EFFECT OF GUANFACINE ON PITUITARY HORMONES IN MAN

IOANA LANCRANJAN

Clinical Research, Sandoz AG, 4002 Basel, Switzerland

1 Animal studies have shown that adrenaline and noradrenaline are involved in the control of pituitary function. As very few data on this topic were available in man, some studies were carried out mainly in young normal volunteers using guanfacine, a new drug with central α -adrenoceptor properties.

2 Single oral doses of guanfacine 1 or 2 mg increased GH secretion. After 90–180 min, this increase was significant for the 2 mg dose. No effect on prolactin, ACTH, FSH and LH plasma levels was recorded. Four days of treatment with guanfacine showed:

- (a) no additional stimulation of GH released by insulin;
- (b) no effect on resting levels of prolactin and on prolactin released by metoclopramide, but a significant decrease of prolactin released by insulin;
- (c) a statistically significant ($P < 0.01$) but biologically unimportant increase in LH secretion ($\Delta = 1.58 \text{ mg/ml}$);
- (d) a non-significant decrease of ACTH released by metyrapone (an 11- β -hydroxylase inhibitor) but a significant ($P < 0.01$) decrease in ACTH released by stress (insulin-induced hypoglycaemia).

3 A 7-d treatment period with guanfacine (3 mg daily) showed that the drug did not have a sustained stimulatory effect on GH and LH secretion in man.

4 These data on hormonal balance support the assumption that, in man, the central α -adrenergic system exerts a stimulatory control on GH secretion and that an adrenergic pathway, hypothalamic or extrahypothalamic, may be involved in the inhibitory control of prolactin and ACTH release induced by stress.

Introduction

Guanfacine (BS 100–141) is a phenylacetylguanidine with a powerful BP reducing effect in animals and man. Like clonidine, guanfacine exhibits central and peripheral α -adrenoceptor stimulating effects and reduces the noradrenaline (NA) turnover in the brain stem; but, unlike clonidine, guanfacine is not active at the level of the neural surface of the medulla oblongata in cats, does not inhibit dopamine (DA) turnover in the corpus striatum in rats, has no effects on central histamine receptors, and has a weaker sedative effect than clonidine in dogs and rats (Paakkari, Karppanen & Paakkari, 1976; Scholtysik, 1978; Scholtysik, Lauener & Eichenberger, 1975). Furthermore, intraventricular administration of low doses of guanfacine in rats (like clonidine) stimulates GH secretion, and this effect can be blocked by phentolamine (Ruch, Jatton, Bucher, Marbach & Doepfner, 1976; Ruch, Marbach, Jatton, Bucher & Doepfner, 1978). Therefore, it was of interest to test the effect of guanfacine on pituitary secretion in humans.

Methods

Several studies were carried out in order to test the effect of guanfacine, given in single or repeated doses over a short period, on the secretion of GH, prolactin, ACTH, LH and FSH. Some of these studies have been published previously (Lancranjan & Marbach, 1977a, 1977b; Lancranjan, Ohnhaus & Girard, 1979; Lancranjan, del Pozo & Ohnhaus, 1978).

Effect of guanfacine on GH secretion

In young normal volunteers, single doses of guanfacine 1 and 2 mg were compared with clonidine 0.15 and 0.30 mg (Lancranjan & Marbach, 1977b). Data showing guanfacine's lack of effect on GH secretion in older hypertensive patients (aged 44–60 yr) have already been published (Lancranjan & Marbach, 1977a). This paper contains a report on:

(1) the effect of 7 days treatment with guanfacine on GH secretion in six young volunteers investigated

in basal conditions and during an oral glucose tolerance test;

(2) the effect of 4 days' treatment with guanfacine on GH secretion in another group of young volunteers (six subjects) who underwent an insulin-induced hypoglycaemia test;

(3) the GH pattern in hypertensive patients aged over 40 yr and treated with guanfacine (6 mg daily) for periods ranging from 2–6 months.

The subjects in the first two studies were male volunteers, aged 21–30 yr, with no history of mental illness and no personal or family history of diabetes mellitus. They were screened by history, physical examination, complete blood count and blood chemistry profile. Written informed consent was obtained. Six of the subjects (first study) received glucose 50 g orally before and after receiving guanfacine 3 mg daily for 7 days. Six other subjects (second study) received an intravenous bolus of insulin (0.1 IU/kg) before and after 4 days' treatment with guanfacine 4 mg daily for 4 days'. Blood was withdrawn at –15, 0, +15, +30, +60, +90 and +120 min after glucose or insulin administration on the control day and after treatment with guanfacine. GH plasma levels were measured using a radioimmunoassay method (Lancranjan & Marbach, 1977b).

