

Effect of Bzotropine on Haloperidol-Induced Prolactin Secretion¹

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Abstract. The effect of bzotropine on haloperidol-induced prolactin secretion was investigated in 10 normal male volunteers. Bzotropine had no effect on basal prolactin secretion but significantly enhanced the increase induced by haloperidol. The magnitude of the enhancement, however, was relatively small. These data suggest that in man cholinergic mechanisms have no effect on basal prolactin secretion but exert a weak inhibitory effect under conditions of dopamine receptor blockade. Differences in intrinsic anticholinergic properties may account for some of the variations in potency of different neuroleptics in increasing circulating prolactin concentrations.

Introduction

In previous work we found that in patients maintained on chronic neuroleptic therapy some of the groups had higher basal prolactin concentrations if they were also receiving concomitant anticholinergic antiparkinsonian drugs (De Rivera *et al.*, 1976). Whereas there is evidence that cholinergic mechanisms modulate prolactin secretion in animals (Chen and Meites 1975; Gala *et al.*, 1976, Subramanian and Gala, 1976; McLean and Nikitovitch-Winer, 1975), less information is available in man.

Neuroleptics show considerable variation in central anticholinergic potency (Snyder *et al.*, 1974) and also in their capacity to stimulate prolactin secretion (Langer *et al.*, 1977). Recently, it has been shown that clozapine, an effective antischizophrenic agent with potent central antimuscarinic properties (Miller and Hiley, 1974), has no (Sachar *et al.*, 1976) or

only weak stimulatory effects on prolactin secretion (Nair *et al.*, 1978) in man. In order to investigate the possible role of anticholinergic mechanisms in neuroleptic-induced prolactin secretion, we have looked at the effect of bzotropine, a muscarinic receptor-blocking agent, on haloperidol-induced prolactin secretion in normal subjects. Haloperidol was chosen because of its weak central antimuscarinic effects (Snyder *et al.*, 1974).

Subjects and Methods

10 physically healthy, nonobese male volunteers, aged 21-37 years and on no medication, served as subjects. After an overnight fast, at 7:30-8:00 a.m., a 19-gauge scalp vein needle was inserted into an arm vein and kept open with heparin saline. 60 and 90 min after insertion of the needle (-45 and -15 min), baseline samples of blood were drawn. Immediately after the sample at -15 min, subjects received either bzotropine mesylate (2 mg intramuscularly, Cogentin®) or saline intramuscularly. 15 min later, at time 0 min, the subjects were injected with haloperidol (1 mg intramuscularly, Haldol®) or saline intramuscularly. Additional samples of blood were taken at 30, 60, 90, 120 and 150 min. Specimens were centrifuged and the serum stored at -20 °C until assayed

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for prolactin by radio immunoassay (Hwang *et al.*, 1971). Subjects remained recumbent throughout the procedure. Also, in view of the fact that prolactin secretion may increase during a daytime nap (Parker *et al.*, 1973), subjects were asked to remain awake during the test session. Each of the 10 subjects was tested with benztropine plus haloperidol and saline plus haloperidol. 7 of the volunteers were also tested with benztropine plus saline and saline plus saline. The sequence of treatments was randomized. The interval between treatments was at least 72 h. Data were analyzed by factorial analysis of variance with repeated measurements and the paired t test.

Results

Haloperidol induced at least a twofold increase in prolactin above baseline values in 9 of the 10 subjects. The mean baseline concentration (samples at -45 and -15 min) was 6.3 ± 1.1 ng/ml (mean \pm standard error of the mean), and this increased to a mean individual peak of 29.4 ± 6.7 ng/ml (range 11.5-80). When benztropine was given prior to injection of haloperidol, all 10 subjects showed at least a doubling of baseline concentrations. Values increased from 6.3 ± 0.8 to 37.7 ± 6.4 ng/ml (range 18-80). The mean prolactin concentrations after haloperidol were higher following benztropine pretreatment at each time interval (fig. 1), but none of the differences were statistically significant. Also, the difference in mean individual peak concentration was not statistically significant. However, when the data were analyzed by factorial analysis of variance, the prolactin concentrations for the 30 to 150 min sampling period were significantly higher when

the subjects received benztropine prior to haloperidol than when they received saline prior to haloperidol ($F_{1,36} = 16.4$; $p < 0.001$).

Prolactin concentrations following benztropine plus saline were not significantly different from those following saline plus saline ($F_{1,72} = 0.38$; NS).

7 of the subjects complained of restlessness and irritability (akathisia) after receiving haloperidol, and 2 other subjects appeared restless during the test though did not complain of this symptom. When pretreated with benztropine, these symptoms were abolished or considerably attenuated. Haloperidol with or without benztropine had a sedative effect in 7 of the subjects. No discomforting side effects were reported after saline or benztropine in the absence of haloperidol.

