

Non-puerperal lactation associated with antidepressant drug use

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Aims The aim of the present study was to estimate the relative risk of non-puerperal lactation in patients using antidepressants in general, and specifically for serotonergic (selective serotonin reuptake inhibitors (SSRIs) and clomipramine) and non-serotonergic antidepressants.

Methods All suspected adverse drug reactions in women and reported from January 1986 until August 1996 to the Netherlands Pharmacovigilance Foundation, a spontaneous adverse drug reaction reporting programme, were analysed. Adverse drug reaction (ADR) reporting odds ratios, defined as the ratio of the exposure odds among reported cases of non-puerperal lactation to the exposure odds of reported other ADRs, were calculated adjusted for age and year of reporting.

Results Thirty-eight cases of non-puerperal lactation were reported, of which 15 were associated with the use of antidepressant drugs. In general, antidepressants were associated with a higher risk of non-puerperal lactation in comparison with other drugs (ADR reporting odds ratio 8.3 [95%CI: 4.3–16.1]). Serotonergic antidepressants (selective serotonin reuptake inhibitors (SSRIs) and clomipramine) were associated with a higher risk (OR 12.7 [95%CI: 6.4–25.4]), whereas other antidepressants were not (OR 1.6 [95%CI: 0.2–11.6]), compared with all other drugs.

Conclusions Our results indicate that serotonergic antidepressants are associated with an approximately eight times higher risk of non-puerperal lactation compared with other antidepressants. This effect is probably mediated by an indirect inhibition effect of serotonin on the dopaminergic transmission. This finding is in line with the occurrence of other antidopaminergic effects, such as extrapyramidal symptoms, in patients using serotonergic antidepressants.

Keywords: non-puerperal lactation, antidepressant drugs, adverse drug reaction reporting systems, serotonin

Introduction

Non-puerperal lactation or galactorrhoea occurs relatively frequently as an adverse drug reaction (ADR) in patients treated with antipsychotic agents and other medicines acting as dopamine antagonists [1]. This effect has rarely been associated with the use of antidepressant drugs. Although several case reports of non-puerperal lactation associated with the use of antidepressant drugs have appeared in the medical scientific literature since 1964, it is still unknown whether the risk is the same for patients using different antidepressants.

The aim of this study was to evaluate the cases of non-puerperal lactation associated with antidepressant drugs reported to a spontaneous adverse drug reaction programme in the Netherlands and to assess whether these data show a difference in risk between classes of antidepressants.

Methods

Source

The Netherlands Pharmacovigilance Foundation is a network of eight regional centres for spontaneous adverse drug reaction reporting by health care professionals which has operated since 1986 and performs its tasks for the Dutch Medicines Evaluation Board since 1996. Health care professionals report suspected adverse drug reactions on a standard form. Data on this report form include gender and date of birth of the patient involved, information about the suspected medicine (name, dose, frequency, route of administration), information about the event (description of the event, onset of symptoms), concomitantly used medication, and other available information considered relevant by the reporter (including diseases and factors possibly related to the event, laboratory findings). The identity of the patient is only known to the reporting health care professional in accordance with current privacy legislation. All reported suspected adverse drug reactions are evaluated by a trained physician and/or pharmacist. The evaluation includes an assessment of each individual case, provision of

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feedback to the reporting health care professional, and classification according to the adverse reaction terminology of the World Health Organisation (WHO-ART) [2].

Validation of the cases

All cases of non-puerperal lactation (i.e. discharge of milk or milk-like secretions from the breast in the absence of pregnancy or beyond 6 months post-partum) reported in association with antidepressant drugs from January 1986 until August 1996 were analysed in detail. The health care professionals who reported these cases were approached, if necessary, for additional information using a mailed questionnaire. The main purpose of this questionnaire was to verify whether it probably was an adverse drug reaction (i.e. caused by the antidepressant drug) or whether it occurred during treatment with the antidepressant but was not likely to be caused by it. The following questions were asked: 1) What was the course and outcome of the lactation? 2) Have prolactin levels been determined and, if so, what were they? 3) Was any other illness present which could have caused the lactation disorder, such as prolactinoma, hypothyroidism, liver cirrhosis or severe renal disease? 4) Was the woman ever pregnant and, if so, when was the last pregnancy? In addition, information about concomitantly used medication (including oral contraceptives) was obtained from pharmacy dispensing records.

