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Effects of 4 Weeks Treatment with Chlorpromazine and/or Trihexyphenidyl on the Pituitary-gonadal Axis in Male Paranoid Schizophrenics

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Summary. Serum prolactin (PRL), luteinizing hormone (LH) and testosterone (T) levels were estimated in a group of 30 male paranoid schizophrenics before and after 4 weeks treatment with chlorpromazine and/or trihexyphenidyl, and in a group of 14 healthy male individuals. After treatment with chlorpromazine (100 mg t.i.d., p.o.), 10 patients presented a significant increase in serum PRL values and a significant decrease in serum T values. A significant increase in serum PRL values was also found in 10 patients who were treated with chlorpromazine (100 mg t.i.d., p.o.) plus trihexyphenidyl (5 mg t.i.d., p.o.). No significant difference in any of the investigated endocrine parameters was detected in 10 patients after 4 weeks administration of trihexyphenidyl (5 mg t.i.d., p.o.). Following chlorpromazine treatment with or without concomitant administration of trihexyphenidyl, 20 patients showed a significant increase in serum PRL levels and a significant decrease in serum LH and T levels.

Key words: Chlorpromazine – Trihexyphenidyl – Prolactin – Luteinizing hormone – Testosterone – Paranoid schizophrenia

Introduction

Two groups of investigators have previously reported that male psychiatric patients receiving chronic neuroleptic therapy and concomitant administration of anticholinergic antiparkinsonian drugs had significantly higher serum prolactin (PRL) levels than cross-matched patients receiving neuroleptics alone (DeRivera et al. 1976; Martin-DuPan et al. 1979). On the other hand, Kolakowska et al. (1976) did not observe a significant change in serum PRL levels after administration for 7 to 14 days of an anticholinergic drug (benzhexol) in male schizophrenic patients receiving chronic neuroleptic treatment. This discrepancy, in conjunction with the conflicting findings which have been reported concerning serum luteinizing hormone (LH) and testosterone (T) values in male schizophrenic patients receiving chronic neuroleptic treatment (Davis et al. 1984), prompted us to investigate the effects of 4 weeks treatment with chlorpromazine and/or trihexyphenidyl on serum PRL, LH and T values in male paranoid schizophrenic patients.

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Methodology

A total of 30 male patients with chronic (or subchronic) paranoid schizophrenia in an acute exacerbation, by DSM-III criteria, participated in this study. All patients were hospitalized at Eginition Hospital (Department of Psychiatry, Athens University Medical School) and were assigned to the study group solely on the basis of the following criteria: (a) absence of clinical or biochemical evidence of hepatic, renal, cardiovascular or endocrine dysfunction and (b) abstinence from psychotropic or other drugs for at least 6 weeks prior to admission. The age of the patients ranged from 21 to 40 years (mean 29.7 ± 5.3) and the duration of illness from 1 to 14 years (mean 4.4 ± 3.7).

All patients were placed under the same nursing care and diet. Following admission each patient was allowed 1-week of adaptation in the ward, during which he received 10 mg of diazepam every night. Two blood samples were collected from each patient on the 2nd and 5th days of hospitalization. At 1 h before each blood collection, the mental state of the patient was assessed by means of the rating scale of Krawiecka et al. (1977) (KRS) and the mean of the two scores for each item was taken.

For the next 4 weeks, patients were randomly given chlorpromazine 100 mg t.i.d., chlorpromazine 100 mg plus trihexyphenidyl 5 mg t.i.d., or trihexyphenidyl 5 mg t.i.d., p.o. Thus, of the 30 male paranoid schizophrenics who participated in this study, 10 were treated with chlorpromazine, 10 were treated with chlorpromazine plus trihexyphenidyl and in 10 patients trihexyphenidyl was administered. At the end of the 4 weeks treatment, the mental state of each patient was assessed by means of the KRS and a blood sample was collected. Then, 3 days later, the mental state of the patient was reassessed and a second blood sample was obtained. The mean of the two post-treatment scores for each item was taken. All patients completed the trial, since none of them manifested a notable clinical deterioration.

