Clomipramine-Resistant, Fluoxetine-Responsive Obsessive Compulsive Disorder : A Case Report

SUCHAT PAHOLPAK, M.D.*

Abstract

Serotonin re-uptake inhibitors (SRIs), clomipramine and selective serotonin re-uptake inhibitors (SSRIs), are the first-line pharmacologic therapies for patients with obsessive compulsive disorder (OCD). However, 40 to 60 per cent of patients do not respond to adequate treatment trials of SRIs. SRI partial- and non-responders must be treated with augmentation strategies or put on another SRI since non-response to the first SRI does not necessarily indicate a non-response to a second SRI. Each treatment trial should run at least 10 weeks and if successful, the drug should be continued for at least 1 to 2 years and withdrawn gradually. The presented patient had a second episode of OCD which was resistant to more than 10 weeks of high dosage clomipramine even though he responded very well during the first episode 4 years earlier and had been off clomipramine for 3 years. Augmentation to clomipramine with lithium and then haloperidol consecutively also failed. When clomipramine was changed to fluoxetine, the OCD symptoms were responsive even at a starting dosage of 20 mg/day. The response improved as the dosage of fluoxetine was increased. The response reached a maximum and the patient coped very well in every aspect of daily life when the dosage of fluoxetine was increased to 60 mg/day. He had taken fluoxetine at this daily dosage for one year before the drug was tapered off. It has now been more than two years since he has had any OCD symptoms and clomipramine was terminated.

Key word : Resistant OCD, Clomipramine, Fluoxetine

PAHOLPAK S
J Med Assoc Thai 2002; 85: 1135-1138

* Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

CASE REPORT

A Thai male, 24 years of age, working as an engineer, sought psychiatric treatment for moderate distress. For a period of six months, he had a second episode of an irrational, unpleasant repetitive impulse to glance at the genital area of other males. He knew that the impulse originated in his own mind and was not imposed by any outside person(s) or influence(s). He tried to block the impulse but failed. His impulse caused him distress and interfered both with his occupational functioning and with enjoyment of leisure activities. He was diagnosed as having a moderately severe second episode of an obsessive-compulsive disorder (OCD).

The first episode occurred 4 years earlier, had the same symptoms, and responded well to 50 mg of clomipramine daily. He had been able to discontinue the clomipramine after taking it for one year. He then coped very well with every aspect of daily life. For this reason, he agreed to use clomipramine again. During the first few weeks of stepping-up the clomipramine dosage, he developed a single episode of major depressive disorder (MDD) accompanied by a moderately severe suicidal attempt. This necessitated hospitalization for a period of two weeks during which time clomipramine was increased to 300 mg/day. Sedation and an increased appetite were the significant side-effects. His MDD responded well but the obsessive compulsive symptoms lessened only slightly. He agreed to the suggestion that clomipramine at this dosage should be continued for at least ten weeks at the outpatient clinic. However, he was still distressed with the intrusive repetitive impulse throughout the trial period. Another two 4-week periods of augmentation with 1,200 mg of lithium daily and 20 mg of haloperidol daily, consecutively, still proved unsuccessful.

Finally, the medication was changed to fluoxetine and the OCD symptoms and global functioning began to improve within the first two weeks of the initial dosage of 20 mg/day. His response reached an optimum level when administering 60 mg of fluoxetine/day. He had a high tolerance to this high dosage of fluoxetine. It is known that the course of OCD tends to be chronic and continuous treatment is associated with a significant reduction in the rate of relapse. So it was suggested, he continue on this high dosage fluoxetine for at least one year to prevent a relapse before tapering off 20 mg/day every two months. He has now abstained from medication for over 2 years and has not experienced any relapse. He has had a complete remission from OCD. He is functioning very well in every aspect of daily life.

DISCUSSION

This report demonstrates three clinical points. The first is that the patient's OCD was completely controlled by a high dosage of fluoxetine despite the initial resistance of the OCD to a high dosage of clomipramine. Theoretically, both clomipramine and fluoxetine have a similar efficacy as first-line anti-OCD agents[1,2]. However, a non-response to each anti-OCD drug will occur in between 40 and 60 per cent of the time and some patients have a preferential response. A non-response to one anti-OCD agent does not necessarily indicate a non-response to a second one[3]. The presented patient's resistance to clomipramine was not caused by the drug's side-effects since he had tolerated it very well throughout the trial period. He also showed no response to lithium or haloperidol augmentation while on the clomipramine. Augmentation will be successful if the response to the ongoing SRI is at least partial[4].