The GH pattern in eight hypertensive patients was determined by measuring the GH plasma levels after 2–6 months' treatment with guanfacine. Measurements were made between 0800h and 0900h and again 2–3 h later, after an additional 2 mg dose of guanfacine. This interval was chosen on the basis of our previous results in young volunteers.

Effect of guanfacine on prolactin secretion

We report here the effect of a single 2 mg dose and of 10 days' treatment with guanfacine on plasma levels of prolactin in six hypertensive patients aged 45–60 years.

Plasma levels were measured using Friesen's method (Hwang, Guyda & Friesen, 1971) before and half-hourly for 3 h after the administration of guanfacine 2 mg, and every second day thereafter for a period of 10 d (6 mg guanfacine daily). Finally, an additional 2 mg dose of guanfacine was given on the day 10 and blood was collected half-hourly for 3 h to measure prolactin levels.

Effect of guanfacine on ACTH secretion

This report covers the effect of single doses of 1 and 2 mg guanfacine on ACTH plasma levels in six young male volunteers (aged 21–30 years).

Blood was collected after 30 min bed rest by way of a forearm venous cannula at –15, 0, 30, 60, 90, 120, 150 and 180 min after guanfacine administration. ACTH and cortisol plasma levels were measured

using a previously reported method (Girard, Baumann, Buehler, Zuppinger, Haas, Staub & Wyss, 1978).

Effect of guanfacine on LH and FSH plasma levels

LH and FSH plasma levels were measured:

(1) in six normal male volunteers after single doses of 1 and 2 mg guanfacine or placebo;

(2) in six young male volunteers treated with guanfacine daily 4 mg for 4 d;

(3) in six other young subjects (five men, one woman) treated with guanfacine 3 mg daily for 7 days.

Blood was collected by way of a forearm venous cannula at –15, 0, 15, 30, 45, 60, 75, 90, 105 and 120 min during the control days (after placebo administration) and after the randomized administration of guanfacine.

LH and FSH-CIS kits were used to measure hormone plasma levels.

Results

Effect of guanfacine on GH secretion

Study I

Three out of six subjects, given the first 2 mg dose of guanfacine, overcame the inhibitory effect of high glucose plasma levels induced by the oral administration of glucose (Table 1). On day 8 of treatment only one of the six subjects showed high basal GH plasma levels; and only two overcame the inhibitory effect of glucose administration.

Study II

Figure 1 shows that GH plasma levels after 4 days' treatment with guanfacine were within the normal range. Moreover, no significant effect on GH secretion stimulated by insulin was observed after treatment with guanfacine. Data on hormonal balance were analyzed using a paired *t* test for the area under plasma concentration/time curves before and after treatment with guanfacine.

Study III

Table 2 shows GH plasma levels in eight hypertensive patients treated with guanfacine for 2–6 months. In all patients investigated, GH plasma levels were within the normal range both in basal conditions and 2 h after an additional 2 mg dose of guanfacine.

Effect of guanfacine on prolactin secretion

Table 3 shows prolactin plasma levels recorded after a single 2 mg dose and before and after 10 days' treatment with guanfacine (2 mg three times daily) in the group of hypertensive patients aged 45–60 years. As reported previously for young normal volunteers

Table 1 Effect of (a) placebo, (b) guanfacine 2 mg and (c) guanfacine 1 mg three times daily for 7 d on GH levels (ng/ml)

