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CLONIDINE WITHDRAWAL. MECHANISM AND FREQUENCY OF REBOUND HYPERTENSION

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1 The frequency and pathophysiology of the clonidine withdrawal syndrome was studied in fourteen hypertensive patients on chronic clonidine therapy.

2 After sudden cessation of clonidine (900 μg daily) almost all of the patients showed an excessive increase of the heart rate and blood pressure. Seven of the fourteen patients had subjective symptoms, in three severe enough to require interruption of observation by therapeutic intervention 12 to 60 h after the last dose of clonidine. After clonidine withdrawal, NAE increased to abnormally high values in correlation with the blood pressure ($P < 0.01$) and heart rate ($P < 0.001$), whereas PRA even decreased initially, probably secondary to the rise of the blood pressure, and only rose, although not significantly, 48 h after withdrawal. PRA was not correlated with NAE, heart rate, or blood pressure.

3 It is concluded that the clonidine withdrawal phenomenon is a frequently occurring and potentially dangerous syndrome. Overactivity of the sympathetic nervous system is mainly responsible, without the mediation of the renin angiotensin system. This also explains our experience that adrenergic β-receptor blocking drugs do not prevent the rise in BP, although they alleviate some of the symptoms.

Introduction

Clonidine is a widely used antihypertensive drug that suppresses the sympathetic nervous system and plasma renin activity (PRA), probably via a central mechanism (Kosman, 1975). In occasional patients a syndrome of exaggerated sympathetic activity has been described after discontinuation of therapy called the clonidine withdrawal syndrome. Although recent reports (Goldberg, Raftery & Wilkinson, 1976; Reid, Dargie, Davies, Wing, Hamilton & Dollery, 1977) well documented the frequent occurrence of this syndrome and the increase in noradrenaline excretion by which it is accompanied, there is insufficient information on the role played by the PRA in the pathogenesis of the increase in BP. To evaluate the possible risks patients run if they do not take their medication regularly or when their medication is withdrawn by their physician, we analysed the frequency, severity, and pathophysiology of this withdrawal syndrome. Chronic clonidine therapy was continued in fourteen hospitalized hypertensive patients, and subjective symptoms, BP, pulse rate, urinary noradrenaline excretion, and plasma renin activity were recorded for 3 days before and 3 days after the withdrawal of the drug.

Methods

The study was performed during a period of hospitalization in fourteen hypertensive patients (eight males and six females, age range 25–61 years) with normal serum urea and creatinine and a normal ECG, all with essential hypertension. All had been on chronic clonidine treatment for more than 1 month. Informed consent was obtained, and the patients were instructed, without further specifications, that they might feel uncomfortable after discontinuation of the drug.

While the patients were on a 60 mEq Na^+ diet, all treatment was stopped with the exception of clonidine, which was given in a uniform dose of 900 μg daily, divided over the day into six doses given between 08.00 h and 22.00 h. When the blood pressure and body weight became stable, this regimen was continued for 3 days (clonidine period). Thereafter, no medication was given for 3 days (withdrawal period), with the exception of three patients who required interruption (cases 1–3).

The blood pressure was taken on the ward by well trained nurses with a standard sphygnomanometer at least four times daily (at 8, 11, 16 and 22 h) after 5 min recumbancy; at the same time the pulse rate

was taken. The fourth Korotkoff sound was taken as diastolic blood pressure. From these data daily blood pressure and heart rate were calculated. Mean arterial pressure was calculated with the formula (systolic + 2x diastolic):3. Subjective symptoms were recorded only when the patients had spontaneous complaints.

In nine of the fourteen patients, plasma renin activity (PRA) and urinary noradrenaline excretion (NAE) were studied. Venous blood for PRA determination was drawn supine and after standing for 30 min on the last day of clonidine treatment, on the first day after withdrawal at 08.00 h and 16.00 h and on the second and third days of the withdrawal period only at 08.00 h. PRA was measured by radioimmunoassay with a slight modification (deproteinization step) of Haber method (Geyskes, Boer, Vos, Leenen & Dorhout Mees, 1975).

Twenty-four hour urine was collected with $K_2S_2O_5$ and the noradrenaline content was measured after Al_2O_3 adsorption by the fluorimetric trihydroxyindol method (Anton & Sayre, 1962; Laverty & Tailor, 1968). Corrections were made for adrenaline and for losses of NA during the procedure. The normal value ± s.e. mean determined in nine healthy volunteers on the same Na^+ diet was 36 ± 7 μg/24 h. The between-assay variation was 9%, the within-assay variation 7%. Statistical analysis was performed with the paired *t*-test and the paired Wilcoxon test.

