EFFECTS OF NOMIFENSINE, AN INHIBITOR OF ENDOGENOUS CATECHOLAMINE RE-UP TAKE, IN ACROMEGALY, IN HYPERPROLACTINAEMIA, AND AGAINST STIMULATED PROLACTIN RELEASE IN MAN

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1 Nomifensine, an inhibitor of endogenous catecholamine re-uptake, did not affect the growth hormone (GH) or prolactin levels in patients with acromegaly or hyperprolactinaemia. It does not, therefore, have any therapeutic role in these conditions at the dosage used in this study.

2 It had no effect on thyrotrophin-releasing hormone (TRH)-induced thyrotrophin (TSH) or prolactin release in males, yet caused marked suppression of monoiodotyrosine (MIT)-induced prolactin release in males but not in females.

3 The significant suppression of MIT-induced prolactin release in males is likely to reflect the dopamine (DA) agonist activity of the drug and its lack of effect in the other situations tested could be dose related.

4 It is proposed that the difference in male and female patterns of prolactin response to MIT after nomifensine, could be due to a 'damping' effect of oestrogen on the hypothalamic dopaminergic system.

Introduction

Nomifensine (8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline) is a powerful inhibitor of catecholamine re-uptake (Gerhards *et al.*, 1974; Hunt *et al.*, 1974; Schacht & Heptner, 1974), and recent *in vivo* studies in rats have confirmed its DA agonist activity (Costall *et al.*, 1975).

In view of the now well established therapeutic role of DA agonists in states of hyperprolactinaemia associated with galactorrhoea and hypogonadism (Del Pozo *et al.*, 1973; Thorner *et al.*, 1974), and acromegaly (Liuzzi *et al.*, 1974; Gomez-Pan *et al.*, 1975), this study was designed to investigate the DA agonist potential of nomifensine in these clinical conditions.

Furthermore, its effects have been assessed against two known stimuli to prolactin release in man: TRH, which has a direct pituitary action (Jacobs *et al.*, 1971; Lister *et al.*, 1974); and 3-iodo-L-tyrosine (MIT), a potent inhibitor of tyrosine hydroxylase (Udenfriend *et al.*, 1965), which selectively inhibits hypothalamic dopaminergic pathways and may also have DA receptor-blocking activity (Donoso *et al.*, 1971; Smythe *et al.*, 1974; Smythe *et al.*, 1975).

Methods

All subjects gave informed consent to the investigation which received ethical committee approval. Blood sampling was carried out through forearm venous cannulae inserted under local anaesthetic. GH, TSH and prolactin were measured by specific radioimmunoassays as described previously (Hartog *et al.*, 1964; Hall *et al.*, 1971; Reuter *et al.*, 1976), using as standards GH, MRC A, TSH, MRC 68/38 and prolactin MRC 71/222. All statistical analyses were carried out using the paired *t* test.

Clinical conditions

Acromegaly Three males and two females were studied. All had previously received pituitary DXT or undergone transphenoidal hypophysectomy, but were subsequently shown to have persistently elevated GH levels. Two acromegalic subjects with galactorrhoea also had elevated prolactin levels.

Hyperprolactinaemia Four subjects were studied. These included one male who had undergone Yttrium implantation for a lactotroph adenoma several years previously, but showed persistently elevated prolactin levels and had galactorrhoea to expression; and three

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females with 'functional hyperprolactinaemia' who presented with galactorrhoea/amenorrhoea.

The protocol for the clinical investigation was the same in each group.

Day 1 Basal profile: blood sampling every 2 h from 0900 to 1700 hours.

Day 2 Acute response: all subjects were fasting and recumbent. Cannulation was carried out at -30 min and subjects received nomifensine 50 mg orally at 0 min. Thereafter, sampling continued every 15 min for the first hour and every 30 min for the next 3 hours. All subjects were discharged taking nomifensine 50 mg three times daily for 1 week.

Day 8 Repeat basal profile with subjects taking nomifensine 50 mg orally at 0900 and 1300 hours.

