NOTE

Effects of Domperidone on Serum Prolactin Levels in Human Beings

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Abstract

Effects of domperidone, a dopaminergic antagonist, on serum prolactin levels were studied in 6 normal men and 6 normal cyclic women at the different phases of their menstrual cycles (i.e., the follicular, the preovulatory and the luteal phases). Domperidone (10 mg, i.v.) caused significant increases in serum prolactin in all cases within 15 min after the injection. The prolactin response was significantly ($p < 0.01$) higher in women than in men, and there was no significant difference in the prolactin responses among the three phases of the menstrual cycles. These results indicate that domperidone may be an effective stimulator of serum prolactin secretion in human beings.

It is well known that the dopaminergic mechanism plays an important role in regulating prolactin secretion (Takahara *et al.*, 1974; Shaar and Clemens, 1974; MacLeod and Lehmeyer, 1974; Donoso *et al.*, 1971). Some dopamine antagonists such as pimozide (Ojeda *et al.*, 1974; Maurer and Gorski, 1977) or metoclopramide (Judd *et al.*, 1976; Quigley *et al.*, 1979) have therefore been applied for clinical purposes as a dynamic test for prolactin secretion or to stimulate milk secretion in post-partum women.

Recently, an anti-emetic drug, domperidone (Figure 1), has been found to be a potent dopamine antagonist (Laduron and Laysen, 1979), and the stimulatory effect of this drug on prolactin secretion has been noted in rats (Denef and Follebouck, 1978; Kato *et al.*, 1980). The stimulatory effect of domperidone on prolactin release has also been demonstrated in human beings (Kamiji

et al., 1979; Camanni *et al.*, 1980). However, detailed information regarding the clinical use of this drug still remains to be provided. The present study was undertaken to investigate the effect of domperidone on serum prolactin levels in human beings, particularly studying the responses in normal cyclic women at different phases of the menstrual cycle.

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Fig. 1. Chemical structure of domperidone.

Materials and Methods

Six normal men and 6 normal cyclic women volunteered for this study. All subjects were informed and consented, and fulfilled the following criteria; normal physical examinations, normal routine blood chemistry and blood count, and stable serum creatinine levels. In every normal woman, tests were performed at the follicular phase (7–8 days after the onset of the menstruation), the preovulatory phase (2–3 days before the elevation of the basal body temperature, BBT), and the luteal phase (7–8 days after the elevation of BBT) of the different menstrual cycles. All tests were carried out between 09:00 and 11:30 with the subjects resting in a supine position after an overnight fast. Ten mg of domperidone was injected intravenously, and blood specimens were collected from the antecubital vein before, and 15, 30, 60, 90 and 120 min after injection. Blood samples were allowed to clot, centrifuged, and serum samples were stored at -20°C until assay. Serum prolactin levels were determined with a radioimmunoassay kit supplied by Daiichi Radioisotope Laboratories Ltd. (Japan). Serum estradiol levels were determined by a radioimmunoassay method using a specific antiserum to estradiol, which was supplied by Dr. A. Kanbegawa (Teikoku Hormone Mtg. Co. Ltd., Japan). Serum domperidone levels were measured in the laboratory of Kyowa Hakko Kogyo Co. Ltd. (Japan), using a specific radioimmunoassay method. Domperidone was supplied by Janssen Research Laboratory (Belgium), through the courtesy of Kyowa Hakko Kogyo Co. Ltd. (Japan). The statistical significance of differences between means were evaluated by Student's *t*-test.

Results

In the pilot study, the effect of different doses of domperidone on the prolactin responses was studied serially in the same normal men on 2 or 3 different occasions, 2–4 weeks apart. As shown in Table 1, 0.2 mg of domperidone produced a small but significant elevation in serum prolactin, and greater release occurred as doses of the drug were increased. A dose of 10 mg was used in the following studies. Figure 2 shows serum domperidone levels after i.v. injection of 10 mg domperidone. Serum domperidone levels reached the maximum

Table 1. Effects of different doses of domperidone on prolactin responses in normal men. Domperidone produced significant ($p < 0.01$) increases in serum prolactin after the injection in all groups.

Dose of domperidone mg	(N)	Serum prolactin, ng/ml	
		Baseline	15 min after injection
10	(N=6)	10.5 ± 1.6	$83.5 \pm 10.0^*$
2.5	(N=5)	10.9 ± 1.2	$54.0 \pm 14.1^*$
0.5	(N=3)	9.3 ± 2.1	$38.1 \pm 1.9^*$
0.2	(N=3)	11.5 ± 2.4	$31.4 \pm 5.3^*$

* $p < 0.05$ versus baseline level.

within 15 min after injection in all cases. The levels were slightly higher in women than in men, but there was no statistical significance. Figure 3 demonstrates the effect of domperidone on serum prolactin levels in normal subjects. Domperidone induced a significant ($p < 0.01$) rise in serum prolactin levels in all cases within 15 min after injection, and the responses were significantly ($p < 0.01$) higher in women than in men. Both serum estradiol levels and prolactin responses in the luteal phase were the highest, median in the preovulatory phase and the lowest in the follicular phase. However, there was no statistical difference (Table 2).

There was no serious adverse effect in any case. However, 2 female subjects noted slight stiffness on their cheeks, 2–3 min after domperidone injection, which continued for approximately 5 min.