Results

Objective symptoms, blood pressure, and heart rate

Data on the incidence of subjective symptoms, heart rate, and blood pressure are shown in Table 1. The most striking observation is the high frequency of withdrawal reactions including headache, nervousness, lack of sleep, palpitations, and nausea in variable combinations. In three patients the syndrome of complaints and the height of the blood pressure were serious enough to make therapeutic intervention advisable 12 to 60 h after the last clonidine dose. Details of these last three patients are described in the case reports, and their data are shown in Figures 2–4.

All patients but one (including the 7 patients without subjective symptoms) showed a marked rise of the blood pressure after cessation of therapy. The average mean blood pressure on all withdrawl days was significantly elevated as compared with the last day of clonidine therapy ($P < 0.001$), and increased further from the first to the second withdrawal day ($P < 0.025$; day 4–5). After 48 h the blood pressure was variable and did not change significantly.

The average heart rate of most of the patients who completed the study was elevated on all withdrawal days as compared with the last day of clonidine therapy ($P < 0.05$). Further increases during days 4, 5, and 6 were not significant, while two patients (Mo and E-M) requiring interruption of the study had the highest heart rates recorded during the withdrawal period. The other (patient A-B) showed an abnormally low heart rate.

Urinary noradrenaline excretion and plasma renin activity

Data of seven patients for whom complete biochemical data were obtained during all 3 withdrawal days, are shown in Table 2. NA excretion was suppressed during clonidine administration in most patients, while the excretion was significantly increased on the second and third withdrawal days ($P < 0.05$). A significant correlation was found between daily NAE and daily MAP ($r = 0.45$, $P < 0.01$) and between daily NAE and HR ($r = 0.55$, $P < 0.001$).

Plasma renin activity during clonidine was slightly lower than normal and only rose 48 h after withdrawal. These changes were not statistically

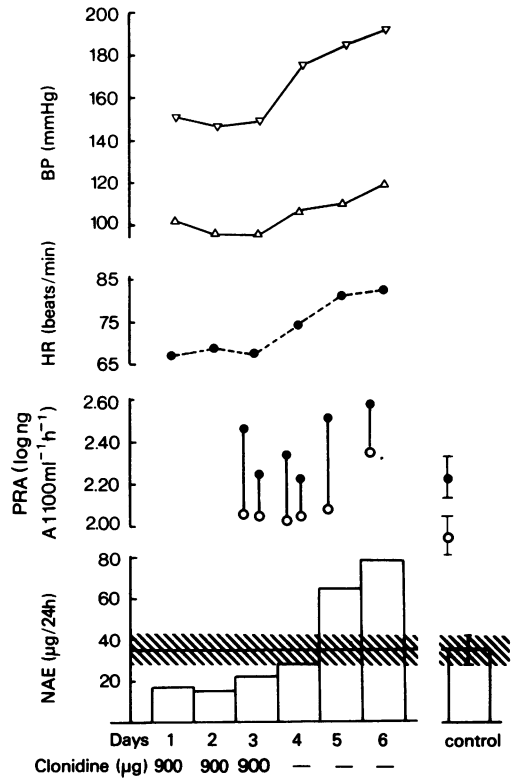

Figure 1 Average daily blood pressure (BP) (▽ systolic; △ diastolic), heart rate (HR), plasma renin activity (PRA) (● upright; ○ recumbent), and urinary noradrenaline excretion (NAE) (first seven patients in Table 1). Hatched area indicates average ± s.d.

