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CHANGES IN BLOOD PRESSURE, PLASMA CATECHOLAMINES AND PLASMA RENIN ACTIVITY DURING AND AFTER TREATMENT WITH TIAMENIDINE AND CLONIDINE

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1 Tiamenidine (Hoe 440) is an imidazoline with blood pressure lowering properties. Its pharmacology resembles that of clonidine.

2 The effect of both drugs on blood pressure, plasma noradrenaline (NA), plasma adrenaline (Ad), urinary catecholamines and plasma renin activity (PRA) was assessed in four previously untreated male hypertensive patients in a cross over study.

3 The maximum daily dose of tiamenidine was 3 mg. The maximum daily dose of clonidine was 450 μg.

4 During treatment, blood pressure, systolic and diastolic, supine and erect, fell on average between 12 and 15%. Levels of NA, Ad, PRA were reduced during treatment.

5 During withdrawal of either drug there was rebound of blood pressure and NA, Ad, PRA, overshooting baseline levels.

6 The withdrawal effects caused by clonidine were similar for tiamenidine.

Introduction

Tiamenidine is an imidazoline derivative which lowers blood pressure and its pharmacology resembles that of clonidine. In cat, dog and rabbit, single doses intravenously produce an initial rise in blood pressure followed by a sustained fall (Lindner & Kaiser, 1974). In dogs, oral administration produces a sustained hypotensive effect. Injection into CSF in dog, or lateral ventricle in rat, produces a dose related fall in blood pressure not preceded by a transient elevation (Schoelkens & Lindner, 1977). In renal and genetic hypertensive rats tiamenidine also produces a dose dependent fall in blood pressure. In this species it also inhibits plasma renin activity (Lindner & Schoelkens, 1977).

In man tiamenidine produces a substantial hypotensive effect in the dose range 1–3 mg per day. Blood pressure and heart rate changes in response to tilt are only minimally modified by tiamenidine. It induces a marginally decreased response to the cold pressor test, and a very small reduction in response to Valsalva's manoevre.

Therefore like clonidine it possesses a transient peripheral α-adrenergic receptor stimulant effect and a dominant central effect exerted through adrenergic receptors inhibitory to sympathetic nerve activity. It is an effective hypotensive which does not significantly modify homeostatic cardiovascular reflexes.

It is now well documented that the cessation of clonidine therapy may be associated with withdrawal phenomena, of which the clinically most serious is a rise in blood pressure which may overshoot pretreatment levels. This is usually accompanied by a rise in plasma catecholamine levels and plasma renin activity. The implications of the phenomena are potentially serious for the patient who does not reliably take his tablets or who abruptly stops treatment.

Preliminary results in hypertensive rats suggested that following 14 days treatment with equihypotensive doses, withdrawal of medication resulted in an increase in catecholamines which was approximately half as great with tiamenidine as that in a control group of rats who received clonidine (Ellis, Novick & Wilker, 1979).

The present study was designed to quantify the hypotensive effect of both tiamenidine and clonidine, to determine their effect on plasma and urinary catecholamine levels and on plasma renin activity and to determine the effects of withdrawing therapy, if any.

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Methods

Selection of patients

Newly diagnosed patients with primary essential moderate hypertension (WHO Grade 2) were eligible to participate in the study if they were aged between 20 and 65 years, male, intellectuably able to comply with the study and suitable for outpatient therapy. They could not participate if they had severe concomitant renal, cardiovascular or cerebrovascular complications or severe intercurrent illness, or were receiving sedatives, tranquillisers, antidepressants, cardiac glycosides or diuretics prior to the start of the study. The protocol was reviewed by the ethical committee of the medical faculty Lund University, and informed consent to participate was sought from eligible patients.

Procedure

In this cross over study the participants were admitted to hospital for the clinical and laboratory investigations outlined below. The baseline data was obtained over a 3 day period after which the patients were allocated to treatment with tiamenidine or clonidine according to a random code. Treatment began in hospital, but after 2 days was continued on an outpatient basis for 4 to 6 weeks. The dose was titrated during this time between the ranges 450 μg–900 μg, clonidine, and 1.5 mg–3.0 mg, tiamenidine, to produce an optimum effect.