Subject number	Guanfacine/Placebo						Glucose					
	-15 min	0 min	30 min	60 min	90 min	15 min	30 min	45 min	60 min	90 min	120 min	
a												
1	0.6	0.6	0.7	1.9	5.6	4.0	2.1	1.2	0.9	0.7	0.6	
2	0.6	0.7	1.1	0.7	0.6	0.6	0.6	0.5	0.6	0.5	0.5	
3	1.6	5.6	2.0	1.9	1.5	1.1	0.8	0.5	0.6	0.5	0.7	
4	1.1	—	4.7	1.6	1.0	0.8	0.8	0.8	0.6	0.7	0.5	
5	0.6	—	5.7	1.6	0.9	0.8	0.7	0.6	0.6	0.7	0.6	
6	0.8	0.6	0.6	0.6	0.6	0.6	0.7	0.7	0.6	0.7	1.2	
Mean	0.9	1.9	2.5	1.4	1.7	1.3	0.9	0.7	0.6	0.6	0.7	
s.d. $\pm$	0.4	2.5	2.2	0.6	1.9	1.3	0.6	0.3	0.0	0.0	0.1	
s.e. mean $\pm$	0.2	1.2	0.9	0.2	0.8	0.5	0.2	0.1	0.0	0.0	0.1	
b												
1	0.5	0.6	0.7	0.6	1.5	1.5	1.4	0.8	0.7	0.7	1.7	
2	0.5	0.6	0.9	0.5	0.6	0.7	0.7	0.7	0.6	0.5	0.7	
3	0.7	0.7	1.3	4.4	1.9	1.0	0.8	0.7	0.6	0.6	0.9	
4	2.1	6.3	28.3	27.4	14.8	10.6	6.3	9.1	17.6	14.6	13.4	
5	1.3	2.8	2.2	1.0	0.8	0.7	2.3	23.8	100.0	31.8	14.3	
6	0.8	1.1	0.8	0.7	0.8	1.8	5.6	5.6	2.9	1.3	1.1	
Mean	1.0	2.0	5.7	5.8	3.4	2.7	2.8	6.8	20.4	8.2	5.3	
s.d. $\pm$	0.6	2.3	11.1	10.7	5.6	3.9	2.5	9.0	39.5	12.8	6.6	
s.e. mean $\pm$	0.2	0.9	4.5	4.0	2.3	1.6	1.0	3.7	16.1	5.2	2.7	
c												
1	0.9	1.4	1.0	0.8	1.5	2.3	1.5	1.1	0.8	1.2	5.1	
2	0.7	0.6	0.6	0.6	0.8	0.6	0.7	0.6	0.5	0.6	0.9	
3	1.4	1.9	2.6	1.0	1.1	1.4	1.4	1.0	0.8	0.7	1.4	
4	20.9	21.0	4.4	2.0	16.6	16.9	12.7	10.1	8.8	3.0	3.7	
5	0.6	0.9	16.8	6.0	1.5	1.0	0.9	0.8	0.9	6.1	10.7	
6	1.5	0.9	0.8	0.7	0.6	0.5	0.6	0.6	0.7	0.7	2.0	
Mean	4.3	4.4	4.4	1.8	3.7	3.8	3.0	2.4	2.1	2.0	4.0	
s.d. $\pm$	8.1	8.1	6.3	2.1	6.3	6.5	4.8	3.8	3.3	2.2	3.6	
s.e. mean $\pm$	3.3	3.3	2.6	0.9	2.6	2.6	1.9	1.5	1.3	0.9	1.5	

Table 2 GH response to guanfacine treatment in hypertensive patients aged over 40 years

Patient	Plasma growth hormone (ng/ml)	
	During long-term treatment (first sample at 0800–0900h)	2–3h after an additional 2mg dose of guanfacine
1	7.3	2.5
2	12.5	1.1
3	1.0	0.6
4	1.2	1.0
5	2.5	1.7
6	2.3	1.9
7	2.7	0.9
8	1.2	1.5
Mean	3.8	1.4
± s.e. mean	1.4	0.2

(Lancranjan & Marbach, 1977b; Lancranjan *et al.*, 1978), guanfacine had no effect on the prolactin resting levels of these patients.

Effect of guanfacine on ACTH secretion

No effect on resting plasma levels of either ACTH and cortisol was noted in normal volunteers after single doses of guanfacine 1 or 2 mg.

Effect of guanfacine on FSH and LH secretion

No effect on FSH secretion was recorded either after single doses of guanfacine 1 or 2 mg, or after 4 or 7 days' treatment with guanfacine. On the other hand, a minor but statistically significant increase of LH secretion ($\Delta = 1.56$ mg/ml; $P < 0.01$) occurred after 4 days' treatment with guanfacine 4 mg daily. However, as no effect was recorded after single doses of guanfacine 1 or 2 mg, or after 7 days' treatment, one may conclude that guanfacine has no consistent effect on LH secretion in man.

