PAPERS AND ORIGINALS

Blood pressure and heart rate and withdrawal of antihypertensive drugs

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Summary

The immediate effects on heart rate and blood pressure of withdrawing antihypertensive drugs were studied over three-day periods in 26 patients. Four groups of drugs were studied. After withdrawal all patients taking clonidine showed a considerable increase in heart rate and blood pressure with intense ectopic activity. Patients taking postganglionic neurone-blocking drugs showed a similar but less pronounced reaction with increased ventricular ectopic activity. No alarming reactions were seen after withdrawal of methyldopa or beta-blocking drugs. Methyldopa and, especially, beta-blocking drugs are less likely to produce withdrawal reactions than clonidine or the postganglionic neurone-blocking drugs, and patients taking these drugs are therefore less likely to suffer violent reactions if they forget to take their tablets.

Introduction

When patients who have been taking antihypertensive drugs for long periods of time stop taking their tablets the blood pressure in about two-thirds of the patients rises to pretreatment levels over six months.[1] This reaction is more common in those whose blood pressure was high before treatment began. The remaining patients, usually those with only slightly raised pretreatment blood pressures, continue to have recordings within the normal range.

Apart from reports of an "overswing" in blood pressure in patients taking clonidine,[2-5] we know nothing about the immediate haemodynamic consequences of stopping antihypertensive treatment or on the time course of such consequences. In view of the known irregularity of tablet-taking among people with hypertension this is clearly important. We therefore studied the immediate effects on the heart rate and blood pressure of withdrawing several commonly used antihypertensive drugs from patients with varying degrees of hypertension.

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Patients and methods

Twenty-six ambulant hypertensive patients attending the Harrow hypertension clinic and receiving chronic single drug treatment for hypertension were studied. Clinical details are given in the table. Nine were receiving clonidine, seven oxprenolol, one propranolol, six methyldopa, two bethanidine, and one guanethidine. The purposes and methods of the study were fully explained to the patients, and their consent was obtained. The study was approved by the hospital ethical committee. All patients continued their usual treatment until

TABLE I—*Clinical details of patients studied*

Case No	Sex	Age (years)	Clinic blood pressure	Drug	Dose (mg/day)
1	F	39	154/100	Clonidine	0·3
2	M	52	151/98	"	0·3
3	M	49	151/104	"	0·9
4	F	66	230/130	"	0·8
5	F	52	163/104	"	0·3
6	M	61	142/95	"	0·6
7	M	54	156/99	"	0·9
8	M	48	143/103	"	0·6
9	M	49	190/115	"	0·6
10	F	68	226/136	Bethanidine	90·0
11	F	64	175/110	"	75·0
12	M	60	204/116	Guanethidine	25·0
13	F	48	198/114	Methyldopa	1000·0
14	F	54	220/139	"	1500·0
15	F	55	165/108	"	1500·0
16	M	54	172/110	"	1000·0
17	M	48	170/110	"	2000·0
18	F	51	156/91	"	1500·0
19	M	60	142/96	Oxprenolol	960·0
20	M	48	152/99	"	800·0
21	M	50	131/96	"	480·0
22	M	46	131/85	"	640·0
23	F	64	176/109	"	480·0
24	M	50	145/103	"	480·0
25	M	31	154/96	"	240·0
26	F	49	130/94	Propranolol	240·0

*Mean of three consecutive pressures measured at the clinic.

they arrived in the hospital ward at 9 am on the day of the study. They each surrendered their tablets before admission.

The method of recording the blood pressure and electrocardiogram (ECG) has been fully described elsewhere.[5] Briefly, each patient had a cannula inserted percutaneously into the left brachial artery, and the recording apparatus was attached. The patients were then observed for two hours and their pulses were palpated frequently. No patient was allowed to leave the ward until the observers were satisfied that his condition was stable and the recording satisfactory. Each patient reported back every 12 hours so that the equipment could be serviced and calibrated.

The tape recordings were replayed on a tape deck (Oxford Instruments Ltd) which had a continuous paper write-out at 0·04 mm/s and the facility to write out at up to 40 mm/s for more detailed waveform analysis. A computer was used to read the peaks and troughs of each pressure pulse and also the time between successive troughs and store this information in incidence histogram form. The histograms were reproduced at the end of each timed analysis, and a statistical program was used to produce the mean and variance of each value. Consequently, for analysis of any part of a 24-hour period a histogram and mean and variance data were produced for systolic pressure, diastolic pressure, and pulse interval time.