Our control group consisted of 14 male volunteers who (a) had no clinical or biochemical evidence of hepatic, renal, cardiovascular or endocrine dysfunction, (b) did not use any drug for a period of at least 1 month prior to the study and (c) were found on interview to be mentally healthy persons. The age of these normal subjects ranged from 20 to 37 years (mean 30.4 ± 5.1). No significant difference was found between the group of 30 patients and the group of 14 normal subjects with respect to age (Mann-Whitney U test). Two blood samples were obtained from each normal volunteer during the course of 1 week.

All blood samples were obtained from patients and normal controls between 9 a.m. and 9.30 a.m. following an overnight fast. In medicated patients, blood samples were taken 12 h after the last dose of the medicament. Serum was separated and stored at −20°C until hormone assays were carried out. All subjects (patients and normal controls) gave informed consent to participate in this study.

Serum PRL, LH and T levels were estimated using radioimmunoassay kits from Biodata. Normal values for males (range) were: PRL, 5–15 ng/ml; LH, 4.5–20 mIU/ml; T, 3.0–9.0 ng/ml.

Reported hormone values are the average of the two blood samples obtained from each patient, either before or after 4 weeks drug therapy, as well as the averages of the two blood samples obtained from each normal volunteer. Statistical analyses were made using non-parametric methods (Wilcoxon test for pair differences, Mann-Whitney U test, Spearman correlation coefficient).

Results

Serum PRL, LH and T levels were within the normal range for most of our drug-free patients and normal controls. Table 1 shows the mean ± SD values of the total score on the KRS and the mean ± SD values of the endocrine parameters investigated in the patients and the controls.

The group of 30 drug-free male paranoid schizophrenics did not differ significantly from the group of 14 normal male controls with regard to serum PRL, LH and T values. No significant correlation was found (a) between the age or the duration of illness (in years) and the values of the hormones tested in the 30 drug-free patients, (b) between the age and the values of the hormones investigated in the 14 normal controls, (c) between the total score on the KRS and the hormonal values in the drug-free patients and (d) between the values of the hormones tested in the group of drug-free patients, and in the group of normal controls.

The three groups of drug-free patients who subsequently underwent 4 weeks therapy with either chlorpromazine, chlorpromazine plus trihexyphenidyl, or trihexyphenidyl, did not differ significantly with re-

Table 1. Total Krawiecka rating scale (KRS) score and serum prolactin (PRL), luteinizing hormone (LH) and testosterone (T) values in male paranoid schizophrenics before and after 4 weeks treatment, and in normal controls (mean ± SD)

Subjects	Total KRS score (0–32)	PRL (ng/ml)	LH (mIU/ml)	T (ng/ml)
Drug-free patients (n = 30)	10.4 ± 4.7	6.8 ± 3.5	9.4 ± 3.4	5.9 ± 2.0
Normal controls (n = 14)	–	7.4 ± 3.8	11.0 ± 5.8	5.6 ± 1.7
Chlorpromazine (n = 10)				
Pre-treatment values	10.1 ± 5.9	7.5 ± 5.4	10.6 ± 4.1	6.5 ± 2.8
Post-treatment values	6.1 ± 5.4**	15.7 ± 13.2**	8.9 ± 2.8	5.9 ± 2.4*
Chlorpromazine plus trihexyphenidyl (n = 10)				
Pre-treatment values	11.9 ± 5.0	6.4 ± 1.8	8.2 ± 2.3	5.2 ± 1.5
Post-treatment values	7.7 ± 5.3**	23.2 ± 14.0**	7.1 ± 1.2	4.9 ± 1.6
Trihexyphenidyl (n = 10)				
Pre-treatment values	9.2 ± 2.9	6.5 ± 2.5	9.5 ± 3.4	6.0 ± 1.5
Post-treatment values	8.5 ± 3.2	7.7 ± 5.2	9.0 ± 4.7	5.6 ± 1.4
Chlorpromazine with or without trihexyphenidyl (n = 20)				
Pre-treatment values	11.0 ± 5.4	7.0 ± 4.0	9.4 ± 3.5	5.8 ± 2.3
Post-treatment values	6.9 ± 5.3**	19.4 ± 13.8**	8.0 ± 2.3*	5.4 ± 2.0*