Stimulated prolactin release

TRH Seven healthy male volunteers (aged 25-32 yr) were studied. Tests were carried out between 0700 and 0900, after an overnight fast and with subjects in the recumbent position. Blood sampling was carried out at -30, -15, 0, 10, 20, 30, 40, 60 and 90 min, subjects receiving TRH 200 µg i.v. at zero time. The procedure was repeated at least 1 week later after taking nomifensine 50 mg three times daily on the day before, and 50 mg at -60 min (4 subjects), 50 mg at -210 min (2 subjects), and 50 mg at -300 min (1 subject) on the day of the test.

MIT Eight healthy female and eight healthy male volunteers (aged 21-33 yr) were studied. Tests were

carried out between 0700 and 0900, after an overnight fast and with subjects in the recumbent position. Blood sampling was carried out at -30, -15, 0, 30, 60, 75, 90, 105 and 120 min, subjects receiving MIT 1g orally at zero time. The procedure was repeated at least 1 week later after taking nomifensine 50 mg three times daily on the day before, and 50 mg at zero time on the day of the test.

Results

Acromegaly

There was no reduction in elevated GH levels after either acute or chronic treatment (Tables 1 and 3). Although GH levels fell in subject 3 after nomifensine 50 mg (Table 3), it is unlikely that this indicates a response to treatment since GH levels remained high despite treatment with nomifensine 50 mg three times daily for 1 week (Table 1, day 8). Subjects 1 and 4 also showed hyperprolactinaemia but this did not respond to acute or chronic treatment (Tables 1 and 3).

Hyperprolactinaemia

There was no reduction in elevated prolactin levels after either acute or chronic treatment (Tables 2 and 4).

TRH

Nomifensine had no effect on TRH-induced TSH or prolactin release (Table 5 and 6, Figures 1 and 2) in any subject.

Table 1 GH (mU/l) and prolactin (mU/l) in acromegaly before and after treatment with nomifensine

	Time	0900	1100	1300	1500	1700
GH						
Subject 1	Day 1	41	35	41	82	67
	Day 8	34	49	54	57	40
Subject 2	Day 1	14	18	18	19	13
	Day 8	15	19	22	21	18
Subject 3	Day 1	7	27	8	7	18
	Day 8	37	29	20	25	28
Subject 4	Day 1	75	91	83	78	80
	Day 8	82	78	62	70	73
Subject 5	Day 1	100	84	82	96	140
	Day 8	96	135	98	135	110
Prolactin						
Subject 1	Day 1	1400	1600	1680	1920	1760
	Day 8	1280	1260	1560	1600	1660
Subject 4	Day 1	3700	5600	4300	4100	3500
	Day 8	5200	4500	4300	3100	4200

Table 2 Prolactin (mU/l) in hyperprolactinaemia before and after treatment with nomifensine

	Time	0900	1100	1300	1500	1700
Subject 1	Day 1	6000	6400	6000	5400	6000
	Day 8	8000	8000	8000	8000	8000
Subject 2	Day 1	1560	1280	1290	1240	1250
	Day 8	2800	3300	2460	2120	2700
Subject 3	Day 1	8000	8000	8000	8000	8000
	Day 8	8000	8000	8000	8000	8000
Subject 4	Day 1	650	650	680	980	1030
	Day 8	1300	1170	1150	1550	1550

Table 3 Acute GH and prolactin response (mU/l) to nomifensine in acromegaly

Time (min)	1		2		Subject 3		4		5	
	GH	Prolactin	GH		GH		GH		GH	
-30	41	1400	15		35		82		3800	100
-15	41	1560	13		40		75		3700	115
0	38	1560	14		39		79		4200	96
15	30	1360	15		37		80		4000	130
30	31	1920	17		30		85		4000	110
45	34	1520	17		28		91		5600	150
60	35	1600	19		25		88		4300	135
90	37	1600	18		21		83		4300	125
120	40	1680	18		16		106		4300	110
150	46	1920	21		16		95		4100	98
180	41	1920	21		15		78		3500	135
210	58	1760	20		16		81		3800	142
240	82	1700	18		21		85		3900	110

MIT

Nomifensine did not alter MIT-induced prolactin release in females (Table 7, Figure 3) but suppressed prolactin release in males (Table 8, Figure 4). This

suppression was statistically significant ($P < 0.05$) at 60, 75 and 90 min after MIT administration.