From the continuous write-outs we saw that the 24 hours could be divided into two very distinct periods: that of sleep and that of daytime activities. These were separated by a variable length of time in the evening, when pressures and rates were gradually falling due to lack of activity. For this reason each tape was studied in two parts: the period between 1 am and 6 am, when we knew that the patient was asleep and the qualitative record showed lowered pressures and loss of variability; and daytime between 9 am and 7 pm, when the patient was active as either an inpatient or outpatient.

For a characterisation of each subject during the day it was necessary to minimise the effect of brief variations induced by physiological processes such as exercise, feeding, sitting still, smoking, etc. We found that a random hour analysed in consecutive two-minute periods contained great variation in pressure and heart rates. By progressively reducing the resolution to a three-hour analysis, these effects could be balanced, and little variation was found in daytime pressures and heart rates between consecutive three-hour periods on successive days. We therefore decided to characterise each patient's daytime pressures and rates numerically by analysing a single three-hour period of the day between 9 am and 7 pm after assessing the paper chart recording to ensure that the quality of recording was satisfactory. A three-hour sample selected from the period between 1 am and 6 am was analysed to characterise the night time.

All patients were fully ambulant during the study and each study was continued for three days. On the first day treatment was continued as prescribed in the outpatient clinic and on the second day it was replaced by matched placebo tablets. Those patients who were withdrawn from clonidine and bethanidine had to restart the drugs on the third day, but the other patients continued on placebo.

Results

CLONIDINE

Four patients reported no symptoms after the change to placebo. All but one were receiving 300 μg of clonidine daily, and none had had severe hypertension before treatment was started. The remaining five patients complained of some or all of the symptoms of headache, palpitation, sweating, restlessness, nausea, and vomiting. It was difficult to determine the onset of symptoms using this method of tape analysis, but in all cases symptoms began between 12 noon and 6 pm on the second (withdrawal) day and increased in severity throughout the night, reaching severe proportions in three patients. In all cases the symptoms subsided within 30 minutes of reintroducing oral clonidine.

The paper chart records (fig 1) showed that heart rate and blood pressure increased continuously through the second day and into the third day until the drug was reintroduced. Initially the increased heart rate was due to the development of a sinus tachycardia, but in five subjects increasing numbers of atrial ectopic beats appeared and persisted until the end of the study (fig 2). Episodes of supraventricular tachycardia up to 180 beats/min appeared late in the second night.

One patient in atrial fibrillation increased her mean heart rate from 62 beats/min on the first day to 131 beats/min on the third day with short bursts in excess of 300 beats/min. Large numbers of ventricular ectopic beats were seen in this patient, but not in any of the others. The blood pressure showed a similar rise during the second day and

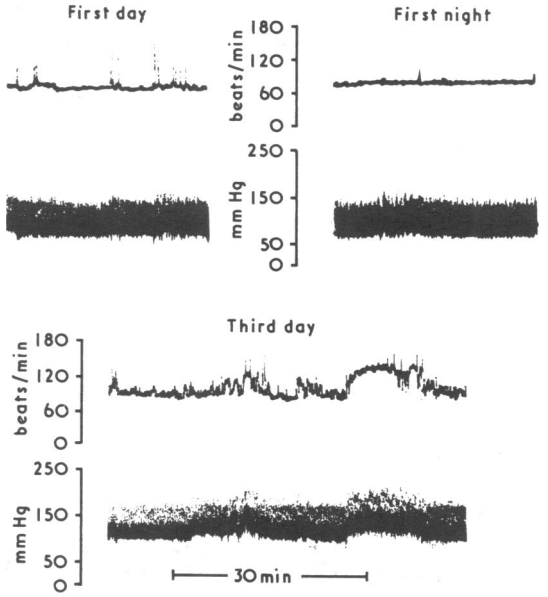

FIG 1—Representative tracings of heart rate and blood pressure during first (treated) day and third (untreated) day in patient who was taking clonidine 600 μg/day. Note overall rise in heart rate and blood pressure, punctuated by short-lived surges of increased rate and pressure.