Analysis

All reported suspected ADRs classified as the WHO-ART included terms 'non-puerperal lactation', 'galactorrhoea' or 'hyperprolactinaemia' were defined as the cases. All reported suspected ADRs classified other than the included terms mentioned above were defined as the controls. The analyses were restricted to women, because predominantly women are at risk for developing non-puerperal lactation. An ADR-reporting odds ratio was calculated based upon the concepts of Finney [3], and as has been applied by Stricker *et al.* [4]. It is defined as the ratio of the exposure odds among reported cases of a certain suspected ADR to the exposure odds among reported non-cases (controls). The ADR reporting odds ratio provides an estimate for the risk of developing a certain event (i.e. non-puerperal lactation) for patients using the index drug relative to patients using reference drug(s). The index group consisted of antidepressants and the reference consisted of all medicines other than antidepressants.

For calculating the ADR reporting odds ratio two approaches were used. In the first approach, the ADR reporting odds ratio estimated the risk of non-puerperal lactation for all antidepressants relative to all medicines other than antidepressants. In the second approach, two categories of antidepressants were considered: those antidepressants that are rather selectively blocking the reuptake of serotonin in comparison with noradrenaline (i.e. the selective serotonin reuptake inhibitors (SSRIs) and clomipramine) [5], and antidepressants which do not have this selectivity (i.e. all other antidepressants). The second approach resulted in two ADR reporting odds ratios: one providing an estimate of the risk of non-puerperal lactation for women using

'serotonergic' antidepressants *vs* non-antidepressants, and the other providing an estimate of the risk of the other antidepressants relative to non-antidepressants.

The ADR reporting odds ratios were calculated as: $(a/c)/(b/d)$ (see Figure 1) and expressed as point estimates with 95% confidence intervals (95%CI). In addition, ADR reporting odds ratios adjusted for age and year of reporting were calculated using logistic regression analysis. Student's *t*-test was used to compare the mean ages of the cases and the controls. All statistical analyses were performed using EGRET.

Results

In total 14 439 suspected adverse drug reactions, restricted to women, were reported to the Netherlands Pharmacovigilance Foundation during the study period. There were 38 (3 per 1,000) reports of non-puerperal lactation. Fifteen cases (14 per 1,000) out of a total of 1,097 reported ADRs to antidepressant drugs were attributed to the use of an antidepressant drug by the reporting health care professionals. Characteristics of these fifteen patients are summarised in Table 1. Prolactin was measured in five patients and was within the normal range in four of these. The disorder resolved in all patients either after continuation, cessation or dose reduction of the drug. Other medicines associated with non-puerperal lactation were antidopaminergic antiemetics (5 cases), antipsychotic drugs (4), histamine H₂-receptor blockers (2), oral contraceptives (3), progestagens (3), fenfluramine, captopril, co-trimoxazole, valproic acid, astemizole and acetazolamide (1 each).

The reports of non-puerperal lactation (whether or not associated with an antidepressant) concerned women who were significantly younger than the women involved in other reports (mean (s.d.) age: 33 (10.6) *vs* 51 (18.9) years; $P < 0.001$). There was a clear association between the use of an antidepressant drug and the reporting of non-puerperal lactation (Table 2). Because the ADR reporting odds ratios were hardly affected by differences in age and year of reporting, only the adjusted ratios are shown. The ADR reporting odds ratio for the risk of non-puerperal lactation

		Reported suspected ADR	
		Nonpuerperal lactation	Other than nonpuerperal lactation
Suspected medicine	Antidepressant*	a	b
	Other than antidepressant	c	d

* either all antidepressants, or serotonergic antidepressants, or other antidepressants

Figure 1 Two-by-two table used for the calculation of the ADR reporting odds ratios.

Table 1 Characteristics of the case reports of non-puerperal lactation associated with antidepressant drugs.