The second clinical point is that SRI as an antidepressant will have the same efficacy to treat depression if it was once efficacious in a previous depressive episode. But in the presented patient clomipramine as an anti-OCD drug did not show the same efficacy as it had before. In the body, clomipramine will be converted to desmethylclomipramine, which is a major metabolite and will accumulate on repeated administration of clomipramine[5]. Desmethylclomipramine is a potent inhibitor of norepinephrine re-uptake. If clomipramine's action as an anti-OCD depends on its ability to block 5 HT re-uptake (and not norepinephrine) then this action should be a function of the relative ratio between clomipramine and desmethylclomipramine. Clomipramine could lose effectiveness for OCD if the patient is an efficient converter of clomipramine to the active metabolite[6,7]. However, this does not explain the patient's positive response to clomipramine in his first OCD episode.

The third clinical point is that the improvement of the comorbid major depressive disorder did not correspond with the clinical severity of the OCD. A comorbid depression does not have any major

influence on the prognosis of OCD. Changes in depression and changes in OCD can occur independently (3,8). However, some researchers proposed that OCD is dominant over depression, dominates the course, dictates treatment choice and if OC symptomatology decreases longitudinally, depressive symptoms disappear too(9,10).

The author would like to re-emphasize that medications that increase central nervous system serotonergic transmission are efficacious in OCD. Both clomipramine and fluoxetine have similar efficacy and both drugs are first-line anti-OCD agents. The treatment strategy will, therefore, require using the serotonergic transmission drug in high dosages. As an anti-OCD drug, SRI will have a therapeutic lag longer than an antidepressant, so treatment in the trial period should last at least 10 weeks. The average response rate to each of the increasing serotonergic transmission drugs is between 40 to 60 per cent. The first drug, if unsuccessful, should be augmented by lithium, buspirone or haloperidol before changing to the second drug(11). Patients not responding to one drug may respond to the other. Therefore, several anti-OCD drugs should be tried sequentially before concluding severe drug resistance. The course of OCD tends to be chronic(12,13) so for those patients who are responsive in the acute phase of treatment, consideration should be given to administering maintenance doses of the SRIs for up to a year. When discontinuing SRIs, a gradual tapering process is indicated.

ACKNOWLEDGEMENT

The author wish to thank Bryan Roderick Hamman for assistance in improving the English and language presentation of the manuscript.

(Received for publication on May 26, 2002)

REFERENCES

1. Hollander E, Kaplan A, Allen Andrea, Cartwright C. Pharmacotherapy for obsessive-compulsive disorder. Psychiatr Clin North Am 2000; 23: 643-56.
2. Kaplan HI, Sadock BJ. Pocket handbook of emergency psychiatric medicine. Baltimore: Williams & Wilkins, 1993: 286.
3. Ellingrod VL. Pharmacotherapy of primary obsessive-compulsive disorder: Review of the literature. Pharmacotherapy 1988; 5: 936-60.
4. Griest JH, Jefferson JW. Obsessive-compulsive disorder. In: Gabbard GO, Atkinson SD, editors. Synopsis of treatments of psychiatric disorders. 2nd ed. Washington DC: American Psychiatric Press, 1996: 633.
5. Micallef J, Blin O. Neurobiology and clinical pharmacology of obsessive compulsive Disorder. Clin Neuropharmacol 2001; 24: 191-207.
6. Janical PG, Davis JM, Preslorn SH, Ayd F. Principal and practice of psychopharmacotherapy. Baltimore: Williams & Wilkins, 1993: 70.
7. Malcolm L, Herrington R. Biological treatments in psychiatry. Oxford: Oxford University Press, 1990: 143.
8. Robertson MM, Yakeley I. Gilles De La Tourette syndrome and obsessive-compulsive disorder. In: Fogel BS, Schiffer RB, Rao SM, editors. Neuropsychiatry. Baltimore: Williams & Wilkins; 1996: 851-3.
9. Zitterl W, Demal U, Aigner M, et al. Naturalistic course of obsessive compulsive disorder and comorbid depression. Longitudinal results of a prospective follow-up study of 74 actively treated patients. Psychopathology 2000; 33: 75-80.
10. Perugi G, Akiskal HS, Pfanner C, et al. The clinical impact of bipolar and unipolar affective comorbidity on obsessive-compulsive disorder. J Affect Disord 1997; 46: 15-23.
11. Romano S, Goodman W, Tamura R, Gonzales J and the collaborative research group. Long-term treatment of obsessive-compulsive disorder after an acute response: A comparison of fluoxetine *versus* placebo. J Clin Psychopharmacol 2001; 21: 46-52.
12. Etain B, Bonnet-Perrin E. Value of fluoxetine in obsessive-compulsive disorder in the adult: Review of the literature. Encephale 2001; 27: 280-9.
13. Vythilingum B, Cartwright C, Hollander E. Pharmacotherapy of obsessive-compulsive disorder: Experience with the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 2000; 15 (Suppl): 7-13.