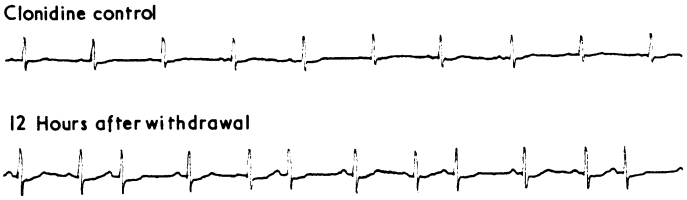

FIG 2—ECG tracings taken before and at height of withdrawal reaction in man taking clonidine. Note sinus tachycardia and the many supraventricular ectopic beats.

night and into the third day, when the studies were terminated by an oral dose of clonidine.

During this period there were surges of high blood pressure associated with tachycardia lasting up to 30 minutes each. The mean increase (±SD) in heart rate for the whole group on the second day was 12·0±9·7 beats/min ($P < 0·01$) and on the third day 22·0±21·7 beats/min ($P < 0·01$). The night heart rate rose by 18·3±12·9 beats/min ($P < 0·01$) (fig 3). The mean increase in systolic pressure on the second day was 21·1±14·3 mm Hg ($P < 0·01$) and on the third day 33·9±19·8 mm Hg ($P < 0·01$). The mean increase in diastolic pressure was 16·8±14·3 mm Hg ($P < 0·01$) on the second day and 24·0 ±9·7 mm Hg ($P < 0·01$) on the third day (fig 4). The mean increase in night-time pressures were 49·0±27·2 mm Hg ($P < 0·01$) for systolic and 26·5±17·4 mm Hg ($P < 0·01$) for diastolic.

In the three patients taking more than 600 μg/day the mean increase in systolic pressure on the third day was 71 mm Hg; in the three taking 600 μg/day the mean increase was 52 mm Hg; and in the three taking 300 μg/day the mean increase was 10 mm Hg.

POSTGANGLIONIC NEURONE-BLOCKING DRUGS

Bethanidine—Neither patient complained of symptoms. In both, the postural hypotension present on the first day was absent on the second day. In one of these patients (case 10) the mean first daytime pressure was 132/78 mm Hg, rising on the second day to 234/130 mm Hg, while the heart rate rose from 72 to 91 beats/min. On the first night the mean pressures were 118/68 mm Hg rising to 194/110 mm Hg, as the heart rate rose to 94 beats/min on the second night. At about 11 pm she had a short episode of ventricular tachycardia (fig 4). The following day bethanidine was reintroduced and the mean day pressures fell to 186/108 mm Hg with evidence of postural hypotension, but the heart rate remained raised at 103 beats/min.

In the other patient (case 11) the mean day pressures rose from 130/78 mm Hg on the first day to 206/112 mm Hg on the second day, and at night from 170/98 mm Hg to 194/106 mm Hg. During the second night she developed a sinus and supraventricular tachycardia, which returned to rapid sinus rhythm soon after the reintroduction of bethanidine. On the third day the blood pressures were reduced to 156/100 mm Hg, but the heart rate remained at 98 beats/min.

Guanethidine—On the first day the patient showed postural hypotension with mean daytime pressures of 152/98 mm Hg and night-time pressures of 116/86 mm Hg. On the second day no significant changes were seen.

METHYLDOPA

No patient complained of symptoms. There was a small increase in the mean daytime systolic pressure on the second day (mean increase $9{\cdot}0 \pm 3{\cdot}8$ mm Hg; $P = 0{\cdot}01$) and in the mean daytime heart rate (mean increase $17{\cdot}3 \pm 10{\cdot}2$ beats/min; $P = 0{\cdot}05$), but there was no significant change in diastolic pressure or night-time values.

BETA-BLOCKING DRUGS

No patient complained of symptoms on stopping the tablets. The paper chart records showed a gradual increase in heart rates and pressures but there were no episodes of sudden changes such as were seen with clonidine. In all patients the heart rates increased on the second day (mean increase $20{\cdot}8 \pm 12{\cdot}0$ beats/min) and on the second night (mean increase $6{\cdot}0 \pm 6{\cdot}1$ beats/min). This was entirely due to an increase in the sinus rate and no new ectopic activity appeared. The mean systolic and diastolic pressures rose in all but one patient when beta-blockers were withdrawn (daytime mean systolic increase $17{\cdot}3 \pm 12{\cdot}5$ mm Hg ($P < 0{\cdot}01$), mean diastolic increase $12{\cdot}8 \pm 12{\cdot}9$ mm Hg ($P < 0{\cdot}01$)). The increases in heart rate and pressures recorded were not related to the dose of the drug.

