

Citalopram and priapism

Introduction

In December 1997 citalopram was granted a marketing authorisation in the Netherlands as antidepressant. Citalopram is a highly selective and potent serotonin (5-hydroxytryptamine, 5 HT) reuptake inhibitor with minimal effects on the neuronal reuptake of norepinephrine and dopamine. Priapism is not listed in the Dutch SPC of citalopram [1].

Priapism is the presence of a persistent, usually painful, erection of the penis unrelated to sexual stimulation or desire. Priapism of the clitoris has been reported but is extremely rare. Priapism is a true urologic emergency that may lead to permanent erectile dysfunction and penile necrosis if left untreated. Priapism should be medically evaluated and requires immediate medical intervention.

Reports

Until September 1st 2006 the Netherlands Pharmacovigilance Centre Lareb received 5 reports in which priapism was associated with citalopram. The reported latency was less than 48 hours after start of the treatment or after dose increase. In none of the patients permanent damage was reported. These reports are listed in table 1.

Table 1. reports of priapism associated with the use of citalopram

Patient, Sex, age*	Daily Dose	Concomitant medication	Other reported adverse drug reactions	Time to onset	Outcome
A M, 51	20 mg	none	sweating increased, dreaming abnormal, nausea, depersonalization, photophobia	day of dose increase from 10 mg to 20 mg	not reported
B M, 63	20 mg	sertraline, terbinafine	none	not reported	recovered without sequelae
C M, 33	20 mg	none	none	1 day	recovered without sequelae
D M, 60	40 mg	quetiapine	none	2 days after dose increase of 20 to 40 mg and addition of quetiapine	recovered without sequelae
E M, 32	40 mg	quetiapine	drug interaction	hours	recovered without sequelae

* No consumer reports included; A, B and E were reported by marketing authorization holders

Patient B was concomitantly treated with sertraline; priapism is listed in the Dutch SPC of sertraline [2]. Patients D and E were concomitantly treated with the antipsychotic quetiapine. In both cases the priapism occurred after citalopram was added to the treatment. Quetiapine was withdrawn in both patients; in patient D the dose of citalopram was reduced from 40 to 20 mg and in patient E the dose of citalopram was increased. Priapism is listed in the Dutch SPC of quetiapine [3]. In

addition to the 2 reports listed in table 1 Lareb received reports on 4 more cases of priapism associated with treatment with quetiapine. One of these reported cases was published [4].

We did not receive any reports of priapism associated with the recently marketed escitalopram, the active S-enantiomer of citalopram.

Other sources of information

Literature

Several case-reports on citalopram-induced priapism have been published: a 58-year-old man with a history of priapism resulting from trazodone use developed priapism after an inadvertent overdose of citalopram (60 mg) in addition to his usual daily dose of 40 mg [5], a 29-year-old man experienced an increase in frequency and duration of idiopathic priapism when citalopram 40 mg was added to maintenance risperidone dose of 3 mg [6]. Another three cases of clitoral priapism associated with treatment with citalopram were reported [7]. No publications could be retrieved of priapism in male patients with citalopram as monotherapy.

SPC

Priapism is listed in the Dutch SPCs of paroxetine, fluoxetine and sertraline but is not listed in the SPC of citalopram, the second most frequently used SSRI in the Netherlands. Priapism is also not listed in the Dutch SPCs of fluvoxamine or escitalopram.

Databases

Until September 1st 2006, the Netherlands Pharmacovigilance Centre Lareb received 62 reports on priapism. Of these, 21 reports concerned drugs with an ATC code starting with N06A (antidepressants) and 14 starting with ATC-code N06AB (SSRIs). The latter include the aforementioned five reports on citalopram, five on paroxetine, two on sertraline, one on fluoxetine and one on fluvoxamine. The association of citalopram and priapism is disproportional in the Lareb database (ROR 16.5 95% CI 6.6 – 41.5).