Table 1 Daily averages of supine, resting mean arterial pressure and heart rate before and after clonidine withdrawal

				Mean arterial pressure (mmHg)						*Heart rate (beats/min)*					
				Clonidine (0.9 mg/day)			*No medication*			*Clonidine (0.9 mg/day)*			*No medication*		
			Day	*1*	*2*	*3*	*4*	*5*	*6*	*1*	*2*	*3*	*4*	*5*	*6*
Patient	*Sex*	*Diagnosis*	*Subjective symptoms*												
M	M	EH	yes	137	137	137	147	143	163	64	72	69	76	87	75
R	M	EH	no	118	117	119	131	139	140	73	72	71	80	87	82
D-E	F	EH	no	127	123	126	129	128	127	78	77	79	80	78	82
W	M	HSK	no	100	102	103	108	123	162	84	78	74	70	90	82
H	M	EH	yes	100	103	105	115	142	137	66	66	66	82	84	88
B-R	F	EH	yes	109	101	100	123	139	139	49	51	54	56	66	66
Mo	M	EH	serious	107	103	101	137	152	153†	60	68	64	74	80	110†
B-V	F	EH	no	112	113	113	120	137	133	72	60	61	66	60	62
E	M	EH	yes	112	108	95	100	157	163	68	70	70	68	80	87
K	M	EH	no	100	102	92	98	117	117	61	62	66	66	69	100
D	M	EH	no	111	110	113	120	131	129	63	66	68	70	84	84
Z	F	EH	no	112	110	112	132	128	128	64	66	64	70	79	92
mean				112	111	110	123**	135**	141**	67	67	67	72*	79*	84**
s.e. mean				3	3	4	4	4	5	3	2	2	2	3	4
A-B	F	EH	serious	120	120	111	173†			75	74	67	56†		
E-M	F	EH	serious	139	123	138	165†			84	68	78	120†		

*=$P<0.025$, **=$P<0.001$ (P values for comparison with day 3 (last of clonidine treatment) (paired t-test).
†=value obtained before the study in this patient was interrupted on that day.
Data of the two last patients in whom the study had to be interrupted during days 4 and 5 were not included in the calculation of averages.

Table 2 PRA and urinary NA excretion before and after clonidine withdrawal in first seven patients in Table 1

	Plasma renin activity (log ng angiotensin/100 ml^{-1}h^{-1})												*Urinary noradrenaline excretion (μg/24 h)*					
	Clonidine (0.9 mg/day)				*No medication*								*Clonidine (0.9 mg/day)*			*No medication*		
Day	*3*				*4*				*5*		*6*		*1*	*2*	*3*	*4*	*5*	*6*
Time of day (h)	*08.00*		*16.00*		*08.00*		*16.00*		*08.00*		*16.00*							
Position	*r*	*st*	*r*	*st*	*r*	*st*	*r*	*st*	*r*	*st*	*r*	*st*						
M	1.40	1.78	1.74	1.82	1.48	1.78	1.74	1.93	1.93	2.24	2.13	2.23	22	30	32	33	66	35
R	2.15	2.70	2.18	2.35	2.29	2.46	2.15	2.28	2.29	2.53	2.50	—	5	7	6	14	25	39
D-E	2.16	2.86	2.06	2.40	1.98	2.71	2.04	2.45	2.02	2.73	2.33	2.77	35	29	33	62	58	53
W	2.74	3.13	2.48	2.85	2.48	2.91	2.54	2.74	2.65	2.92	2.87	2.97	8	7	9	12	37	68
H	1.67	1.98	1.95	1.81	1.48	1.65	1.81	1.81	1.08	2.31	2.37	2.41	22	8	19	30	90	196
B-R	1.30	1.48	1.34	1.65	1.67	1.60	1.54	1.70	1.78	1.90	2.11	2.42	8	8	5	4	35	46
Mo	2.88	3.10	2.48	2.57	2.70	3.08	2.37	2.50	2.50	2.75	2.06	2.48	16	13	51	41	137	110
Mean	2.04	2.43	2.03	2.21	2.01	2.31	2.03	2.20	2.04	2.48	2.34	2.55	17	15	22	28	64*	78*
s.e. mean	0.25	0.28	0.17	0.18	0.20	0.26	0.15	0.16	0.21	0.14	0.12	0.12	4	4	7	8	16	24

r = recumbent
st = standing
* = $P < 0.02$ (P value for comparison with day 3 (last of clonidine treatment) (paired Wilcoxon test).