ความผิดปกติชนิดย้ำคิดย้ำทำที่ดื้อต่อยาคลอมิพรามีนแต่ดีด้วยยาฟลูโอซีทีน : รายงานผู้ป่วย 1 ราย

*สุชาติ พหลภาคย์, พ.บ.**

ยายับยั้งการดูดซึโรโทนินกลับคืน (Serotonin re-uptake inhibitors หรือ SRIs) ได้แก่ยาคลอมิพรามีน (clomipramine) และยา selective serotonin re-uptake inhibitors (SSRIs) เป็นยาที่ใช้เป็นลำดับแรกในการรักษาความผิดปกติชนิดย้ำคิดย้ำทำ (obsessive compulsive disorder หรือ OCD) อย่างไรก็ตามผู้ป่วยประมาณร้อยละ 40-60 จะไม่ตอบสนองต่อ SRI แม้จะให้ในขนาดที่เพียงพอแล้ว ผู้ป่วยที่ไม่ตอบสนองต่อ SRI เลยและผู้ที่ตอบสนองต่อ SRI บ้างควรจะได้รับการรักษาด้วยการ augmentation หรือ เปลี่ยนเป็น SRI ขนานอื่น การไม่ตอบสนองต่อ SRI ชนิดแรกไม่ได้หมายความว่าจะไม่ตอบสนองต่อ SRI ชนิดอื่น การทดลองรักษาแต่ละครั้งควรจะนานอย่างน้อยที่สุด 10 สัปดาห์ และถ้าตอบสนองดีก็ควรจะให้ผู้ป่วยใช้ยานั้นนานอย่างน้อยที่สุด 1-2 ปี จากนั้นจึงค่อย ๆ ลดขนาดของยาลงจนกระทั่งหยุดยาในที่สุด ผู้เขียนได้รายงานผู้ป่วย 1 ราย ที่เป็น OCD ครั้งที่ 2 และมีอาการดื้อต่อการรักษาด้วยยาคลอมิพรามีนในขนาดสูงซึ่งใช้นานมากกว่า 10 สัปดาห์แล้ว ทั้งที่ตอนที่เป็น OCD ครั้งแรกเมื่อ 4 ปีก่อนอาการก็ดีขึ้นด้วยยานี้จนกระทั่งหยุดยานี้ได้นานถึง 3 ปี การ augment ยาคลอมิพรามีนด้วยยาฮาโลเพอริดอล (haloperidol) และยาลิเธียม (lithium) ตามลำดับก็ไม่ได้ผล เมื่อเปลี่ยนยาคลอมิพรามีนเป็นยาฟลูโอซีทีน (fluoxetine) อาการ OCD เริ่มดีขึ้นตั้งแต่เริ่มต้นใช้ยานี้ ในขนาดวันละ 20 มิลลิกรัม การตอบสนองต่อยาเพิ่มขึ้นเมื่อขนาดของยาฟลูโอซีทีนถูกเพิ่มขึ้น การตอบสนองได้ขึ้นถึงสูงที่สุดและผู้ป่วยสามารถทำหน้าที่ได้ดีทุก ๆ ด้านเมื่อใช้ยาฟลูโอซีทีนในขนาดวันละ 60 มิลลิกรัม ผู้ป่วยได้รับประทานยาฟลูโอซีทีนในขนาดนี้นาน 1 ปี จากนั้นจึงได้ค่อย ๆ ลดขนาดของยาลงจนกระทั่งงดรับประทานยานี้ ขณะนี้ผู้ป่วยสบายดีนานเกิน 2 ปีแล้ว โดยไม่ได้รับประทานยาเลย

คำสำคัญ : ความผิดปกติชนิดย้ำคิดย้ำทำที่ดื้อต่อการรักษา, ยาคลอมิพรามีน, ยาฟลูโอซีทีน

สุชาติ พหลภาคย์
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 1135-1138

* ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น, ขอนแก่น 40002