Discussion

Our previous studies (Lancranjan & Marbach, 1977a, 1977b) have shown that a single oral dose of guanfacine 2 mg significantly increased ($P < 0.001$) GH secretion in young normal volunteers. These data are in agreement with results obtained with clonidine, and support the idea that the α -adrenoceptor system regulates GH secretion in man.

We have also observed that guanfacine has no effect on the GH pattern in hypertensive patients aged 45–60 yr, in whom the sensitivity or the number of α -adrenoceptors involved in the control of GH secretion (Lancranjan & Marbach, 1977b) were reduced.

The data presented here show that:

(1) a single dose of guanfacine 2 mg overcame the inhibitory effect of high glucose plasma levels in only

Figure 1 Effect of guanfacine on insulin-induced GH secretion. GH concentrations were measured in plasma after insulin alone and after insulin following pretreatment with guanfacine, as described in the text. GH values are given as the mean $\pm$ s.e. mean ○, Guanfacine; ●, placebo pretreatment.

three out of six subjects. These results are in agreement with those of other studies showing that hyperglycaemia can inhibit GH release induced by all stimuli except sleep (Lancranjan & Marbach, 1977b);

(2) guanfacine has no additive stimulatory effects when insulin-induced hypoglycaemia, the most potent stimulus for GH secretion, is used to release GH;

(3) the stimulatory effect of guanfacine on GH secretion is not long-lasting even in young subjects. Bromocriptine, a drug with dopamine-agonist properties, also has only short-lasting stimulatory effects on GH secretion (del Pozo, Darragh, Lancranjan, Ebeling, Burmeister, Buchler, Marbach & Braun, 1977). This strongly suggests that the neural control of GH secretion in humans is very complex and well balanced in maintaining GH homeostasis. Clearly, in young humans, as in animals, the adrenergic system affects GH secretion, but this is only one link in the chain of neurotransmitters involved in the modulation of GH secretion.

Guanfacine has no effect on the resting prolactin plasma levels of both normal young volunteers (Lancranjan & Marbach, 1977b) and hypertensive patients with normal prolactin plasma levels. On the other hand, it has been reported that guanfacine treatment may reduce prolactin secretion in hypertensive patients with moderately high prolactin plasma levels (Hauger-Kleven, Rastrilla, Pinkas, Grosman & Degrossi, 1978). Furthermore, it has been reported that a single oral dose of guanfacine 2 mg could significantly decrease prolactin secretion in postpartum women while not having any effect on the prolactin secretion in patients with prolactin secreting adenoma (Genazzani & Lancranjan, unpublished observations). These data suggest that guanfacine decreases prolactin secretion only in

Table 3 Prolactin plasma levels (ng/ml) before and after oral administration of guanfacine 2 mg three times daily for 10 days

Subject	Age (yr)	Control	30 min	120 min	150 min	180 min	
1	44	First day	4.5	2.7	11.2	6.7	5.4
2	50	First day	3.9	8.4	—	5.5	5.0
3	60	First day	6.1	9.1	15.4	5.6	5.1
4	48	First day	4.8	7.8	2.7	6.2	2.5
5	54	First day	3.8	6.9	10.2	16.9	11.1
6	48	First day	5.5	2.7	5.5	3.4	4.4
Mean (ng/ml)			4.8	6.2	8.8	5.4	5.5
s.e. mean			0.4	1.1	2.1	0.6	1.1
1		Tenth day	4.2		4.1	4.9	5.5
2		Tenth day	4.5		4.6	4.5	6.8
3		Tenth day	3.1		1.3	2.8	—
4		Tenth day	4.6		4.1	4.4	5.7
5		Tenth day	18.0		9.0	7.0	5.8
6		Tenth day	7.3		7.6	8.3	12.7
Mean (ng/ml)			6.9		5.1	5.3	7.3
s.e. mean			2.2		1.1	0.8	1.4
2 h after the first daily dose of guanfacine				Day 2	Day 4	Day 6	Day 8
1				8.5	4.3	5.3	1.9
2				—	4.3	—	3.2
3				13.17	5.9	5.3	19.1
4				1.8	6.9	—	10.21
5				5.6	9.1	7.3	8.4
6				2.8	4.1	4.0	3.1
Mean (ng/ml)				6.4	5.8	5.5	5.4
s.e. mean				2.1	0.8	0.7	1.6

patients with functional hyperprolactinemia. The results confirm our previous observation that treatment with guanfacine significantly decreases prolactin released by insulin, and has no effect on prolactin released by metoclopramide, and support the assumption that guanfacine acts above the pituitary level by stimulating hypothalamic or extrahypothalamic adrenergic pathways involved in the inhibitory control of prolactin secretion.