Discussion

Neuroleptics increase prolactin secretion in animals (Clemens *et al.*, 1974) and man (Langer *et al.*, 1977). The prolactin-elevating potency correlates well, in general, with clinical neuroleptic potency (Langer *et al.*, 1977) which in turn correlates with potency of dopamine receptor blockade (Seeman *et al.*, 1976). In addition to dopaminergic modulation (Martin *et al.*, 1974); cholinergic mechanisms may also play a role in prolactin secretion though this has been less well studied in man.

In the rat, the presence of a tuberoinfundibular cholinergic pathway has been described (Carson *et al.*, 1977). Pilocarpine or physostigmine inhibit prolactin secretion (Chen and

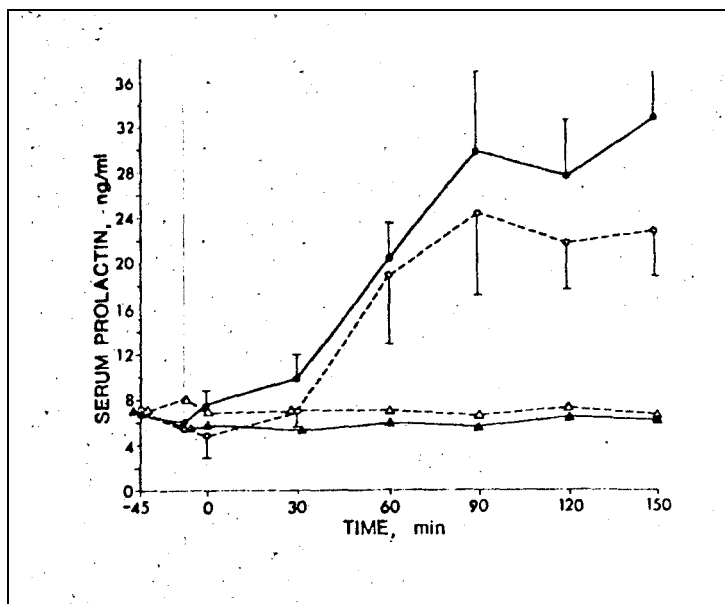


Fig. 1. Effect of benztropine on haloperidol-induced prolactin secretion. 10 male volunteers were injected with either haloperidol, 1 mg intramuscularly at time 0 min (○), or benztropine, 2 mg intramuscularly, 15 min before haloperidol (●). Each point represents the mean \pm standard error of the mean. 7 of the subjects also received either benztropine alone (▲) or saline alone (△). The increase induced by haloperidol is significantly greater following benztropine pretreatment ($p < 0.001$).

Meites, 1975; Grandison and Meites, 1976), and atropine reverses the effect of pilocarpine in both the estrogen-primed male and the pro-estrous rat (Grandison and Meites, 1976). In the monkey, atropine has no effect on basal prolactin secretion but potentiates the elevation induced by perphenazine (Gala et al., 1976): These data are compatible with an inhibitory muscarinic-cholinergic mechanism. However, pilocarpine has no effect on neuroleptic-induced prolactin secretion in the rat (Grandison and Meites, 1976), and in the pseudopregnant animal there is evidence for a stimulatory cholinergic mechanism controlling the nocturnal surge of prolactin secretion (McLean and Nikitovitch-Winer, 1975). In man, neither physostigmine (Sachar et al., 1976) nor the muscarinic receptor agonist bethanechol (McCallum et al., 1976) affect basal prolactin secretion. Also, atropine has no effect on metoclopramide-induced prolactin secretion (McCallum et al., 1976).

In previous work, we found that some groups of patients who were receiving anticholinergic antiparkinsonian drugs in addition to chronic neuroleptic treatment had higher circulating prolactin concentrations than subjects on neuroleptics alone (De Rivera et al., 1976). However, following short-term administration of clozapine, a neuroleptic with potent antimuscarinic properties (Miller and Hiley, 1974), only a small increment in prolactin secretion was noted (Nair et al., 1978). In the present study, the antimuscarinic agent, benztropine, had no effect on basal prolactin secretion but significantly enhanced the elevation promoted by haloperidol. The magnitude of the increase in mean individual peak, however, was only 28%. These data suggest that in man cholinergic systems have no effect on basal prolactin secretion but may exert a weak inhibitory, effect under conditions of dopamine receptor blockade. The results also suggest that differences in intrinsic anticholinergic properties may account for some of the variations in potency of different neuroleptics in inducing prolactin secretion. In addition, the weak ability of clozapine to induce prolactin secretion (Nair et al., 1978) cannot be explained on the basis of an inhibitory antimuscarinic effect of the drug.

It is unlikely that benztropine enhances prolactin secretion by inhibiting haloperidol metabolism, as Gauthier et al. (1977), have shown that benztropine decreases plasma levels of haloperidol.