The database of the WHO contains a disproportional number of 19 reports of priapism associated with citalopram (ROR 2.8, 95% CI 1.8 – 4.4) and three reports of priapism associated with escitalopram (ROR 4.1, 95% CI 1.3 – 12.7).

Mechanism

Both vascular and neural mechanisms are involved in the pathophysiology of priapism; however, the mechanism that initiates the process is unclear. The most commonly proposed mechanism for drug-induced priapism is through α -adrenergic blockade, especially α 1-blockade. Another proposed mechanism in the pathogenesis of priapism which is relevant in the context of this discussion is serotonin mediated. In rats serotonin facilitates penile erections through stimulation of central 5HT_{1C} receptors and spinal/corporal 5HT_{2C} receptors [8,9].

Prescription data

Prescription data for SSRIs in the Netherlands over the last five years are presented in table 2.

Table 2. Number of patients treated with SSRIs in the Netherlands.

	2001	2002	2003	2004	2005
paroxetine (<i>Seroxat</i> [®])	328,450	323,840	304,380	303,580	284,860
citalopram (<i>Cipramil</i> [®])	59,721	82,826	101,280	121,090	130,130
fluoxetine (<i>Prozac</i> [®])	82,125	78,213	72,348	71,066	68,097
sertraline (<i>Zoloft</i> [®])	34,888	42,966	48,076	57,657	56,918
fluvoxamine (<i>Fevarin</i> [®])	44,795	41,147	38,457	36,687	34,252
escitalopram (<i>Lexapro</i> [®])				702	9,860

Source: GIP/College voor zorgverzekeringen 2006 (<http://www.gipdatabank.nl>)

Discussion and Conclusion

Although the frequency of SSRI-induced priapism is rare, the condition is a medical emergency with the risk of permanent erectile dysfunction. Priapism is listed in the Dutch SPCs of paroxetine, fluoxetine, sertraline and escitalopram but is not listed in the SPC of citalopram. Lareb received 5 reports of priapism associated with treatment with citalopram. Two of these reports concern citalopram as monotherapy. In 3 of these reports a causal contribution of another drug (sertraline or quetiapine) can not be excluded. However, the potential causal role of citalopram in cases of priapism is supported by case reports from literature, disproportionality for this association in both the Lareb and the WHO databases and the availability of a plausible mechanism involving serotonin in animals, although the mechanism that initiates the process is unclear.

References

1. Dutch SPC Citalopram[®]. (version date 19-9-2005) <http://www.cbg-meb.nl/nl/prodinfo/index.htm>.
2. Dutch SPC Zoloft[®]. (version date 18-08-2006) <http://www.cbg-meb.nl/nl/prodinfo/index.htm>
3. Dutch SPC Seroquel[®]. (version date 21-10-2003) <http://www.cbg-meb.nl/nl/prodinfo/index.htm>
4. Laan MHCM and Hummelen JW. Priapism and atypical antipsychotic agents: A case study. *Tijdschr Psychiatr* 2005; 47(3):175-179
5. Dent LA, Brown WC, Murney JD. Citalopram-induced priapism. *Pharmacotherapy*. 2002 Apr;22(4):538-41.
6. Freudenreich O. Exacerbation of idiopathic priapism with risperidone-citalopram combination. *J Clin Psychiatry*. 2002;63(3):249-50
7. Berk M, Acton M. Citalopram-associated clitoral priapism: a case series. *Int Clin Psychopharmacol*. 1997;12(2):121-2.
8. Millan MJ, Peglion JL, Lavielle G, Perrin-Monneyron S. 5-HT_{2C} receptors mediate penile erections in rats: actions of novel and selective agonists and antagonists. *Eur J Pharmacol*. 1997;325(1):9-12.
9. Simon P, Bertrand J, Costentin J. 5-HT_{1A} receptor blockade increases penile erections induced by indirect serotonin agonists. *Neuroreport*. 1993;5(3):229-30