This paper also confirms the lack of effect of single oral doses of guanfacine 1 and 2 mg on ACTH and cortisol resting plasma levels. Four days of treatment with guanfacine 4 mg daily has no effect on basal ACTH and cortisol plasma level, or on ACTH released by metyrapone, but causes a significant reduction in ACTH and cortisol released by insulin ($P < 0.02$; $P < 0.01$) (Lancranjan *et al.*, 1979). These results are in agreement with animal experimental data obtained with clonidine (Ganong, 1975) and are the first evidence in man that α -adrenoceptor agonists have an inhibitory effect on stress induced ACTH release.

A good deal is known from animal experiments about the stimulatory role of noradrenaline on LH secretion (Fuxe, Löfström, Agnati, Eneroth, Gustafsson, Hökfelt & Skett, 1977; Fuxe, Löfström,

Agnati, Hökfelt & Skett, 1977; Fuxe, Löfström, Skett, Jeffcoate & Fraser, 1977; Kalra, 1977). Moreover, there are data suggesting that noradrenaline is the neurotransmitter involved in the mid-cycle peak of LH-RH and LH secretion in rats (Kalra, 1977).

In spite of these animal data, the results recorded with guanfacine in young men showed only an inconsistent stimulatory effect on LH secretion. However, no definitive conclusion concerning the role of the α -adrenergic system in the control of LH secretion in man can be reached before obtaining data on hormone balance in young women treated throughout at least two complete ovarian cycles.

Conclusions

Single oral doses of guanfacine 1 or 2 mg increased GH secretion. After 90–180 min, the increase was significant for the 2 mg dose. No effect on prolactin, ACTH, FSH and LH plasma levels was recorded. Four days of treatment with guanfacine showed:

(1) no additional stimulation of GH released by insulin;

(2) no effect on resting prolactin levels and on prolactin released by metoclopramide, but a significant decrease in PRL released by insulin;

(3) a significant ($P < 0.01$) but not biologically important increase in LH secretion ($\Delta = 1.58$ mg/ml);

(4) a nonsignificant decrease in ACTH released by metyrapone (an 11- β -hydroxylase inhibitor), but a significant ($P < 0.02$) decrease in ACTH released by stress (insulin-induced hypoglycaemia).

Seven days of treatment with guanfacine 3 mg daily showed that the drug did not have a sustained stimulatory effect on GH and LH secretion in man.

These data support the hypothesis that, in man, the central α -adrenergic system exerts a stimulatory

control on GH secretion and that an adrenergic pathway, hypothalamic or extrahypothalamic, may be involved in the inhibitory control of prolactin and ACTH release induced by stress.

The author is grateful to Dr E. Nuesch, Medical Research Department, Sandoz Ltd, Basel, who carried out the statistical evaluation of all data on hormone balance and to Professor Girard, Endocrine Laboratories of the University Pediatric Clinic of Basel, who kindly carried out the ACTH and cortisol plasma determinations.

