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Brief Report

Domperidone-Induced Acute Dystonia and Polycystic Ovary Syndrome

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Summary: The occurrence of acute dystonic reactions (ADRs) due to domperidone administration in two young women is reported. In both patients, a typical polycystic ovary (PCO) syndrome was found. The possibility that the relative hyperestrogenism typical of PCO syndrome acted as a facilitating factor for ADR is discussed. **Key Words:** Domperidone—Acute dystonia—Polycystic ovary syndrome—Hyperestrogenism.

Acute dystonic reaction (ADR) commonly appears with dopaminergic receptor blockers such as classical antischizophrenics or antiemetics (1). New antiemetics penetrate at least partially the blood brain barrier (BBB), thus blocking central D_2 receptors in addition to the ones in the area postrema where the emetic chemoreceptor trigger zone of the medulla is located (2). Metoclopramide, more frequently than other antiemetics, induces ADR (3–7).

Domperidone has a butyrophenone structure but it has been marketed in the last decade as an antiemetic with a very low degree of penetration of the BBB (8). Because of this, only 10 cases of domperidone-induced ADR have been reported to date (Table 1) (9–18). Domperidone is considered a safe and effective drug in counteracting nausea and vomiting caused by dopamine agonists and it is widely used in Parkinson's disease (PD) patients undergoing dopaminergic treatments (19).

We now report the occurrence of ADR after domperidone administration in two young women. Clinical assessment revealed that both women showed a polycystic ovary (PCO) syndrome with a typical relative hyperestrogenism (20), which might have acted as a facilitating factor for ADR.

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CASE REPORTS

Patient 1 was a 16-year-old girl who complained of a history of hirsutism; for 6 months before observation she had been amenorrheic. From the endocrine point of view, she proved anovulatory according to basal body temperature. Ultrasonographic monitoring showed typical enlarged ovaries and current hormonal evaluation demonstrated slightly elevated testosterone (T) and luteinizing hormone (LH) levels with low sex hormone-binding globulin (SHBG) levels (Table 2). These data confirm the clinical diagnosis of PCO syndrome and the presence of the so-called relative hyperestrogenism. After a total oral dose of 20 mg of domperidone, prescribed because of nausea and vomiting, she had orolingual dyskinesia and eye and head dystonia for about 1 h at the end of the 1st day of domperidone treatment.

Patient 2 was a 28-year-old obese woman with a history of menstrual disorders. Repeated previous endocrine study results demonstrated that her menstrual cycle was oligoanovulatory since increases in basal body temperature and progesterone plasma levels during the luteal phase of the cycle were occasionally observed, as is sometimes seen in women with PCO syndrome. Ultrasonographic evaluation showed enlarged ovaries, typically polycystic, with rare follicular development. The current hormonal assays showed slightly elevated blood T, LH, and prolactin levels, whereas blood levels of circulating follicle-stimulating hormone and SHBG were low (Table

TABLE 1. *Acute dystonic reactions due to domperidone*

Authors	No. in case report	Sex/age	Concomitant therapy	Dystonic features	Domperidone dose
Franck and Noel (9)	1	M/3 mo	None	?	4.2 mg/day p.o.
Biasini and Alberti (10)	1	M/4 mo	None	Opisthotonus, oculogyric crises, grimacing	10 mg/day p.o.
Sol et al. (11)	1	M/4 mo	None	Opisthotonus, oculogyric crises	4 mg/day p.o.
Shafrir et al. (12)	1	M/6 mo	None	Opisthotonus, oculogyric crises	2.7 mg/day p.o.
Steinherz et al. (13)	1	M/6 mo	None	Oculogyric crises	8.1 mg/day p.o.
Casteels-Van Daele et al. (14)	1	F/12 yr	Antiblastics	Trunk dystonia	10 mg i.v. (bolus)
Gonce et al. (15)	1	F/14 yr	Antiblastics	Oculogyric crises	20 mg i.v. (bolus)
Kofoed and Kamper (16)	1	F/15 yr	Antiblastics	Oculogyric crises	4 mg/kg/day p.o.
Madej (17)	1	F/21 yr	Fentanyl	Oculogyric crises, torticollis, upper limb dystonia	20 mg i.v. (bolus)
Debontridder (18)	1	F/27 yr	None	Oculogyric crises, opisthotonus	10 mg/day i.m.
This report	1	F/16 yr	None	Orolingual dyskinesia, oculogyric crises, opisthotonus	20 mg p.o.
This report	1	F/28 yr	None	Orolingual dyskinesia	50 mg p.o.

p.o., orally.