Patient	Age (years)	Antidepressant	Dose	Time of onset	Concomitant drugs	Remarks
A	36	fluvoxamine	100 mg once daily	1 year	bromazepam	
B	17	fluoxetine	20 mg once daily	14 days	fluconazole	prolactin normal
C	30	fluoxetine	20 mg once daily	10 weeks	oral contraceptive	
D	44	paroxetine	20 mg once daily	5 months	oral contraceptive indomethacin	prolactin slightly elevated
E	41	paroxetine	20 mg once daily	6 months	diazepam acetylsalicylic acid codeine	
F	21	fluvoxamine	150 mg once daily	3 weeks	oral contraceptive pimozide doxycycline	
G	28	fluvoxamine	50 mg twice daily	4 months	oxazepam paracetamol	also amenorrhoea
H	38	paroxetine	20 mg once daily	2 months	–	prolactin normal
J	36	clomipramine	50 mg twice daily	6 months	levothyroxine	also amenorrhoea
K	31	fluoxetine	20 mg once daily	1 month	oxazepam	
L	50	fluvoxamine	50 mg once daily	several months	budenoside (nasal)	prolactin normal
M	32	amitriptyline	50 mg once daily	1 week	oral contraceptive pipamperon midazolam	
N	18	paroxetine	20 mg once daily	2 years	co-trimoxazole carbamazepine temazepam	
O	64	fluoxetine	20 mg once daily	3 months	–	
P	49	fluvoxamine	100 mg twice daily	2 months	domperidone temazepam alprazolam verapamil	prolactin elevated

Table 2 Comparison between reported suspected ADRs of non-puerperal lactation and reported other suspected ADRs.

	Reported suspected ADRs	
	Non-puerperal lactation (n = 38)	Other than non-puerperal lactation (n = 14,401)
Mean age (s.d.)	33.1 (10.6)	50.9 (18.7)
Ascribed to any antidepressant	15 (39%)	1,082 (8%)
ascribed to serotonergic antidepressant	14 (37%)	682 (5%)
ascribed to non-serotonergic antidepressant	1 (3%)	400 (3%)
Ascribed to other medicines	23 (61%)	13,319 (92%)

ADR-reporting odds ratios (95% CI) adjusted for age and year of reporting are: antidepressants *vs* non-antidepressants: 8.3 (4.3–16.1); non-serotonergic antidepressants *vs* non-antidepressants: 1.6 (0.2–11.6); serotonergic antidepressants *vs* non-antidepressants: 12.7 (6.4–25.4); serotonergic antidepressants *vs* non-serotonergic antidepressants: 8.2 (1.1–64).

associated with any antidepressant use *vs* non-antidepressant use was 8.3 (95%CI: 4.3–16.1). The serotonergic antidepressants were associated with a higher risk (odds ratio: 12.7 [95%CI: 6.4–25.4]) than were the other antidepressants (odds ratio: 1.6 [95%CI: 0.2–11.6]) in comparison with non-antidepressants. From these results, we may conclude that the risk in women using serotonergic antidepressants is eight times (odds ratio: 8.2 [95%CI: 1.1–64]) higher than in women using non-serotonergic antidepressants.

Discussion

The first case report concerning the occurrence of non-puerperal lactation associated with the use of an antidepressant

drug appeared in the medical scientific literature a few years after the introduction of imipramine [6]. Several case reports suggesting a (causal) relationship between the use of antidepressant drugs and the occurrence of non-puerperal lactation have been published since. These reports concerned a variety of antidepressant drugs, including amitriptyline [7], amoxapine [8, 9], clomipramine [10, 11], maprotiline [12], dothiepin [13], fluvoxamine [14, 15], fluoxetine [16, 17] and sertraline [18, 19]. According to our data we can add paroxetine to this list.

Although medicines are a common cause of non-puerperal lactation, this disorder can also have other etiologic origins or occur without an obvious pathologic reason [20]. Non-puerperal lactation can occur in patients with, for example,

hypothyroidism, prolactinoma, liver cirrhosis, or renal failure. Our patients with antidepressant associated galactorrhoea, did not have illnesses which may have led to lactation, nor had they recently been pregnant. Several women, however, used other medicines which have been associated with the occurrence of non-puerperal lactation: four women used oral contraceptives, two used an anti-psychotic drug and one woman used an antidopaminergic propulsive drug. With regard to oral contraceptives the effect on lactation is complex. Lactation is more likely to occur after cessation of the oral contraceptive than during its use [21]. Oestrogens may, however, also enhance the sensitivity of the breast to other lactation inducing factors. The use of oral contraceptives may therefore have predisposed these women to the development of lactation after the start of the antidepressant [22]. The same may be true for the women using an antipsychotic or domperidone: although they did not experience non-puerperal lactation without the antidepressant, the addition of the antidepressant may have triggered off the lactation. Although causality is difficult to establish from case reports, our findings provide further evidence that antidepressant drugs may occasionally induce non-puerperal lactation in susceptible patients.