Discussion

Nomifensine did not reduce the elevated GH or prolactin levels in patients with acromegaly or hyperprolactinaemia. It does not, therefore, have any therapeutic role in these diseases at the dosage used in this study, unlike 2-bromo- α -ergocryptine (bromocryptine), a powerful and long-acting DA agonist of established therapeutic value in these conditions (Del Pozo *et al.*, 1973; Gomez-Pan *et al.*, 1975; Liuzzi *et al.*, 1974; Thorner *et al.*, 1974; Thorner *et al.*, 1975).

The significant suppression of MIT-induced prolactin release in males, by nomifensine, is likely to reflect the DA agonist activity of the drug, as nomifensine has been shown to inhibit the re-uptake of endogenous DA (Gerhards *et al.*, 1974; Hunt *et al.*, 1974; Schacht & Heptner, 1974). Since it is well recognized that both DA receptor agonists (bromocryptine) and DA itself effectively lower

Table 4 Acute prolactin (mU/l) response to nomifensine in hyperprolactinaemia

Time (min)	Subject			
	1	2	3	4
-30	8000	2000	8000	1750
-15	8000	1960	8000	1880
0	8000	1400	8000	1350
15	8000	1920	8000	1450
30	8000	2300	8000	1650
45	8000	1920	8000	1750
60	8000	1930	8000	1130
90	8000	2100	8000	1620
120	8000	1920	8000	1350
150	8000	1680	8000	800
180	8000	1830	8000	1070
210	8000	2100	8000	1070
240	8000	1800	8000	1320

Figure 1 TSH response to TRH 200 µg i.v. before (●) and after treatment with nomifensine in seven males (○). Mean ± s.e.

Figure 2 Prolactin response to TRH 200 µg i.v. before (●) and after treatment with nomifensine in seven males (○). Mean ± s.e.

Table 5 TSH response (mU/l) to TRH in seven males before and after nomifensine

Time (min)	Before		After	
	Mean	s.e.	Mean	s.e.
-30	1.8	0.2	1.6	0.3
-15	1.6	0.2	1.8	0.3
0	1.6	0.2	1.8	0.3
10	5.6	0.6	6.3	0.8
20	7.4	0.6	7.6	1.1
30	7.5	0.8	7.8	1.2
40	7.0	0.8	7.6	1.0
60	5.9	0.8	6.0	0.9
90	4.7	0.7	4.9	0.7

Table 6 Prolactin response (mU/l) to TRH in seven males before and after nomifensine

Time (min)	Before		After	
	Mean	s.e.	Mean	s.e.
-30	205	32	192	22
-15	180	18	199	23
0	204	18	184	12
10	1013	212	1037	236
20	929	184	1017	187
30	850	196	847	178
40	663	127	767	155
60	456	66	533	102
90	312	42	350	68

Table 7 Prolactin response (mU/l) to MIT in eight females before and after nomifensine

Time (min)	Before		After	
	Mean	s.e.	Mean	s.e.
-30	390	100	367	87
-15	422	99	349	68
0	345	73	354	76
30	584	110	1081	437
60	2589	800	3011	930
75	2948	987	3255	948
90	3034	947	3140	962
105	2789	971	2654	868
120	2199	661	2024	491

Table 8 Prolactin response (mU/l) to MIT in eight males before and after nomifensine

Time (min)	Before		After	
	Mean	s.e.	Mean	s.e.
-30	277	37	338	57
-15	227	19	249	46
0	238	24	218	30
30	460	157	358	59
60	1056	254	576	97
75	881	120	614	94
90	803	99	576	57
105	721	67	572	51
120	611	66	526	66

Figure 3 Prolactin response to MIT 1 g orally before (●) and after treatment with nomifensine in eight females (○). Mean $\pm$ s.e.

Figure 4 Prolactin response to MIT 1 g orally before (●) and after treatment with nomifensine in eight males (○). Mean $\pm$ s.e.

pathologically elevated GH and prolactin levels (Gomez-Pan *et al.*, 1975; Malarky *et al.*, 1971; Thorner *et al.*, 1974; 1975) and suppress TRH-induced prolactin release in man (Besses *et al.*, 1975; Del Pozo *et al.*, 1973; Noel *et al.*, 1973; Spaulding *et al.*, 1972), it is possible that the lack of effect of nomifensine in these situations is dose related. The effects of DA receptor agonists and exogenous DA on MIT-induced prolactin release are unknown, although it seems likely that a similar inhibition would be observed, for both bromocryptine and DA have a direct inhibitory effect on prolactin release from cultured pituitary cells (Pasteels *et al.*, 1971; Hill-Sanli & MacLeod, 1974; Takahara *et al.*, 1974).

