. Grandiosity, decreased need of sleep, flight of ideas and becoming more talkative than usual were seen during the hypomanic period. These periods returned over the period of a few days. Y's aunt suffered from major depression. Initial medical work-up including whole blood count, blood chemistry panel, liver function

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tests, ECG, and thyroid function tests revealed nothing of significance.

Methylphenidate was started at 5 mg t.i.d. and was increased to 10 mg t.i.d. for the ADHD symptoms. Additionally, first 10 mg/kg.d valproic acid was started which was increased to 20 mg/kg.d for bipolar disorder symptoms. This treatment was continued for 1 yr and there were no significant side-effects. ADHD symptoms improved significantly and frequency and severity of labile mood periods were reduced with this combination treatment. Because of depressive mood and aggression, 25 mg/d imipramine was added to the treatment by an adult psychiatrist. Oculogyric crisis symptoms including ocular pain and sustained upward gaze occurred on day 3 of this combination treatment. No physical findings, abnormal movements, or other EPS were observed in 'Y'. A dose of 2 mg benztropine was administered intramuscularly. Oculogyric crisis symptoms improved completely within a few hours. Valproic acid blood level and liver function tests were normal at this time. Imipramine administration was discontinued. Benztropine did not need to be administered again after the discontinuation of imipramine. Following this, methylphenidate and valproic acid treatment was continued for 1 yr. She did not re-experience EPS.

Discussion

ADHD and childhood bipolar disorder are frequent comorbid conditions. Lithium and anti-epileptics are effective in the treatment of bipolar disorder in children. Lithium is not used because of the high risk of side-effects in children. For these reasons valproic acid was used in this case (Biederman and Faraone, 1999; Woolston, 1999).

Polypharmacy may cause adverse effects including the serotonin syndrome, withdrawal phenomena, extrapyramidal side-effects, and drug–drug interactions. Teoh et al. (2002) reported on a child who developed EPS while receiving a combination of risperidone, methylphenidate, sertraline, tropisetron and ketorolac. Moreover, Conforti et al. (1999) reported EPS associated with a combination of nortriptyline, venlafaxine and valproic acid in an adult. It is almost impossible to discern which effects or side-effects belong to which drug in such situations. In this case, EPS appeared just after the addition of imipramine to methylphenidate and valproic acid treatment. In spite of the continuation of methylphenidate and valproic acid treatment EPS did not appear again throughout the year. It seems that the EPS were related to imipramine but can also be related to a change in blood level of the drugs and this change is connected with drug interactions. However, valproic acid blood level was normal at this time.

Drug-related EPS frequently occurred within the first month of treatment (Caley, 1997) but can appear at various times during treatment (Masmoudi et al., 2000). In this case, oculogyric crisis occurred on day 3 of imipramine treatment.

EPS are usually reversible by discontinuing the responsible agent or lowering the dose (Gill et al., 1997). In this case EPS decreased rapidly after benztropine administration. After the discontinuation of imipramine EPS did not occur again.

There is a dramatic increase in the availability of new psychotropic drugs and their use is growing in the paediatric population. Polypharmacy is becoming commonplace in clinical practice. The effects and side-effects caused by drug dosage can differ from children to adults. For this reason, treatment should be administered to children who require polypharmacy by experienced child psychiatrists.

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None.

Statement of Interest

None.

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