Besides the individual case reports, also the ADR reporting odds ratios suggest a causal relationship between antidepressant drug use and the occurrence of non-puerperal lactation. We observed a disproportionate share of antidepressant drugs in the total number of case reports of non-puerperal lactation, as is reflected in the ADR reporting odds ratio of antidepressants as a group versus other medicines. Furthermore, our data indicate that this side-effect occurs approximately eight times as often with antidepressants relatively selectively blocking the reuptake of serotonin in comparison with other antidepressants.

One can argue whether estimates for the relative risk of actually developing an ADR derived from spontaneously suspected ADRs are valid, because only a fraction of all ADRs is actually reported. Non-differential under-reporting is not relevant with respect to validity but only with respect to precision [23]. Selective underreporting on the other hand is a serious threat to validity. It has, for example, been shown that side-effects which are known to the physician are less frequently reported than unknown or serious side effects [24]. This phenomenon may explain the small number of reported cases of non-puerperal lactation associated with the use of drugs which are known to cause this ADR rather frequently such as antipsychotic drugs and other antidopaminergic drugs. This effect may have led to an overestimation of the risk of all antidepressants when compared with other medicines. With respect to the difference between serotonergic and non-serotonergic antidepressants, we think, however, that it is unlikely that selective underreporting greatly overestimated or diluted the relative risk. Although the occurrence of non-puerperal lactation as a side-effect of treatment with an antidepressant has been reported in the literature, prescribers in general were not aware of this ADR and it is not mentioned in the official labelling of most of these medicines, nor was this ADR highlighted in the medical or lay press during the study period. In addition, in the Netherlands particular emphasis is not placed on the reporting of ADRs related to

new drugs, in contrast to many other countries. We feel, therefore that the ADR-reporting odds ratio provides a valid estimate of the actual relative risk of serotonergic vs non-serotonergic antidepressants for causing non-puerperal lactation. Unfortunately we were not able to study in detail whether the reporting rates for the newer antidepressants (predominantly serotonergic) were higher than for the older antidepressants (predominantly non-serotonergic).

In general, the mechanism that most frequently leads to non-puerperal lactation is an increase in serum prolactin [1]. The secretion of prolactin primarily is under the inhibitory control of hypothalamic dopamine which binds to dopaminergic-2-receptors on lactotrophic cells. Antidepressant drugs are not directly acting dopamine antagonists [5]. Several pharmacological studies showed that prolactin secretion is also mediated by serotonin. The serotonergic anorectic agent, fenfluramine, for example, is known to increase serum prolactin level [25]. Serotonin mediated prolactin release may be a result of either direct stimulation of postsynaptic serotonin receptors in the hypothalamus or presynaptic serotonin receptor mediated inhibition of dopamine release. The latter seems the most likely mechanism. It also explains the occurrence of extrapyramidal symptoms induced by selective serotonin reuptake inhibitors [26]. This means that serotonergic agents can actually cause effects related to dopaminergic inhibition: not via direct effects on the secretion or reuptake of dopamine or on the dopamine receptor, but indirectly via serotonin [27].

The role of prolactin in non-puerperal lactation is not clear. The results of animal and human studies investigating the effects of individual antidepressants on plasma concentrations of prolactin are controversial: they showed either normal or elevated levels. Studies with antipsychotics have shown that there is no simple relationship between galactorrhoea and the prolactin increment induced by these drugs [28]. In our study, prolactin levels were measured in five patients; in four of them these were within the range considered normal.

In conclusion, our data provided additional evidence for the existence of a causal relationship between the use of antidepressant drugs and the occurrence of non-puerperal lactation as an adverse event. Furthermore, they indicate that the risk is substantially higher in patients using serotonergic antidepressants in comparison with patients using non-serotonergic antidepressants. Although non-puerperal lactation usually is not harmful, patients may feel embarrassed about it. Furthermore, awareness of this ADR may prevent unnecessary diagnostic and therapeutic procedures.