Discussion

The present results clearly indicate that domperidone raises serum prolactin levels in human beings. Domperidone was reported to be a potent dopamine antagonist (Laduron and Leysen, 1979), and it is well known that the dopaminergic mechanism exerts its inhibitory effect on prolactin secretion *in vivo* (Kamberi *et al.*, 1971; Donoso *et al.*,

Fig. 2. Changes in serum domperidone levels after i.v. injection of 10 mg domperidone. The differences between men and women are not statistically significant.

Fig. 3. Effects of domperidone on serum prolactin levels in normal men and women. Every woman received the test at the follicular, the preovulatory and the luteal phases of the different menstrual cycles.

* $p < 0.01$ versus 3 female groups.

Table 2. Baseline estradiol and prolactin levels and the maximum prolactin increments (Δ ng/ml) in normal men and women. Each value represents mean $\pm$ SEM.

Subjects	(N)	Age	Baseline estradiol pg/ml	Baseline prolactin ng/ml	Maximum prolactin increase Δ ng/ml
Normal men	(N=6)	32.2 ± 1.4	$24.2 \pm 5.0^*$	10.6 ± 1.6	$75.3 \pm 9.4^*$
Normal women		30.3 ± 1.4			
Follicular phase	(N=6)		113.2 ± 19.1	19.5 ± 1.5	129.5 ± 20.1
Preovulatory phase	(N=6)		168.8 ± 27.0	11.5 ± 1.4	148.7 ± 15.4
Luteal phase	(N=6)		186.2 ± 31.3	13.6 ± 2.6	159.1 ± 17.0

* $p < 0.01$ versus 3 female groups.

1971; Takahara *et al.*, 1974) and *in vitro* (MacLeod and Lehmeyer, 1974; Shaar and Clemens, 1974; Smalstig *et al.*, 1974). It seems reasonable, therefore, to suppose that domperidone would affect prolactin secretion through the dopaminergic mechanism.

As for the site of action of domperidone, it was found that this drug decreased prolactin inhibiting factor (PIF) at the hypothalamus in rats (Kato *et al.*, 1980). Furthermore, in our preliminary data, it is seen

that domperidone neither stimulates prolactin release in hypophysectomized pituitary-autotransplanted rats, nor interferes with the inhibitory effect of bromocriptine on prolactin release in the same animals. These results would suggest that domperidone would act via the hypothalamus. This would not conflict with the recent report that domperidone did not cross the blood-brain barrier (Laburon and Leysen, 1979), because the hypothalamus was reported to

be supplied by the vessels arising directly from the basement of the brain (Lengvari and Halasz, 1974), which would make it easier for this drug to enter the hypothalamus. Some other dopamine antagonists such as metoclopramide (McCallum *et al.*, 1976; Judd *et al.*, 1976) or sulpiride (Mancini *et al.*, 1976; Aono *et al.*, 1979) have been reported to raise the serum prolactin level in human beings. Although the sites of action of these drugs have not been fully demonstrated, several investigators have suggested that, at least in part, they act directly on the pituitary (Iwasaki *et al.*, 1976; Debuljuk *et al.*, 1974; MacLead and Robyn, 1976). Thyrotropin releasing hormone (TRH), which also stimulates prolactin release in human beings (Jacoba *et al.*, 1971) has been reported to act primarily on the pituitary (Jacoba *et al.*, 1971; Tashjian *et al.*, 1971). These results, together with our previous data (Kato *et al.*, 1980), suggested that domperidone might stimulate prolactin release in a different manner from TRH or other dopamine antagonists (e.g. sulpiride and metoclopramide), and could therefore be a useful tool in obtaining important information about the regulation of prolactin secretion.

The reason why domperidone causes higher prolactin responses in women than men is not clear yet. Serum domperidone levels were slightly higher in women than in men (Fig. 1) and this might induce higher responses in women. However, the analysis of the individual data indicated that the prolactin responses were not directly related to serum domperidone levels as far as the present concentrations of domperidone are concerned. TRH (Jacobs *et al.*, 1973) and metoclopramide (Judd *et al.*, 1976) were also found to produce higher prolactin responses in women than in men, and it was suggested that estrogen might play an important role in producing such higher prolactin responses in women (Jacobs *et al.*, 1973; Judd *et al.*, 1976; Ehara *et al.*, 1975).

Recently, Judd *et al.* (1978) reported that prolactin responses to dopamine were highly correlated with serum estrogen levels. In the present study, both serum estradiol levels and prolactin responses were higher in women than in men (Table 2), which strongly suggested that there might be some relationship between the two. On the other hand, individual serum estradiol levels were not directly related to prolactin responses in women ($r=0.361$, data are not shown). Further studies on the role of estrogen in affecting prolactin responses to domperidone remains to be verified.

Interestingly, Camanni *et al.* (1980) reported that domperidone was unable to raise serum prolactin levels in some patients with pathological hyperprolactinemia, while it clearly stimulated prolactin release in subjects with puerperal hyperprolactinemia. More extensive studies regarding the nature and the behavior of domperidone should be undertaken before the general application of this drug for clinical purposes. However, it is generally free of side effects, produces a rapid and great increase in serum prolactin levels, and therefore may be useful to use in clinical studies on prolactin secretion.

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