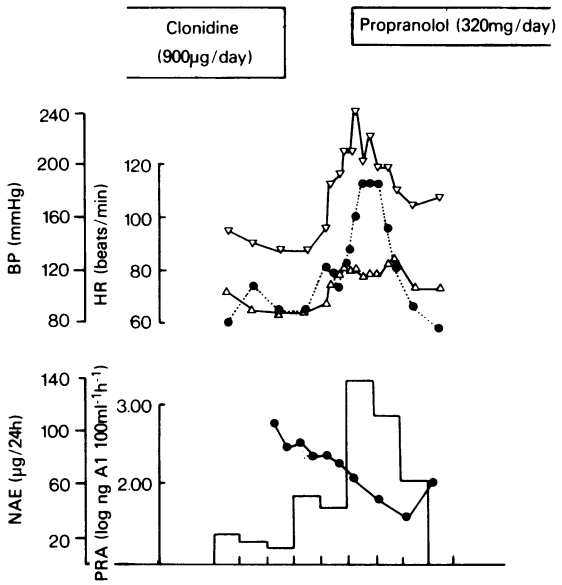

Figure 2 Sequence of events in a 40 years old man (M.) in whom observation without medication had to be interrupted because of severe symptoms. (▽ systolic BP; △ diastolic BP; ● HR).

significant. Unlike NAE, PRA did not show correlation with either MAP or HR. There also was no correlation between the NAE and PRA values. The mean values for heart rate, blood pressure, PRA and NAE are shown in Figure 1.

The three patients with the most severe symptoms were studied in more detail. Their case records are discussed briefly here; their data are shown in Figures 2–4.

Case 1 (Figure 2). A 40-year-old man with essential hypertension (EH) started to complain of restlessness, lack of sleep, headache, and palpitations 24 h after withdrawal of clonidine therapy. HR increased during the second day and the blood pressure rose to 240/120. On the third day he asked for intervention and propranolol was started orally (80 mg four times a day). This relieved the complaints, and the heart rate decreased to normal during the next 24 h. The blood pressure, the maximum values already having been reached, declined, albeit slowly. Urinary NAE rose after withdrawal, but did not reach excessively high levels until the third and fourth days. Remarkably, PRA decreased during the first 3 days and increased again on the fourth day after 36 h of propranolol therapy. On the morning of the third day, before propranolol therapy, an injection of 5 mg phentolamine i.v. resulted in an immediate, but very brief drop of the blood pressure from 195/105 to 120/70.

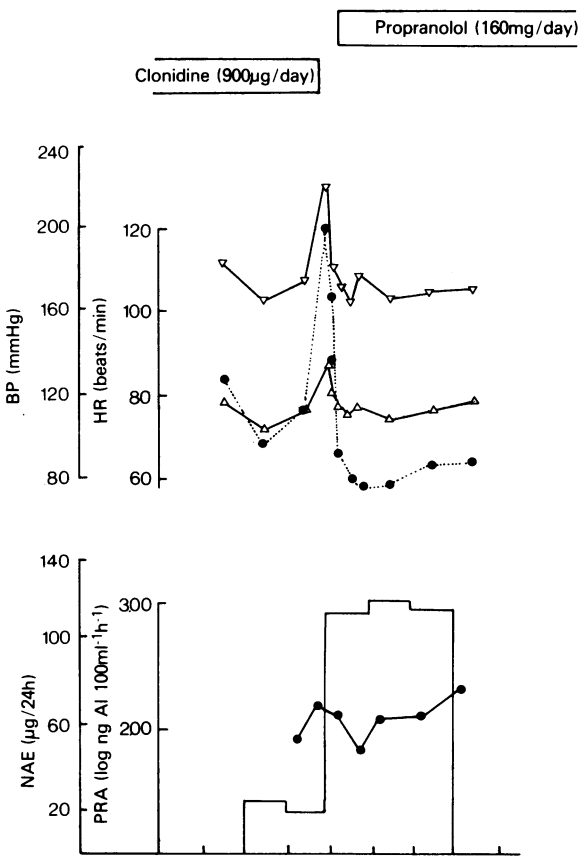

Figure 3 Sequence of events in a 45 years old woman (E.-M.) in whom observation without medication had to be interrupted because of severe symptoms. (▽ systolic BP; △ diastolic BP; ● HR).

Case 2 (Figure 3). A 45-year-old woman with EH complained of nervousness and palpitations 12 h after withdrawal. Blood pressure and heart rate were high and propranolol therapy was started, which resulted in a quick drop of the heart rate and blood pressure and relief of the symptoms. Urinary NA excretion remained abnormally elevated during all three days. PRA (supine) was variable but showed the same changes as in case 1: after an initial drop it became higher, notwithstanding the propranolol therapy.

