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Long-Term Phenothiazine Treatment does not Cause Pituitary Tumours

VICTORIA A. LILFORD, R. J. LILFORD, JANET E. DACIE, LESLEY A. REES, P. D. BROWNE and T. CHARD

Summary: In order to explore the possibility that prolactinomas may be caused by prolonged under-inhibition of prolactin-secreting cells we examined the pituitary fossa in 69 patients on long-term phenothiazine treatment. The average duration of treatment was 12.5 years and 55 (80 per cent) of the patients had persistently raised serum prolactin levels. The incidence of radiologically detectable pituitary fossa abnormalities was not significantly different to that in control populations. In 62 per cent of patients the skull x-rays from an earlier admission were available. Comparison of these with earlier films did not show a higher incidence of pituitary fossa abnormalities after prolonged exposure to phenothiazines.

Prolactin-secreting tumours of the pituitary gland (prolactinomas) typically respond to physiological stimuli and cannot therefore be regarded as autonomous tumours. Thus, they frequently enlarge during exposure to high oestrogen concentrations (Del Pozo and Brownell, 1979; Frantz *et al*, 1972; Yen *et al*, 1974), and regress during treatment with agents such as bromocriptine, which suppress prolactin secretion (George *et al*, 1974). From these observations the concept has arisen that prolactinomas may result from prolonged deficiency of prolactin-inhibiting factors. If this hypothesis is true, then it might be expected that treatment with long-term dopamine antagonists might promote prolactinoma formation as well as growth of any pre-existing overt or occult adenomas. Since prolactinomas frequently result in changes in the morphology of the pituitary fossa we have examined serial x-rays in patients on long-term phenothiazine treatment.

Methods

Informed consent for the study was obtained from 69 psychiatric in-patients who were on long-term phenothiazine treatment. The mean duration of treatment was 12 years 7 months (range 2–24 years). A right lateral skull x-ray was taken and a 9 am blood sample for determination of serum prolactin. In 43 patients (62 per cent) the routine skull x-ray from an earlier admission was also available (these had been lost or destroyed in the other 26 cases). The earlier x-rays had been carried out an average of 9 years previously (range 1 to 15 years). All films were coded and examined without further identification by an experienced radiologist (J.E.D.). Pituitary fossa morphology was graded by the St Bartholomew's Hospital system (Table I).

The experimental and clinical data were stored and analysed using conventional database software on a microcomputer system. The prevalence and severity of pituitary fossa abnormalities in all 69 patients were analysed. Where earlier x-rays were available the pituitary fossa grading was compared with that of the subsequent x-rays; the prevalence of pituitary fossa abnormalities in the earlier and later x-rays was compared using the Wilcoxon matched pairs signed-ranks test.

Results

Prolactin levels were greater than 360 mU/l (the upper limit of normal for our laboratory) in 55 patients (80 per cent), and the mean for the group was 797 mU/l. There was no relationship between the duration of treatment and prolactin levels (Fig).

Of the 69 skull x-rays carried out for this study, 42 were completely normal (80) and 16 had a small 'blister' of the pituitary floor (B1). Seven patients (10 per cent) had a fossa graded as B2 and 4 (6 per cent) had a fossa graded as B3. In the group of 43 patients whose earlier x-rays were available, no change was found in the pituitary fossa in 41 subjects. In one patient the fossa had changed from grade B0 to B2 and in another from Grade B1 to B0 (Table II). Analysis of

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TABLE I

A classification of the radiological appearance of the pituitary fossa as used at St Bartholomew's Hospital

Grade	Appearance on lateral view
B0	Single contour
B1	Less than 1 mm difference between contours
B2	1–3 mm difference between contours; less than 3 mm blister
B3	Over 3 mm blister
B4	Double contour throughout
B5	Fossa expanded in all directions

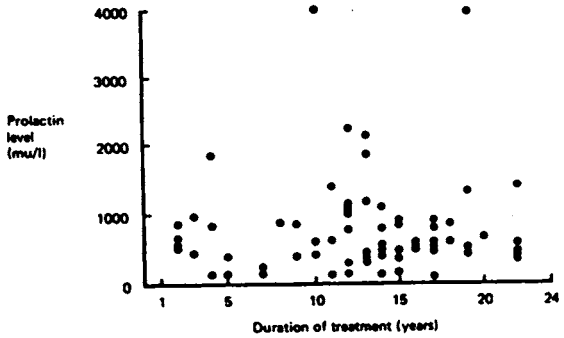

FIG.—Prolactin levels with differing duration of phenothiazine treatment showing the lack of an obvious relationship. This was confirmed by a correlation coefficient of 0.054.

these results by Wilcoxon's signed-ranks test confirmed that there was no significant difference in the incidence of pituitary fossa abnormalities in the earlier and later x-rays. The average duration of phenothiazine treatment prior to the first available x-ray was 2 years, 5 months (range 0 to 14 years).

For this set of prolactin levels it appeared that there was no difference in prolactin levels with regard to the fossa grade (Table III).

Discussion

A single lateral x-ray, though not the most advanced of current techniques, was chosen for the present study because it was the only view available for comparison in those patients who had had previous radiography. Given this technical reservation, the data presented here are reassuring as they show that significant macroadenomas, which cause enlargement of the whole pituitary fossa (grade B4 or more (Klinj *et al,* 1980) are not induced by long-term phenothiazine treatment. The severest grade observed in this series was B3. Only 4 patients were in this category; in one of these the x-ray from 6 years earlier was available and this showed a similar appearance.