After the first treatment period, the patients were readmitted to hospital and the effects of the treatment were measured over 2 days. The effects of withdrawal were measured over the next 3 days and the second treatment then introduced. The programme was repeated.

Blood pressure

The supine pressure was always assessed first, after 30 min recumbency, and measured three times at 1 min intervals. After 3 min in the erect position the pressure was again assessed three times at 1 min intervals. The diastolic pressure was recorded when the sounds disappeared (Korotkoff V). The recordings were always made in the same dominant arm. During hospitalization measurements were made at 8.00, 10.00, 12.00, 14.00, 16.00, 18.00 and 20.00 h every day.

Urine catecholamines (24 h)

These were measured each day during hospitalisation according to the method described by von Euler & Lishajko (1961).

Plasma catecholamines

These were measured daily at 8.00 h (supine) and 12.00 h (erect) during hospitalisation, using a double isotope technique (Engleman & Portnoy, 1970).

Plasma renin activity

This was measured daily during hospitalisation at 8.00 h (supine) and 12.00 h (erect) using the method described by Haber, Koerner, Page, Kliman & Pernode (1969).

Weight

This was measured daily before breakfast during hospitalisation.

The medical history and physical examination, ECG, chest X-ray, ophthalmological examination and routine laboratory tests were also performed on each patient.

Results

Treatment with either drug produced a hypotensive effect even on the first day. On the last day of treatment the mean of the daily blood pressure readings for both drugs was remarkably similar (Tables 1a and 1b). (Systolic and diastolic pressures were reduced by almost 15%). The withdrawal phenomena attributable to both drugs can therefore be interpreted fairly in the context of their equihypotensive activity.

The patients did not respond equally to cessation of therapy, but all patients showed some overshoot of mean daily blood pressure above baseline values at some time in the three days after withdrawal. The mean daily blood pressure of the patient most sensitive to withdrawal exceeded mean baseline daily blood pressure by up to 29 mm Hg systolic and 16 mm Hg diastolic.

The patient whose blood pressure was most sensitive to clonidine withdrawal was also most sensitive to tiamenidine withdrawal. Similarly the least affected by clonidine withdrawal was also least affected by tiamenidine withdrawal.

Plasma noradrenaline was measured in supine and upright positions. The pattern of change was similar for both amines with both drugs. Levels were lower on the last day of treatment than during the control period, and rose successively on the three post treatment days (Table 2), with some overshoot of baseline levels.

Changes in plasma adrenaline levels in the supine position followed a similar pattern, but in the upright position there was no consistent change after withdrawal of treatment (Table 3).

Table 1 a) Mean daily blood pressure variation before, during and after therapy in the supine position

Treatment	*Tiamenidine*				*Clonidine*			
	Blood pressure (mmHg)							
	Systolic		*Diastolic*		*Systolic*		*Diastolic*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
Baseline	160	159–163	110	97–115	160	159–163	110	97–115
Treatment first day	143	137–151	102	96–108	135	127–142	93	90–95
Treatment last day	140	135–145	95	90–100	140	129–145	94	88–99
Withdrawal day 1	161	153–171	106	97–120	150	127–158	99	95–106
Withdrawal day 2	168	156–187	112	100–130	165	145–179	108	97–122
Withdrawal day 3	166	152–183	113	105–129	171	154–179	113	102–127

b) Mean daily blood pressure variation before, during and after therapy in the upright position

	Tiamenidine				*Clonidine*			
	Blood pressure (mmHg)							
	Systolic		*Diastolic*		*Systolic*		*Diastolic*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
Baseline	161	154–165	119	107–124	161	154–165	119	107–124
Treatment first day	145	137–150	110	105–119	133	119–144	100	92–105
Treatment last day	143	132–152	103	101–106	140	117–151	101	91–106
Withdrawal day 1	167	154–186	117	111–130	155	121–170	109	95–118
Withdrawal day 2	171	155–190	120	112–137	169	145–191	119	109–134
Withdrawal day 3	170	156–194	117	112–129	173	151–189	125	117–141