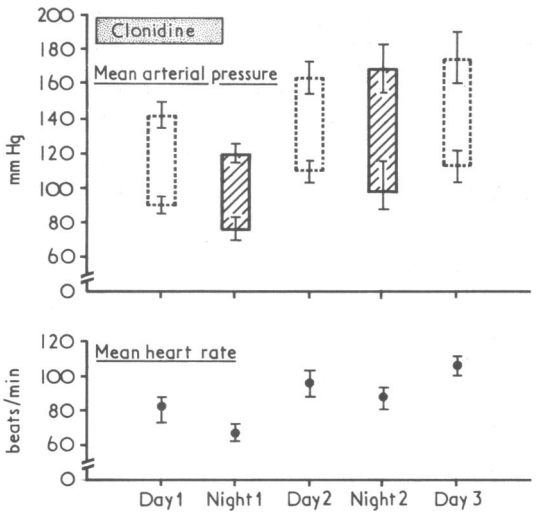

FIG 3—Daytime and night-time mean heart rates and blood pressures in nine patients from whom clonidine was withdrawn. Note progressive increase in all measurements up to third day, when study was stopped.

FIG 4—Case 10. Run of ventricular tachycardia accompanied by severe hypotension seen on second night in one patient from whom bethanidine was withdrawn.

Discussion

An important but neglected aspect of antihypertensive treatment is the effect of drug withdrawal. Patients often forget to take tablets or fail to renew a prescription, thinking that a course of treatment will cure in the same way that a course of antibiotic cures an infection. The withdrawal of clonidine produced a clinical syndrome of headaches, agitation, sweating, palpitations, abdominal pains, and vomiting in all but two patients. This syndrome resembles that seen in patients with phaeochromocytoma and also that seen on acute withdrawal of narcotic agents from an addict. It was hard to assess accurately the time of onset of symptoms and cardiovascular changes, but all began to appear 18 to 24 hours after the last tablet.

The effect worsened until clonidine was reintroduced. The symptoms and cardiovascular changes suggest that the withdrawal syndrome is due to intense sympathetic activity, probably as a result of disappearance of the alpha-mediated nerve terminal inhibitory effect of the drug.[7] Hansson *et al*[4] studied five patients with severe hypertension who had previously shown the clinical signs of the withdrawal syndrome on long-term clonidine treatment (0·3-2·4 mg/day). In all their patients the urinary and arterial catecholamine levels rose on the day of withdrawal. Clonidine is slowly excreted, and the plasma half life after an oral dose is seven to 10 hours,[8] so the withdrawal symptoms must occur when clonidine is disappearing from the tissues. Changes in plasma or brain clonidine concentrations after discontinuing the drug have not been determined, but they are presumably the same as or longer than the plasma changes after a single dose. It has been suggested that clonidine produces increased storage of catecholamine in nerve terminals by stimulating inhibitory alpha-receptors. Removal of the drug might produce a sudden release of these stored catecholamines, which might then produce the observed syndrome. There is no evidence to suggest that a similar effect is seen in the adrenal medulla, which might be a source of large quantities of stored catecholamines. Possibly some of the observed effects result from greatly increased sympathetic nerve activity, but there is no experimental evidence. Whatever the precise mechanism of the reaction, catecholamine release is likely to be an important feature.

The postganglionic neurone blocking drugs also act on the sympathetic nerve terminal, where they are highly concentrated, but they do not produce accumulation of stored catecholamines. Guanethidine depletes nerve-terminal stores,[9] but the response to bethanidine seems to be variable.[10] Predictably, the reaction seen on withdrawal was not as pronounced as that seen with clonidine. The two patients receiving bethanidine had a rapid rise of pressure during the withdrawal day, which necessitated reintroduction of the drug on the next morning. Both patients were severely hypertensive before treatment and their response to withdrawal seemed to be a rapid return to pretreatment levels of blood pressure. The time-course of the reaction is probably determined by the speed at which the drug leaks from the adrenergic nerve terminals. In both patients the maximal response was seen about 18 hours after the last dose.

The bouts of ventricular and supraventricular ectopic activity seen on withdrawal of bethanidine were distinct, but not enough patients were studied for generalisations to be made. No reaction was observed on withdrawal of guanethidine and this is probably related to the different effects of the two drugs on nerve terminal catecholamine stores.