References

- FUXE, K., LÖFSTRÖM, A., AGNATI, L., ENEROTH, P., GUSTAFSSON, J.-Å., HÖKFELT, T. & SKETT, P. (1977). Central monoaminergic pathways. Their role in control of lutropin, follitropin and prolactin secretion. In *Endocrinology*, Vol. 1. Ed. James, V.H.T. Pp. 136–143. Amsterdam and Oxford: Excerpta Medica.
- FUXE, K., LÖFSTRÖM, A., AGNATI, L., HÖKFELT, T., JOHANSSON, O., ENEROTH, P., GUSTAVSSON, J.-Å., SKETT, P., JEFFCOATE, S. & FRASER, H. (1977). Functional morphology of the median eminence: On the involvement of catecholamines in the control of FSH, LH and prolactin secretion. In *Progress in Reproductive Biology Clinical Reproductive Neuroendocrinology* (Sixth International Seminar on Reproductive Physiology and Sexual Endocrinology, Brussels, 1976); Vol. 2. Ed. Hubinont, P.O., L'Hermite, M. & Robyn, C. Pp. 41–53. Basel: S. Karger.
- GANONG, W.F. (1975). Brain amines and the control of ACTH and growth hormone secretion. In *Physiology, Pharmacology and Clinical Uses*. Ed. Motta, U., Crosignani, P.G. & Martini, L. Pp. 237–248.
- GIRARD, J., BAUMANN, J.B., BUEHLER, U., ZUPPINGER, K., HAAS, H.G., STAUB, J.J. & WYSS, H.I. (1978). Cyproterone acetate and ACTH adrenal function. *J. clin. Endocrinol. Metab.*, **47**, 581–586.
- HAUGER-KLEVE, J.H., RASTRILLA, A.M., PINKAS, M.B., GROSMAN, Y.M., & DEGROSSI, O.J. (1978). Estudio comparativo del AH-5158 y el BS-100/141 en la hipertension esencial: efecto en la secrecion de renina y prolactina y en la reactividad vascular. *La Semana Medica. Aug.* **26**, 265–271.
- HWANG, P., GUYDA, H. & FRIESEN, H. (1971). A radioimmunoassay for human prolactin. *Proc. nat. Acad. Sci. U.S.A.*, **68**, 1902–1906.
- KALRA, S.P. (1977). Neuroamines in gonadotropin secretion. In *Endocrinology*, Vol. 1. Ed. James, V.H.T. Pp. 152–157. Amsterdam and Oxford: Excerpta Medica.
- LANCRANJAN, I., MARBACH, P. (1977a). Effect of antihypertensive drugs on growth hormone secretion. *Br. med. J.*, **2**, 1472–1473.
- LANCRANJAN, I. & MARBACH, P. (1977b). New evidence for growth hormone modulation by the α -adrenergic system in man. *Metabolism*, **26**, 1225–1230.
- LANCRANJAN, I., OHNHAUS, E. & GIRARD, J. (1979). The α -adrenoceptor control of ACTH secretion in man. *J. clin. Endocrinol. Metab.*, **49**.
- LANCRANJAN, I., DEL POZO, E. & OHNHAUS, E. (1978). Inhibitory effect of guanfacine, a central α -adrenoceptor agonist, on prolactin secretion stimulated by insulin-induced hypoglycemia. *J. clin. Endocrinol. Metab.*, **47**, 671–673.
- PAAKKARI, I., KARPPANEN, H. & PAAKKARI, P. (1976). Site and mode of action of clonidine in the central nervous system. *Acta Med. Scand. Suppl.* **602**, 106–140.
- DEL POZO, E., DARRAGH, A., LANCRANJAN, I., EBELING, D., BURMEISTER, P., BUEHLER, F., MARBACH, P. & BRAUN, P. (1977). Effect of bromocriptin on the endocrine system and fetal development. *Clin. Endocrinol. Suppl.*, **6**, 47–55.
- ROSNER, J.M., NAGLE, C.A., DE LABORDE, N.P., PEDROZA, E., BADANO, A., FIGUEROA CASAS, P.R. & CARRIL, M. (1976). Plasma levels of norepinephrine (NE) during the periovulatory period and after LH-RH stimulation in women. *Am. J. Obstet. Gynecol.*, **124**, 567–572.
- RUCH, W., JATON, A.L., BUCHER, B., MARBACH, P. & DOEPFNER, W. (1976). Alpha adrenergic control of growth hormone in adult male rats. *Experientia*, **32**, 529–531.
- RUCH, W., MARBACH, P., JATON, A.L., BUCHER, B. & DOEPFNER, W. (1978). Adrenergic and dopaminergic control of growth hormone secretion in urethane anesthetized adult male rats. *Hormone Res.*, **9**, 208–224.
- SCHOLTYSIK, G. (1987). Guanfacine (*N*-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride) lowers systemic blood pressure in DOCA-NaCl-hypertensive conscious rats with oral doses of 0.3–5 mg/kg. Lecture at the VIth International symposium on Medicinal Chemistry, University of Sussex, Brighton, 4–7 September, 1978.
- SCHOLTYSIK, G., LAUENER, H., EICHENBERGER, E. *et al.* (1975). Pharmacological actions of the anti-hypertensive agent *N*-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride (BS-100–141). *Arzneimittel. Forsch.*, **25**, 1483–1491.