* = $P < 0.05$ compared to pre-treatment values (Wilcoxon test for pair differences)
** = $P < 0.01$ compared to pre-treatment values (Wilcoxon test for pair differences)

spect to age, duration of illness, total score on the KRS, or any of the endocrine parameters investigated.

A significant ($P < 0.01$) decrease in total KRS score was noted in the group of 10 patients who underwent 4 weeks treatment with chlorpromazine (100 mg t.i.d., p.o.). However, no significant difference was elicited from the comparison of pre- and post-treatment scores on any of the 8 items of the KRS in these patients. A significant ($P < 0.01$) increase in serum PRL values was found in the group of chlorpromazine-treated patients, with a mean ± SD serum PRL increment (Δ PRL) of 8.2 ± 8.5. Comparison of pre- and post-treatment serum LH and T values of these patients only revealed a significant ($P < 0.05$) decrease in serum T values after 4 weeks chlorpromazine treatment.

A significant ($P < 0.01$) decrease in total KRS score was noted in the group of 10 patients who were treated for 4 weeks with chlorpromazine (100 mg t.i.d., p.o.) plus trihexyphenidyl (5 mg t.i.d., p.o.). A significant ($P < 0.05$) decrease in the scores on the KRS items anxiety and hallucinations was also found in this group of patients after 4 weeks treatment. A significant ($P < 0.01$) increase in serum PRL levels was detected in this group of patients, with a mean ± SD serum PRL increment (Δ PRL) of 16.8 ± 13.3. Admittedly, this group of patients presented a greater average increment in serum PRL values than that in the group of patients who were treated only with chlorpromazine; however, this difference did not reach statistical significance. No significant difference was elicited by comparing the pre- and post-treatment serum LH and T values in the group of patients who were treated with chlorpromazine and trihexyphenidyl.

After 4 weeks administration of trihexyphenidyl (5 mg t.i.d., p.o.) in 10 patients, no significant change in the total KRS score or the serum PRL, LH or T values was detected in this group of patients.

No significant correlation was found (a) between the post-treatment total score on the KRS and the post-treatment hormonal values and (b) between the post-treatment values of the hormones tested, in the three groups of medicated patients.

After 4 weeks chlorpromazine treatment (with or without synchronous administration of trihexyphenidyl) of 20 patients, a significant ($P < 0.01$) increase in serum PRL values and a significant ($P < 0.05$) decrease in serum LH and T levels was detected in these patients.

Discussion

The group of 30 male, drug-free patients with chronic (or subchronic) paranoid schizophrenia in acute exacerbation did not differ significantly from the group of 14 mentally healthy males with regard to serum PRL, LH and T levels. Similar findings have already been reported by previous investigators (Meltzer 1984).

Both groups of patients who were treated for 4 weeks with either chlorpromazine or chlorpromazine and trihexyphenidyl, showed a significant decrease in the total KRS score during the post-treatment period. However, while no significant difference was elicited from the comparison of pre- and post-treatment scores on any of the 8 items of the KRS in the 10 chlorpromazine-treated patients, a significant decrease in the scores on the KRS items anxiety and hallucinations was found in the other group of patients after 4 weeks treatment with chlorpromazine plus trihexyphenidyl. Obviously, these findings are in disagreement with the relatively sparse clinical literature on the issue of the therapeutic antagonism between anticholinergic antiparkinsonian drugs and neuroleptics (Hanlon et al. 1966; Rivera-Calimlim et al. 1973; Singh and Kay 1979).