No patient on methyldopa or beta-blocking drugs suffered

any symptoms when they were withdrawn, and there were no notable changes in heart rate or blood pressure. Beta-blocker withdrawal produced variable results, but unlike clonidine there was no relation between the dose withdrawn and the increase in heart rates and blood pressures. The reason for this difference must lie in the different pharmacological effects of these drugs, but it is clearly important to know that violent reactions are not likely to attend accidental withdrawal of beta-blocking drugs.

The same generalisation can be made with respect to methyldopa, but the doses used were small and the degree of blood pressure control achieved in these patients was not good. None of the recordings showed evidence of postural or exercise hypotension, which are a feature of adequate blood pressure control with this drug, and further studies need to be done in patients taking larger doses whose blood pressure is better controlled, as defined by clinic blood-pressure readings.

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Undescribed toxin in pseudomembranous colitis

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Summary

A girl aged 12 developed pseudomembranous colitis after a short course of oral penicillin. She had no history of adverse reaction to penicillin before or after the illness. No pathogenic bacteria, mycoplasmas, or viruses were found in her faeces, but they did contain a toxin. Toxin was also found in four of five other patients with pseudomembranous colitis but not in six specimens obtained from patients with diarrhoea caused by other disorders. Further studies may show that pseudomembranous colitis is caused by a bacterial toxin.

Introduction

Pseudomembranous colitis is an uncommon condition often occurring in association with the administration of antibiotics. The cause is unknown but drug toxicity, bowel ischaemia, altered intestinal bacterial flora, and viruses have all been suggested[1-4]. We describe intensive studies performed on one patient with this condition in an attempt to determine its cause.

Case report

A 12-year-old schoolgirl was admitted to hospital after four weeks of abdominal pain, vomiting, and diarrhoea. She had been well until she developed a sore throat, for which she took 16 250-mg doses of phenoxymethylpenicillin by mouth over four days. For the next three weeks she had intermittent colicky abdominal pain, diarrhoea, and vomiting, attended school for only one and a half days, and lost 6·4 kg. Before admission her symptoms worsened and she developed a fever. There was no history of allergy or adverse reactions to drugs and she had taken oral penicillin previously without ill effects.

She was acutely ill with a dry mouth, a temperaure of 37·5°C, and a pulse of 120/min. She weighed 35 kg. The abdomen was not distended but was very tender over the hypogastrium and in the left lumbar and iliac areas. There was guarding and severe peritonism, but bowel sounds were active. The peripheral white cell count was $28{\cdot}9 \times 10^9$/l (28 900/mm^3) with an excess of neutrophils and occasional metamyelocytes. Microscopy of fresh faeces showed many leucocytes and a few red blood cells, but no parasites. Results of faecal cultures were negative, as were antibody titres to *Salmonella* and *Yersinia*.

Sigmoidoscopy showed a hyperaemic, but intact, nonfriable mucosa, covered with patches of thick, creamy, semi-adherent pus. At laparotomy the entire serosa of the large bowel was injected. The peritoneal cavity contained 200 ml of turbid but sterile fluid. Subsequent histological examination of a rectal biopsy specimen showed the classic features of the type 1 lesions of pseudomembranous colitis.[5] The patient was treated with codeine phosphate and intravenous fluids, progressing to a light diet as she improved. She received no antibiotics in hospital. When discharged after 25 days she was well, and two weeks later at outpatient attendance she had gained weight and was having one formed stool per day.

SPECIAL STUDIES

Conventional scratch, intradermal, and patch skin tests with benzylpenicillin and a sterile penicillin solution made from the patient's own tablets gave entirely negative results. Stool and rectal biopsy specimens taken during the acute illness and during convalescence were placed in transport medium and quantitatively assayed for aerobic and anaerobic bacteria. The cultures showed only minor qualitative and quantitative differences. Nonfaecal streptococci and one species of *Bacteroides* were found during the acute phase but not during convalescence and more *Arachnia* sp were also present during the acute phase. Electron microscopy of negatively stained grids prepared from ultracentrifuged and immune-precipitated stool suspension failed to show any virus particles. Nevertheless, thin sections of colonic exudate fixed in Karnovsky's fixative did show 40-nm diameter spherical membrane-bound "viral-like" particles.

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