Case 3 (Figure 4). A 44-year-old woman with EH experienced the same symptoms as seen in case 1, 12 h after withdrawal. The blood pressure rose to 260/130, and during the following night intervention was considered necessary. The heart rate had fallen to abnormally low levels. An ECG was not made at this time, but retrospectively an abnormal rythm seems possible.

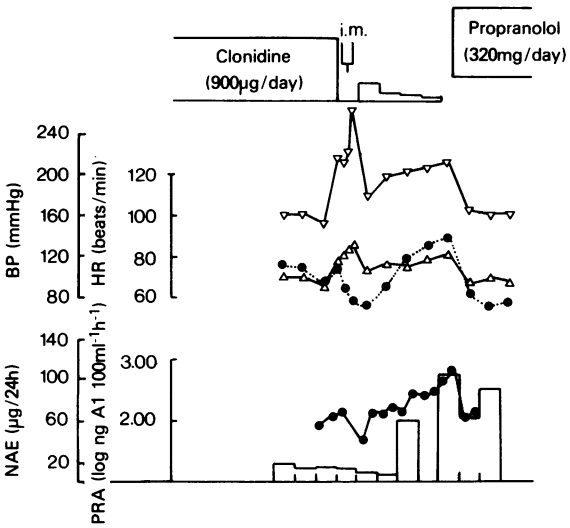

Figure 4 Sequence of events in a 44 years old woman (A.-B.) in whom observation without medication had to be interrupted because of severe symptoms. (▽ systolic BP; △ diastolic BP; ● HR).

An i.m. injection of clonidine relieved the symptoms and lowered the blood pressure. Twenty-four hour NA excretion was not elevated, but the sampling included the period of i.m. therapy. PRA reached the lowest level next morning, which could have been caused by either the period of high blood pressure or by the clonidine therapy, although the latter is less likely because PRA increased during continuation of clonidine therapy, when the blood pressure was on a lower level. During the next few days the resumed clonidine therapy was slowly tapered off; the symptoms did not return, but blood pressure and heart rate showed a marked but less dramatic increase and the urinary NA excretion rose. After the addition of propranolol during this period, the PRA, heart rate, and blood pressure decreased whereas urinary NA excretion rose further to very high levels.

Discussion

Clonidine is a widely used antihypertensive drug and the withdrawal phenomenon, although well documented since the original observation of Hökfelt, Hedeland & Dymling (1969), seemed a rather occasional event until recently.

Hökfelt, Hedeland & Dymling (1970) described a rebound phenomenon after interruption of 6–30 days of clonidine treatment (0.3–0.9 mg/day) in some of his patients. The symptoms consisted of phaeochromocytoma-like complaints, and the excretion of urinary catecholamines and blood pressure showed a marked increase.

Hansson, Hunyor, Julius, Hoobler & Arbor (1973) studied the syndrome in five patients who were selected because they had previously shown blood pressure overshoot when the treatment had been stopped for various reasons. After abrupt termination of chronic treatment with clonidine (0.3–2.4 mg daily), all of these patients had complaints and blood pressure and urinary noradrenaline excretion rose significantly; the heart rate and plasma noradrenaline had also increased, although not significantly.

Goldberg *et al.* (1976) reported the effect of interrupting the treatment for 36 h in nine patients. Seven of them experienced subjective symptoms, increasing in severity up to the re-introduction of clonidine treatment. Blood pressure showed a progressive increase in all subjects, starting 18 h after the last dosage. Sinus tachycardia and atrial as well as ventricular ectopic beats were frequently observed on the continuous ECG recordings. From a partly retrospective study during short-term (24 h) interruption of treatment, Hoobler & Kahima (1977) concluded that the rise in BP is related to the dosage of clonidine that had been taken. Reid *et al.* (1977) also found a dose-related syndrome after cessation of clonidine in six patients, in three of whom the study was terminated because of severe symptoms after 36 to 72 h. In the other three patients BP stabilized after the third day near pre-treatment levels. Plasma and urinary catecholamine levels were increased 24–72 h after cessation of clonidine, while in a seventh patient on the lowest dosage (0.15 mg daily) no change in BP or catecholamine excretion was observed.