No significant difference in the total KRS score (or the score on any of the 8 items of this scale) was observed in 10 patients after 4 weeks administration of trihexyphenidyl. Admittedly, these findings are not in agreement with previous findings, which suggest that anticholinergic antiparkinsonian drug given alone to untreated, actively psychotic schizophrenics had the effect of worsening to a significant degree their clinical symptomatology (Singh and Kay 1979).

Both groups of patients who were treated for 4 weeks with either chlorpromazine or chlorpromazine and trihexyphenidyl, showed a significant increase in serum PRL levels. A well-known effect of neuroleptics is the elevation of the serum PRL level; by blocking dopamine receptors of the tubero-infundibular system, these drugs prevent the dopamine-mediated inhibition of PRL secretion (Rubin and Hays 1980; Meltzer 1984).

The group of patients who were treated with chlorpromazine plus trihexyphenidyl presented a greater average increment in serum PRL (Δ PRL) values than that in the group of patients who were treated only with chlorpromazine; this difference, however, did not reach statistical significance. It is possible that the relatively small number of patients obviated statistical significance in these results. For this reason, we are now investigating the effect of chronic neuroleptic treatment with or without synchronous administration of trihexyphenidyl on PRL secretion in a greater number of patients.

No significant change in serum PRL values was found in 10 male schizophrenic patients after 4 weeks administration of trihexyphenidyl. Consequently,

these findings are at variance with those of other studies which demonstrated that the acute administration of anticholinergic drugs significantly influences PRL secretion in normal male volunteers (Lal et al. 1979; Halbreich et al. 1980; Benkert et al. 1981; Davis et al. 1982). Differences, however, might probably exist between the i.m. or i.v. administration of a single dose of an anticholinergic drug and the p.o. administration of the same drug for 4 weeks in men, with regard to their effect on PRL secretion.

In all 20 male schizophrenic patients who underwent 4 weeks therapy with either chlorpromazine or chlorpromazine plus trihexyphenidyl, post-treatment serum LH values were within the normal range. Similar findings in male schizophrenics receiving chronic neuroleptic treatment have been previously reported (Davis et al. 1984). After 4 weeks chlorpromazine treatment with or without concomitant administration of trihexyphenidyl, 15 or our 20 male schizophrenic patients showed lower serum LH values, in comparison to their initial values; conceivably, then, a significant decrease in serum LH values was detected in these 20 male schizophrenic patients after treatment. Similar findings in a group of 9 pimozide-treated, male schizophrenics have been reported by Siris et al. (1980), whereas no significant change in serum LH values occurred after 4 weeks administration of chlorpromazine (Wode-Helgodt et al. 1977) or haloperidol (Brambilla et al. 1975) in male schizophrenic patients. Also, it must be noted that a decrease in serum LH values after 4 days administration of pimozide to 10 normal male volunteers has been reported by Collu et al. (1975). Admittedly, the significant reduction in serum LH levels which was detected in our 20 male schizophrenic patients after 4 weeks chlorpromazine treatment (with or without synchronous administration of trihexyphenidyl) might be explained by the existing evidence for (a) the stimulatory effect of noradrenaline on gonadotropin-releasing hormone (GnRH) and LH secretion (Rubinstein and Sawyer 1970; Drouva and Gallo 1976; Cass Terry et al. 1982) and (b) the ability of chlorpromazine to block not only dopamine but also noradrenaline receptors in the brain (Anden et al. 1970, 1972; Praag and Korf 1975). Although the role of dopaminergic mechanisms in the control of LH secretion remains controversial (Krulich 1979; Nakagawa et al. 1982), the decrease in serum LH values which has been noticed in 9 male schizophrenic patients after 4 weeks treatment with pimozide, a specific blocker of dopamine receptors (Siris et al. 1980), as well as in 10 normal male volunteers after 4 days administration of the same drug (Collu et al. 1975), together with our findings, render plausible the suggestion of Collu et al. (1975) that "a period of dopamine receptor blockade longer than 4 days is necessary to observe an inhibitory effect on LH secretion."