Stress is known to increase prolactin secretion (Noel et al., 1972). In the present study, however, the subjects were less distressed after

receiving haloperidol plus benztropine than when they received haloperidol without benztropine. Thus, a nonspecific stress effect is unlikely to account for differences observed in the present study.

References

- Carson, K.A.; Nemeroff, C.B.; Rone, M.S.; Young-Blood, W.W.; Prange, A.J.; Hanker, J.S., and Kizer, J.S.: Biochemical and histochemical evidence for the existence of a tubero-infundibular cholinergic pathway in the rat. *Brain Res.* 129: 169-173 (1977).
- Clien, H. J. and Meites, I.: Effects of biogenic amines and TRH on release of prolactin and TSH in the rat. *Endocrinology* 96: 10-14 (1975).
- Clemens, J.A.; Smalstig, E.B., and Sawyer, B.D.: Antipsychotic drugs stimulate prolactin release. *Psychopharmacologia* 40: 123-127 (1974).
- De Rivera, J.L.; Lal, S.; Ettigi, P.; Hontela, S.; Muller H.F., and Friesen, H.G.: Effect of acute and chronic neuroleptic therapy on serum prolactin levels in men and women of different age groups. *Clin. Endocr.* 5: 273-282 (1976).
- Gala, R.R.; Subramanian, M.G.; Peters, J.A., and Jacques, S.: Influence of cholinergic receptor blockade on drug-induced prolactin release in the monkey. *Hormone Res.* 7: 118-128 (1976).
- Gauthier, J.; Jus, A.; Villeneuve, A.; Jus, K.; Pires, P. and Villeneuve, R.: Influence of the antiparkinsonian drugs on the plasma level of neuroleptics. *Biol. Psychiat.* 12: 389-399 (1977).
- Grandison, L. and Meites, J.: Evidence for adrenergic mediation of cholinergic inhibition of prolactin release. *Endocrinology* 99: 775-779 (1976).
- Hwang, P.; Guyda, H., and Friesen, H.: A radioimmunoassay for human prolactin. *Proc. natn. Acad. Sci, USA* 68: 1902-1906 (1971).
- Langer, G.; Sachar, E.J.; Gruen, P.H., and Halpern, F.S.: Human prolactin responses to neuroleptic drugs correlate with antischizophrenic potency. *Nature, Lond.* 266: 639-640 (1977).
- Martin, J.B.; Lal, S.; Tolis, G., and Friesen, H.G.: Inhibition by apomorphine of prolactin secretion in patients with elevated serum prolactin. *J. clin. Endocr. Metab.* 39: 180-182 (1974).
- McCallum, R.W.; Sowers, J.R.; Hershman, J.M., and Sturdevant, R.A.L.: Metoclopramide stimulates prolactin secretion in man. *J. clin. Endocr. Metab.* 42: 1148-1152 (1976).
- McLean, B.K. and Nikitovitch-Winer, M.B.: Cholinergic control of the nocturnal prolactin surge in the pseudopregnant rat. *Endocrinology* 97: 763-770 (1975).
- Miller, R.J. and Hiley, R.J.: Antimuscarinic properties of neuroleptic and drug induced Parkinsonism. *Nature, Lond.* 248: 596-597 (1974).
- Nair, N.P.V.; Lal, S.; Cervantes, P.; Yassa, R., and Guyda, H.: Effect of clozapine on apomorphine induced growth hormone secretion and serum prolactin concentrations in schizophrenia. *Neuro-*

- psychobiology (in press, 1978).
- Noel, G.L.; Suh, H.K.; Stone, J.G., and Frantz, A.G.: Human prolactin and growth hormone release during surgery and other conditions of stress. *J. clin. Endocr. Metab.* 35: 840-851 (1972).
- Parker, D.C.; Rossman, L.G., and Vanderlaan, E.F.: Sleep-related, nyctohemeral and briefly episodic variation in human plasma prolactin concentrations. *J. clin. Endocr. Metab.* 36: 1119-1124 (1973).
- Sachar, E.J.; Gruen, P.H.; Altman, N.; Halpern, F.S., and Frantz, A.G.: Use of neuroendocrine techniques in psychopharmacologic research; in Sachar, Hormones, behaviour and psychopathology, pp. 161-176 (Raven Press, New York 1976).
- Seeman, P.; Lee, T.; Chau-Wong, M., and Wong, K.: Antipsychotic drug doses and neuroleptic dopamine receptors. *Nature, Lond.* 261: 717-719 (1976).
- Snyder, S.H.; Greenberg, D., and Yamamura, H.I.: Antischizophrenic drugs and brain cholinergic receptors. *Archs gen: Psychiat.* 31: 58-61 (1974).
- Subramanian, M.G. and Gala, R.R.: Further studies on the effects of adrenergic, serotonergic and cholinergic drugs on the afternoon surge of plasma prolactin in ovariectomized, estrogen-treated rats. *Neuroendocrinology* 22: 246-249 (1976).

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