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References

- 1 Davies DM. *Textbook of adverse drug reactions*. Oxford University Press, Oxford 1991: 355–356.
- 2 Anonymous. *International monitoring of adverse reactions to drugs. Adverse reaction terminology*. Uppsala, Sweden: WHO

- Collaborating Centre for International Drug Monitoring, 1995.
- 3 Finney DJ. Systematic signalling of adverse reactions to drugs. *Meth Inform Med* 1974; **13**: 1–10.
 - 4 Stricker BHCh, Tijssen JGP. Serum sickness-like reactions to cefaclor. *J Clin Epidemiol* 1992; **45**: 1177–1184.
 - 5 Richelson E. Pharmacology of antidepressants. Characteristics of the ideal drug. *Mayo Clin Proc* 1994; **69**: 1069–1081.
 - 6 Klein JJ, Segal RL, Warner RR. Galactorrhea due to imipramine. *N Engl J Med* 1964; **271**: 510–512.
 - 7 Rees WD. Lactation and ovarian cyst formation following treatment with amitriptyline. *Practitioner* 1967; **198**: 835–838.
 - 8 Gelenberg AJ, Cooper DS, Doller JC, Maloof F. Galactorrhea and hyperprolactinemia associated with amoxapine therapy. Report of a case. *JAMA* 1979; **242**: 1900–1901.
 - 9 Jaffe K, Zisook S. Galactorrhea in a patient treated with amoxapine. *J Clin Psychiatry* 1978; **39**: 821.
 - 10 Fowlie S, Burton J. Hyperprolactinaemia and nonpuerperal lactation associated with clomipramine. *Scot Med J* 1987; **32**: 52.
 - 11 Anand VS. Clomipramine—induced galactorrhea and amenorrhoea. *Br J Psychiatry* 1985; **147**: 87–88.
 - 12 Perez OE, Henriquez N. Galactorrhea associated with maprotiline. *Am J Psychiatry* 1983; **140**: 641–642.
 - 13 Gadd EM, Norris CM, Beeley L. Antidepressants and galactorrhea. *Int Clin Psychopharmacol* 1987; **2**: 361–363.
 - 14 Jeffries J, Bezchlibnyk-Butler K, Remington G. Amenorrhoea and galactorrhea associated with fluvoxamine in a loxapine-treated patient. *J Clin Psychopharmacol* 1992; **12**: 296–297.
 - 15 Bonin B, Vandel P, Vandel S. Fluvoxamine and galactorrhea. A case report. *Therapie* 1994; **49**: 149–151.
 - 16 Iancu I, Ratzoni G, Weitzman A, Apter A. More fluoxetine experience. *J Am Acad Child Adolesc Psychiatry* 1992; **31**: 755–756.
 - 17 Arya DK, Taylor WS. Lactation associated with fluoxetine treatment. *Aust NZJ Psychiatry* 1995; **29**: 697.
 - 18 Bronzo MR, Stahl SM. Galactorrhea induced by sertraline. *Am J Psychiatry* 1993; **150**: 1269–1270.
 - 19 Lesaca TG. Sertraline and galactorrhea. *J Clin Psychopharmacol* 1996; **16**: 333–334.
 - 20 Meyboom RH, Assies J, Bemt PM van den, de Koning GHP. Galactorrhea and gynecomastia as side effect of drugs. *Ned Tijdschr Geneesk* 1993; **137**: 2498–2503.
 - 21 Tyson JE, Zacur HA. Diagnosis and treatment of abnormal lactation. *Clin Obstet Gynecol* 1975; **18**: 65–93.
 - 22 Frantz AG. Prolactin. *N Engl J Med* 1978; **298**: 201.
 - 23 Tubert-Bitter P, Begaud B. Comparing safety of drugs. *Post Marketing Surveillance* 1993; **7**: 119–137.
 - 24 Inman WHW. *Monitoring for drug safety*. MTP Press Limited, Lancaster 1985.
 - 25 Barbieri C, Magnoni V, Rauhe WG, Zanasi S, Caldara R, Ferrari C. Effect of fenfluramine on prolactin secretion in obese patients: evidence for serotonergic regulation of prolactin in man. *Clin Endocrinol* 1983; **19**: 705.
 - 26 Arya DK. Extrapyramidal symptoms with selective serotonin reuptake inhibitors. *Br J Psychiatry* 1994; **165**: 728–733.
 - 27 Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry* 1996; **153**: 466–476.
 - 28 Muller EE, Locatelli V, Cella S, Penalva A, Novelli A, Cocchi D. Prolactin-lowering and releasing drugs. *Drugs* 1983; **141**: 1023–1025.

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