No significant difference in serum LH values was observed in 10 male schizophrenic patients after 4 weeks administration of trihexyphenidyl. Consequently, these findings are compatible with those of a study which demonstrated that no significant change in LH levels occurred after acute (i.v.) administration of an anticholinergic drug (biperiden) in normal male volunteers (Benkert et al. 1981).

Most of our patients who underwent 4 weeks chlorpromazine treatment with or without synchronous administration of trihexyphenidyl, had post-treatment serum T values within the normal range. Similar findings in male schizophrenics receiving chronic neuroleptic treatment have been reported previously (Davis et al. 1984). After 4 weeks chlorpromazine treatment with or without concomitant administration of trihexyphenidyl, 13 of our 20 male schizophrenic patients showed lower serum T values, in comparison to their initial ones; thus, a significant decrease in serum T values was detected in these patients after 4 weeks therapy. Similar findings in a group of 10 chlorpromazine-treated, male schizophrenics has been reported by Apter et al. (1983), whereas no significant change in serum T values occurred after 4 weeks therapy with haloperidol (Brambilla et al. 1975), penfluridol (Nathan et al. 1980) or pimozide (Siris et al. 1980) in male schizophrenic patients. Possibly, chronic treatment with phenothiazines differs from chronic therapy with butyrophenones or diphenylbutylpiperidines with regard to their effects on the hypothalamo-pituitary gonadal axis in men. In order to solve this problem, studies are now in progress in our department.

The significant decrease in serum LH and T values which was detected in our 20 male paranoid schizophrenics after 4 weeks chlorpromazine treatment with or without concomitant administration of trihexyphenidyl, allow us to conclude that this therapy exerts an inhibitory effect on GnRH-LH secretion and consequently on T secretion, since the latter is an LH-dependent phenomenon (Martin et al. 1977).

References

Anden NE, Butcher SG, Corrodi H, Fuxe K, Ungerstedt U (1970) Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. Eur J Pharmacol 11: 303–314

Anden NE, Corrodi H, Fuxe K (1972) Effect of neuroleptic drugs on central catecholamine turnover assessed using tyrosine- and dopamine-β-hydroxylase inhibitors. J Pharm Pharmacol 24:177–182

Apter A, Dickerman Z, Gonen N, Assa S, Prager-Lewin R, Kaufman H, Tyano S, Laron Z (1983) Effect of chlor-

promazine on hypothalamic-pituitary-gonadal function in 10 adolescent schizophrenic boys. Am J Psychiatry 140: 1588–1591

Benkert O, Klein HE, Hofschuster E, Seibold C (1981) Effect of the anticholinergic drug biperiden on pituitary hormones and cortisol. Psychoneuroendocrinology 6:231–238

Brambilla F, Guerrini A, Guastalla A, Rovere C, Riggi F (1975) Neuroendocrine effects of haloperidol therapy in chronic schizophrenia. Psychopharmacologia 44:17–22

Cass Terry L, Crowley WR, Lynch C, Longserre C, Johnson MD (1982) Role of central epinephrine in regulation of anterior pituitary hormone secretion. Peptides 3:311–318

Collu R, Jéquier JC, Leboeuf G, Letarte J, Ducharme JR (1975) Endocrine effects of pimozide, a specific dopaminergic blocker. J Clin Endocrinol Metab 41:981–984

Davis BM, Brown GM, Miller M, Friesen HG, Kastin AJ, Davis KL (1982) Effects of cholinergic stimulation on pituitary hormone release. Psychoneuroendocrinology 7: 347–354

Davis JM, Vogel C, Gibbons R, Pavkovic I, Zhang M (1984) Pharmacoendocrinology of schizophrenia. In: Brown GM, Koslow SH, Reichlin S (eds) Neuroendocrinology and psychiatric disorder. Raven, New York, pp 29–53