Table 2 Plasma noradrenaline (nmol) before, during and after therapy with tiamenidine or clonidine

Position	*Tiamenidine*				*Clonidine*			
	Supine		*Upright*		*Supine*		*Upright*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
Baseline	2.60	1.86–3.75	4.29	3.17–5.31	2.60	1.86–3.75	4.29	3.17–5.31
Treatment last day	1.85	1.60–2.01	2.56	2.20–2.88	1.45	1.09–1.87	2.38	1.49–3.39
Withdrawal day 1	1.56	1.28–1.87	4.60	3.03–6.79	1.13	0.54–1.82	4.17	2.57–5.65
Withdrawal day 2	4.42	2.77–6.74	6.40	3.49–10.06	2.60	1.37–3.97	4.81	2.74–6.19
Withdrawal day 3	4.53	3.42–6.77	9.04	5.48–17.42	4.11	2.96–6.45	8.14	5.43–9.29

Table 3 Mean plasma adrenaline (nmol/l) before, during and after therapy with tiamenidine or clonidine

Position	*Tiamenidine*				*Clonidine*			
	Supine		*Upright*		*Supine*		*Upright*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
Baseline	0.51	0.28–0.94	0.80	0.69–0.92	0.51	0.28–0.94	0.80	0.69–0.92
Treatment last day	0.46	0.35–0.64	0.54	0.39–0.76	0.46	0.31–0.59	0.67	0.37–0.99
Withdrawal day 1	0.46	0.30–0.70	0.96	0.30–1.74	0.40	0.27–0.51	0.58	0.34–0.76
Withdrawal day 2	0.87	0.37–1.47	0.69	0.37–1.00	0.63	0.31–1.16	0.80	0.36–1.29
Withdrawal day 3	0.59	0.38–0.93	0.76	0.37–1.11	0.71	0.43–1.18	0.82	0.64–1.13

Table 4 24 h urine adrenaline and noradrenaline levels (nmol/l) before, during and after treatment with tiamenidine and clonidine

	Tiamenidine				*Clonidine*			
	Adrenaline		*Noradrenaline*		*Adrenaline*		*Noradrenaline*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
Baseline	26.65	12.1–39.7	126.97	96.3–152.9	25.65	12.1–39.7	126.97	96.3–152.9
Treatment last day	18.47	12.2–24.2	63.42	50.5– 76.0	19.30	15.5–24.8	57.67	47.0– 71.5
Withdrawal day 1	30.95	18.3–39.2	147.42	128.1–185.2	20.65	17.2–24.9	92.90	49.0–130.0
Withdrawal day 2	33.07	25.0–46.4	220.92	136.5–404.8	30.75	19.5–36.3	167.47	81.0–243.0
Withdrawal day 3	34.75	26.4–45.0	252.67	157.2–340.0	32.72	22.7–38.2	216.25	127.0–362.7

Mean 24 h urine noradrenaline and adrenaline levels during withdrawal of both drugs were similar, progressively increasing. Neither may have reached its peak by the third day (Table 4). All considerably exceeded baseline levels.

Plasma renin activity (supine and erect) decreased with both drugs during treatment, and increased after withdrawal, above baseline levels for tiamenidine but with no indication of having reached a plateau for either the tiamenidine or clonidine treatment group on the third day (Table 5).

There was no consistent weight change during treatment or after withdrawal.

The classical symptoms associated with the withdrawal of clonidine were sought using a formal check list. Only one patient had distressing symptoms on withdrawal of both drugs, although all patients had some symptoms. The severity of the symptoms bore no consistent relationship to the severity of the biochemical and clinical signs of withdrawal.

Discussion

The phenomena associated with the withdrawal of clonidine treatment are threefold, namely symptoms, signs and biochemical changes. The symptoms include headache, anxiousness, palpitations, sweating, a feeling of rottenness and fatigue. These may be accompanied by agitation and tremor. The other signs include a rise in blood pressure which may substantially exceed baseline pretreatment values, and occasionally be dangerous and a rise in pulse rate. The biochemical accompaniments are a rise in plasma adrenaline, noradrenaline and plasma renin activity. The changes in plasma catecholamines are reflected in the urine (Hökfelt, Dymline & Hedeland, 1968; Hökfelt, Hedeland & Dymling, 1970).