The difference in the male and female pattern of prolactin response to MIT after nomifensine, observed in this study, could also be dose related. Such an effect, after administration of a DA agonist, has not been recorded previously and could be due to a direct effect of oestrogens on the hypothalamic dopaminergic system.

It is known that oestrogens have a direct stimulatory effect on the pituitary lactotroph, both *in vitro* (Lu *et al.*, 1971) and *in vivo* (Frantz *et al.*, 1973; Schmidt-Gollwitzer *et al.*, 1975; Stratmann *et al.*,

1974; Yen *et al.*, 1974). Although this direct effect on the lactotroph might well cause the potentiation by oestrogens of the prolactin response to TRH (Meites, 1973) and to dopaminergic inhibitors such as perphenazine (Buckman & Peake, 1973), it cannot account for the observed difference in the male and female prolactin response to MIT following inhibition of endogenous DA re-uptake by nomifensine. Indeed, if oestrogens have a role, it seems likely that they may have a 'damping' effect on the hypothalamic dopaminergic system, either through a direct action on the DA receptor, or by lowering endogenous DA levels, or both.

The lack of effect of nomifensine on TRH-induced TSH release is not unexpected, since acute administration of bromocryptine itself is ineffective (Del Pozo *et al.*, 1972; Del Pozo *et al.*, 1973; Hirvonen *et al.*, 1975). Both chronic oral administration of L-DOPA and acute DA infusion, however, inhibit the TSH response to TRH in man (Besses *et al.*, 1975; Noel *et al.*, 1973; Spaulding *et al.*, 1972), suggesting an overall inhibitory dopaminergic control of TSH secretion. It is likely that the effective concentration of DA at the receptor site following DA infusion is greater than that achieved by inhibition of

endogenous DA re-uptake by nomifensine.

In conclusion, it is clear that further studies using nomifensine at a higher dosage are required. It would also be interesting and possibly beneficial therapeutically to study its effects in combination with known DA agonists such as L-DOPA and bromocriptine. Finally, the possible oestrogen related 'damping' of the hypothalamic dopaminergic system

in females merits further investigation using nomifensine as an experimental tool.

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Discussion

PROFESSOR TURNER (Chairman) said that the tyramine pressor response was different in males and females, and that values in females varied according to the phase of the menstrual cycle. He had presumed that noradrenergic receptor or uptake activities were influenced by oestrogens in humans as well as in animals. He therefore welcomed Dr Scanlon's evidence that dopaminergic activity was possibly modulated by oestrogens.

DR HASLAM (York) asked whether nomifensine would affect sexual performance in depressed patients, and whether it could be valuable in treating impotence related to hyperprolactinaemia.

DR SCANLON (Newcastle) replied that he could not answer the first question and did not believe it would have any effect in hyperprolactinaemic hypogonadism. He said that the prolactin response to a single small dose of bromocryptine did not compare with the effect of nomifensine.

DR PARKES said that the action of apomorphine, bromocryptine and levodopa on GH release in normal subjects was possibly related to an increase in DA turnover leading ultimately to an increase in the output of GH-releasing factor. In

acromegaly, DA stimulants could directly affect the pituitary cell. As nomifensine had not been shown to have an effect on GH levels in acromegalics, he suggested that it had no direct effect on DA receptors. He then asked what effect it had on growth hormone levels in normal subjects.

DR SCANLON emphasized that he had not studied GH levels in normals, although he believed work showing a transient increase of GH levels in man and dogs after nomifensine had been carried out. He was not prepared to speculate about the role of the DA receptor in the aetiology of acromegaly. He could not interpret his data to confirm whether nomifensine acted postsynaptically but he was prepared to say that nomifensine certainly possessed dopaminergic activity.

PROFESSOR SPENCER (Cardiff), asked to summarize the morning's proceedings, said that in animals there was evidence firstly that nomifensine had a releasing action on DA and secondly, that it could inhibit the uptake of DA and NA and to a lesser extent 5-HT. There was also some evidence that nomifensine or its metabolites could have a postsynaptic agonist action, a view which he accepted with reservations.