DeRivera JL, Lal S, Ettigi P, Hontella S, Muller HF, Friesen HG (1976) Effect of acute and chronic neuroleptic therapy on serum prolactin levels in men and women of different age groups. Clin Endocrinol 5:273–282

Drouva SV, Gallo RV (1976) Catecholamine involvement in episodic luteinizing hormone release in adult ovariectomized rats. Endocrinology 99:651–658

Halbreich U, Sachar EJ, Nathan RS, Asnis GM, Halpern FS (1980) The effect of benztropine mesylate on the prolactin response to haloperidol. Psychopharmacology 72:61–65

Hanlon TE, Schoenrich C, Freinek W, Turek I, Kurland AA (1966) Perphenazine-benztropine mesylate treatment of newly admitted psychiatric patients. Psychopharmacologia 9:328–339

Kolakowska T, Wiles DH, Gelder MG, McNeilly AS (1976) Clinical significance of plasma chlorpromazine levels. Psychopharmacology 49:101–107

Krawiecka M, Goldberg D, Vaughan M (1977) A standardized psychiatric assessment scale for rating chronic psychotic patients. Acta Psychiatr Scand 55:299–308

Krulich L (1979) Central neurotransmitters and the secretion of prolactin, GH, LH and TSH. Annu Rev Physiol 41: 603–615

Lal S, Mendis T, Cervantes P, Guyda H, DeRivera JL (1979) Effect of benztropine on haloperidol-induced prolactin secretion. Neuropsychobiology 5:327–331

Martin JB, Reichlin S, Brown GM (1977) Neuroendocrinology of reproduction. In: Martin JB, Reichlin S, Brown GM (eds) Clinical neuroendocrinology. Davis, Philadelphia, pp 93–128

Martin-DuPan R, Baumann P, Magrini G, Felber JP (1979) Neuroendocrine effects of chronic neuroleptic therapy in male psychiatric patients. Psychoneuroendocrinology 3: 245–252

Meltzer HY (1984) Neuroendocrine abnormalities in schizophrenia: prolactin, growth hormone, and gonadotrophins. In: Brown GM, Koslow SH, Reichlin S (eds) Neuroendocrinology and psychiatric disorder. Raven, New York, pp 1–28

Nakagawa K, Obara T, Matsubara M, Kubo M (1982) Relationship of changes in serum concentrations of prolactin and testosterone during dopaminergic modulation in males. Clin Endocrinol 17:345–352

Nathan RS, Asnis GM, Dyrenfurth I, Halpern FS, Halbreich U, Ostrow LC, Sachar EJ (1980) Plasma prolactin and testosterone during penfluridol treatment. Lancet II:94

Praag HM van, Korf J (1975) Biochemical research into psychosis. Acta Psychiatr Scand 51:268–284

Rivera-Calimlim L, Castaneda L, Lasagna L (1973) Effects of mode of management on plasma chlorpromazine in psychiatric patients. Clin Pharmacol Ther 14:978–986

Rubin RT, Hays SE (1980) The prolactin secretory response to neuroleptic drugs: mechanisms, applications and limitations. Psychoneuroendocrinology 5:121–137

Rubinstein L, Sawyer CH (1970) Role of catecholamines in stimulating the release of pituitary ovulating hormones in rats. Endocrinology 86:988–995

Singh MM, Kay SR (1979) Therapeutic antagonism between anticholinergic antiparkinsonism agents and neuroleptics in schizophrenia. Neuropsychobiology 5:74–86

Siris SG, Siris ES, Kammen DP van, Docherty JP, Alexander PE, Bunney WE (1980) Effects of dopamine blockade on gonadotropins and testosterone in men. Am J Psychiatry 137:211–214

Wode-Helgodt B, Eneroth P, Fyrö B, Gullberg B, Sedvall G (1977) Effect of chlorpromazine treatment on prolactin levels in cerebrospinal fluid and plasma of psychotic patients. Acta Psychiatr Scand 56:280–293

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