The syndrome can be corrected by reintroduction of clonidine, by simultaneous α- *and* β-adrenoceptor blockade, or theoretically by labetolol, a drug combining α- and β-adrenoceptor blocking properties (Farmer, Kennedy, Levy & Marshall, 1972), although in practice the latter has not fulfilled its promise.

Initially the withdrawal phenomenon was thought to be rare, but it is becoming clear that it occurs rather frequently (Geyskes, Boer & Dorhout Mees, 1979; Reid, Dargie, Davies, Wing, Hamilton & Dollery, 1977). The severity of the reaction bears some relationship albeit inconsistent to the dose or the duration of therapy. The onset of the reaction after withdrawal occurs usually within 24 h but may not reach its maximum until after 72 h.

The advantages of clonidine are that it is potent, produces minimal orthostatic or postural hypotension, affects supine and erect blood pressure equally, and does not produce impotence. Any drug possessing equal hypotensive activity without the adverse effects of clonidine would be useful.

There was evidence that tiamenidine possessed equal hypotensive activity but produced quantitatively less minor adverse effects in man, and less biochemical rebound in animals (Ellis *et al.*, 1979). This study was undertaken to determine whether this evidence could be substantiated in patients with moderate hypertension.

The cross over design has often been criticised, mostly because baseline measurements made in patients prior to the second treatment are rarely identical with those made prior to the first treatment.

In this context and in this particular study two sets of values could be regarded as important, namely those of *pre*-treatment blood pressure or those of *post*-treatment blood pressure. Because we were studying withdrawal phenomena we considered that our objective should be to obtain similar *post*-treatment blood pressure measurements for both drugs prior to their withdrawal.

The hypotensive activity of both drugs is similar, although on a weight for weight basis clonidine is more potent. This in itself confers no advantages.

During treatment, both drugs produced lowering of plasma adrenaline and noradrenaline levels, and plasma renin activity. This has previously been reported for clonidine. On withdrawal of therapy all three biochemical variables returned not to pretreatment levels but to higher levels, providing evidence of a biochemical overshoot.

With both drugs plasma renin activity was still rising on the third withdrawal day as was plasma noradrenaline. At this stage, however, plasma adrena-

Table 5 Plasma renin activity (μg angiotension 1/3 h incubation) before, during and after treatment with tiamenidine or clonidine

Position	*Tiamenidine*				*Clonidine*			
	Supine		*Erect*		*Supine*		*Erect*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	*Mean*	*Range*
Baseline	2.97	2.60–3.35	5.02	3.81–6.78	2.97	2.60–3.35	5.02	3.81–6.78
Treatment last day	1.28	0.29–1.75	2.07	0.97–3.07	1.61	0.32–4.44	3.54	0.88–8.97
Withdrawal day 1	1.25	0.45–2.49	2.17	1.75–2.58	0.74	0.20–1.04	3.09	0.82–7.69
Withdrawal day 2	2.76	1.30–5.27	4.11	3.10–5.27	1.71	1.34–2.30	2.85	2.36–3.46
Withdrawal day 3	3.81	2.48–7.03	5.59	3.47–7.03	2.25	1.51–2.75	4.19	3.91–4.36

line levels were probably at or past their peak.

This agrees in principle with the trend shown by Geyskes *et al.* (1979) regarding clonidine, although in this case only urinary noradrenaline was measured with PRA. It also agrees with earlier work from this department (Hökfelt *et al.*, 1970). There is now considerable evidence that the withdrawal syndrome is caused by an increase in sympathetic activity.

It is clear that tiamenidine resembles clonidine closely. It produces an equal hypotensive effect. During treatment it modifies catecholamines and PRA in a similar way, and on withdrawal it is associated in the same patients with a withdrawal syndrome of similar dimensions both clinically and biochemically, which appears at a similar time.

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