2). These data confirm the presence of the relative hyperestrogenism typical of patients with PCO syndrome. After a total dose of 50 mg of domperidone, prescribed because of nausea and vomiting, she had two episodes of orolingual dyskinesia, lasting 10 and 60 min, respectively, during the 3rd day of domperidone treatment.

After withdrawal of domperidone, dystonia/dyskinesia attacks were no longer observed in either patient. An exhaustive clinical and instrumental examination, including magnetic resonance imaging, was negative for CNS damage.

DISCUSSION

Because of the critical temporal relationship between domperidone administration and ADR appearance, this drug was probably the "offending" agent in both cases. Thus, a potential neuroleptic effect of this drug is suggested.

However, in spite of the extensive usage of domperidone, only 12 ADR cases have been described, including those in this report. Eight of these 12 cases conceivably had an increased permeability of the BBB, due to age-related immaturity, underlying disease, or anticancer therapy (Table 1), suggesting that a BBB breakdown could have allowed the drug to enter the brain. Interestingly, all four ADR cases with possibly intact BBB were female subjects of fertile age, indicating a possible role of ovarian steroids in the pathogenesis of ADR. This hypothesis is supported by our finding of PCO with a typical relative hyperestrogenic picture due to the high value of plasma estrogen/progestin levels in both our cases.

Accordingly, one might speculate that in female patients of reproductive age the BBB is disrupted in some way, but no data indicate that hyperestrogenism, typical in PCO patients, might be responsible for such an alteration. However, hyperestrogenism could act on the metabolism of domperidone, enhancing its plasma levels and thus its brain concentration. Steroid hormones strongly influence the drug metabolizing system, and estrogens in particular reduce this activity (21).

In addition, estrogens affect central dopaminergic activity and modify dopaminergic receptor sensitivity. Several clinical observations indicate a cause–effect relationship between increased estrogen plasma levels and extrapyramidal disorders such as chorea gravidarum (22) or chorea due to contraceptives (23). According to Bedard et al. (24) and Sandyk (25), estrogen administration is able to

TABLE 2. *Relevant hormone profile in the two case studies and corresponding range in normal controls*

Hormones	Case 1		Case 2		Control range
	Follicular phase	Luteal phase	Follicular phase	Luteal phase	
Luteinizing hormone, mU/ml	36	30	10.3	43	5–25
Follicle-stimulating hormone, mU/ml	8	4	2.4	3.7	5–15
Estradiol, pg/ml	44	26	35.6	153	50–200
Progesterone, pg/ml		1,800		3,500	above 8,000
Prolactin, mg/ml	8	11	27	41	5–15
Dehydroepiandrosterone, μg/ml	1	1	2.5	2.8	0.7–3.6
Sex hormone-binding globulin, ng/ml	4.6	6.4	7.1	5.1	12–23
Testosterone, pg/ml	783	708	820	950	500–700

decrease levodopa dyskinesias in PD. Moreover, experimental data suggest a neuroleptic-like effect for estrogens that are able to induce behavioural dopaminergic hypersensitivity and increase the number of D_2 striatal receptors (26).

We suggest that brain penetration by domperidone, though minimal, might induce ADR in women with PCO syndrome because of the D_2 striatal receptor hypersensitivity due to the PCO-related chronic estrogenic stimulation. Estrogens are also able to induce a hyposensitivity of D_2 striatal autoreceptors (27), thus facilitating the neuroleptic-induced blocking effect, which in turn enhances dopamine release, thus causing ADR (28). The possible presence of a hypersensitivity of D_2 hypothalamic receptors in PCO syndrome has been suggested to explain the finding of an enhancement of inhibitory effects of dopaminergic drugs on LH secretion in PCO patients (29).

This report needs to be extended to a larger number of cases to evaluate real prevalence and morbidity.

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