In our series of fourteen hypertensive patients who were not selected on the basis of previous withdrawal reactions, we found a significant increase in the heart rate, blood pressure, or urinary NA excretion without exception. Half of them (7/14) experienced subjective complaints and in about 20% (3/14) the syndrome was of such severity that intervention was necessary. During the 3 days of observation after withdrawal, the average 24-h supine heart rate remained below 82 beats/min in only two of the fourteen patients. Also, in only two of the nine patients in whom urinary NAE was measured did the value remain within the normal limits; all of the others showed an elevation above 62 µg/24 h (one patient after slow withdrawal), which is clearly an abnormally high value. It can therefore be stated that clonidine withdrawal reactions can be expected in the majority of patients treated with a moderately high (0.9 mg/day) dose. Our finding that phaeochromocytoma-like symptoms co-incide with parallel increases in the heart rate, blood pressure, and urinary NA excretion supports previous reports and is consistent with the view that the syndrome is caused by increased activity of the sympathetic nervous system. The blocking effect of phentolamine and

propranolol and the soothing of symptoms by pre-treatment with reserpine (Hansson *et al.*, 1973) are in keeping with this concept.

Since sympathetic nerve stimulation is one of the three main inducers of renin release in the kidney (Davis & Freeman, 1976), an increase of PRA could also account for the blood pressure elevation.

Hökfeld *et al.* (1970) have shown that clonidine markedly suppresses both catecholamine excretion, PRA and aldosterone, and suggested that these effects are probably related to its hypotensive action. In phaeochromocytoma clonidine failed to affect either of these variables. These authors noticed that the fall in PRA followed the decrease in catecholamine excretion with some delay, whereas in three patients in whom clonidine was withdrawn BP and catecholamine excretion reached their maximum on the second day, but PRA continued to rise on the third day.

On the other hand Fyhrquist, Kurppa & Huuskonen (1975) found only transient or no decrease of PRA during clonidine treatment and concluded that its antihypertensive effect is independent of PRA changes.

In the present study we found no rise in PRA at all during the first two days, and only a slight non-significant elevation of PRA on the third withdrawal day. Initially, PRA even decreased in some patients, very likely due to the increase of arterial blood pressure. Body weight declined during the withdrawal period in all patients, on average by 1.4 kg, so negative sodium balance and some decrease of the ECF volume must be assumed and the continued suppression of PRA cannot be attributed to salt retention.

In the early phase of the withdrawal period, renin release could have been stimulated by the sympathetic drive via beta receptors but at the same time have been suppressed, via renal baroreceptors by the increase of arterial blood pressure. In man, noradrenalin infusion has been shown to suppress PRA (Wilcox, Aminofff, Kurtz & Slater, 1974). In a later phase, the negative sodium balance stimulates renin release. The balance between different regulators of renin release at a given time determines the ultimate PRA.

As demonstrated by the absolute values and by the lack of correlation of PRA with the blood pressure, PRA does not play an important role in the pathogenesis of the clonidine withdrawal syndrome, and prevention by beta blocking agents that inhibit renin release will not prevent the rise in blood pressure and may even be dangerous because of preponderance of α-adrenergic receptor activity (Bailey & Neal, 1976). In the two patients in our series who were given propranolol there was indeed no immediate decrease in the blood pressure, although no untoward effects were seen and subjective symptoms were acutely ameliorated.

Although the results of our study, combined with previous reports, remove any doubt about the reality of a clonidine withdrawal syndrome, there is still no certain proof that the sometimes very high blood pressures after withdrawal are higher than the basic blood pressure that would have been present without treatment under the same (hospital) conditions. On the other hand, the proven exaggerated sympathetic tone must be assumed to cause higher blood pressure than would be expected during normal sympathetic activity. Observations lasting longer than 3 days could probably solve this question. The high frequency and seriousness of the clonidine withdrawal syndrome must be born in mind when any patient on chronic clonidine treatment is taken off therapy, e.g. for surgery; complications in this situation have been described (Conolly, Briant, George & Dollery, 1972; Raftos, Bauer, Lewis, Stokes, Mitchell, Young & MacLachlan, 1973). Patients on clonidine therapy should be warned to take the tablets regularly and keep a sufficient stock of tablets at hand. Tapering off of the therapy does not guarantee prevention of the withdrawal symptoms (see case 3) (Hökfelt *et al.*, 1970).

β-adrenergic receptor antagonists can prevent many symptoms but theoretically can provoke a further increase of the blood pressure (Bailey & Neal, 1976), which can be managed by α-adrenoceptor blockade (Hansson *et al.*, 1973). It is therefore advisable to initiate this combined therapy before clonidine treatment is discontinued.

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