The incidence of abnormal pituitary fossa x-rays (39 per cent, B1 or more; 16 per cent, B2 or more) is very similar to that which has been reported in normal populations (McLochlan and Banna, 1979; Swanson and du Boulay, 1975). Despite an average of nine years continuous phenothiazine treatment only one patient showed an apparent deterioration. This argues against the original hypothesis, that prolonged deficiency of prolactin inhibition leads to prolactinoma formation. However, there is some dispute as to whether or not the appearance of *micro*-adenomas can be excluded on this basis.

Thus, although positive surgical findings are the rule when the fossa is graded 1, 2 or 3 (Chang *et al,* 1977), the prevalence of minor pituitary fossa abnormalities in patients presenting with hyperprolactinaemia is little different from the population as a whole (McLochlan and Banna, 1979; Swanson and du Boulay, 1975). Recent postmortem studies on unselected patients have shown that the presence of microademonas correlated poorly with the presence of x-ray changes (Burrow *et al,* 1981; Banna *et al,* 1983). Furthermore, computerized tomography frequently shows changes suggestive of pituitary microadenomas in patients with symptomatic hyperprolactinaemia and normal conventional radiology (Jung *et al,* 1982). Thus, our study might not exclude the formation of microadenomas. However, any microscopic 'tumours' which may have preceded or been induced by treatment did not enlarge to the point where adverse effects might be expected.

A final possibility is that psychiatric patients are unusually resistant to prolactinoma formation. Schizophrenia, for example, is associated with excessive dopamine activity which could inhibit prolactin secreting cells (Carlsson, 1977). However, the fact that prolactin levels were elevated in 80 per cent of subjects in this study would seem to indicate a normal functional response to phenothiazine treatment, and there is, therefore, no evidence that the underlying pathology would influence the results of this study. This confirms the observations of other workers (Lal and Nair, 1980) which have shown that prolactin levels rise to a peak within a few weeks of starting phenothiazine treatment and then settle to levels which are only moderately elevated.

Conclusion

In conclusion, our study shows no change in pituitary fossa morphology associated with long-term phenothiazine treatment. There is no evidence that

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TABLE II

Radiographic grading of the pituitary fossa and prolactin levels in the 43 patients with earlier and later x-rays

Duration of treatment (years)	Patient's age (years)	Prolactin level (mU/l)	Year of original x-ray	Pituitary fossa grade on original x-ray	Pituitary fossa grade on current x-ray
2	75	892	71	0	0
2	70	605	71	0	0
3	75	453	75	1	1
3	44	1007	79	0	0
4	75	873	73	1	1
4	58	180	76	0	0
4	76	1875	71	2	2
5	31	375	76	0	0
5	68	264	77	1	1
5	56	123	71	0	0
7	50	129	76	0	0
7	50	234	78	1	1
8	35	937	74	1	1
9	48	396	73	0	0
10	43	407	76	0	0
11	50	637	81	1	1
11	31	1445	74	1	1
12	50	1104	70	0	0
12	40	1034	76	3	3
12	45	1162	79	1	1
12	53	1020	67	2	2
12	62	2628	76	0	0
13	62	414	71	0	0
13	55	339	71	0	0
13	59	2197	72	1	1
14	72	1129	66	1	1
14	60	581	73	2	2
14	65	440	67	0	0
14	50	808	74	0	0
15	53	312	79	1	1
15	53	961	81	3	3
15	43	922	69	0	0
16	61	555	65	0	0
16	53	539	64	1	1
16	59	600	72	2	2
17	55	393	71	1	1
17	50	525	77	0	0
17	50	100	71	0	2
17	64	582	77	0	0
19	69	519	63	1	0
19	55	418	77	0	0
22	77	302	66	0	0
22	57	500	67	0	0

TABLE III

Average prolactin levels in patients with different grades of pituitary fossa

Fossa grade	No. of patients	Median prolactin levels (mU/l)	Average prolactin level (mU/l)	Standard deviation (mU/l)
B0	42	522	654	484
B1	16	755	994	920
B2	7	600	1234	1339
B3	4	873	740	388

There was no significant difference between prolactin levels for these pituitary fossa grades on the Kruskall-Wallis one-way analysis of variance (3 degrees of freedom; $P > 0.05$).

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pituitary macroadenomas are induced by this treatment. However, exclusion of microadenomas in both clinical practice and in selected populations such as this may require soft tissue imaging techniques such as computerized tomography.

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Victoria A. Lilford, M.B., Ch.B., *General Practitioner Trainee, Stamford Hill Group Practice, London N16 (previously Friern Barnet Psychiatric Hospital)*

*R. J. Lilford, M.R.C.O.G., M.R.C.P., *Lecturer in Reproductive Physiology, Department of Obstetrics and Gynaecology, and Reproductive Physiology, St Bartholomew's Hospital Medical College and The London Hospital Medical College, Turner Street, London E1*

Janet E. Dacie, M.R.C.P., F.R.C.R., *Consultant Radiologist, Department of Diagnostic Radiology, St Bartholomew's Hospital, London*

Lesley A. Rees, M.D., F.R.C.P., *Professor of Chemical Endocrinology, St Bartholomew's Hospital Medical College, London*

T. Chard, M.D., F.R.C.O.G., *Professor of Reproductive Physiology, Department of Obstetrics, Gynaecology and Reproductive Physiology, St Bartholomew's Hospital, London*

*Correspondence.

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