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Topical minoxidil: cardiac effects in bald man

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Systemic cardiovascular effects during chronic treatment with topical minoxidil *vs* placebo were evaluated using a double-blind, randomized design for two parallel groups ($n = 20$ for minoxidil, $n = 15$ for placebo). During 6 months of follow-up, blood pressure did not change, whereas minoxidil increased heart rate by 3–5 beats min^{-1}. Compared with placebo, topical minoxidil caused significant increases in LV end-diastolic volume, in cardiac output (by 0.75 l min^{-1}) and in LV mass (by 5 g m^{-2}). We conclude that in healthy subjects short-term use of topical minoxidil is likely not to be detrimental. However, safety needs to be established regarding ischaemic symptoms in patients with coronary artery disease as well as for the possible development of LV hypertrophy in healthy subjects during years of therapy.

Keywords minoxidil baldness cardiovascular effects

Introduction

Treatment of normotensive or hypertensive humans or rats with arterial vasodilators such as hydralazine or minoxidil results in marked haemodynamic changes, which can be described as a 'hyperdynamic circulation'. Acutely, these changes are a consequence of vagal withdrawal, reflex-mediated increases in sympathetic activity and renin release and a shift of blood to the central blood volume (Man In't Veld *et al.*, 1980; Murphy *et al.*, 1982; Reeves *et al.*, 1987; Tarazi *et al.*, 1976). During chronic arterial vasodilator treatment, fluid and sodium retention (Gottlieb *et al.*, 1972; Tsoporis & Leenen, 1988) contribute to the hyperdynamic circulation. The resultant chronic cardiac stimulation is associated with absence of regression or even progression of cardiac hypertrophy in hypertensive rats (Tsoporis & Leenen, 1988) and humans (Leenen *et al.*, 1987) despite BP control. Cardiac hypertrophy can also develop *de novo* in normotensive rats (Tsoporis & Leenen, 1988). In order to blunt the hyperdynamic circulatory state, in hypertensive humans arterial vasodilators are usually prescribed together with a diuretic and β-adrenoceptor blocker (Zacest *et al.*, 1972).

Topical minoxidil is being used as chronic treatment for early male pattern baldness. Small amounts of the applied minoxidil are absorbed and appear in the systemic circulation: 2–5 mg day^{-1} may be systemically available (Franz, 1985) as compared with effective antihypertensive oral doses in the range of 10–40 mg day^{-1}. Although the amount absorbed is relatively small, it is conceivable that the use of topical minoxidil causes systemic cardiovascular effects. In normotensive subjects, most studies did not observe significant decreases in blood pressure during chronic treatment with topical minoxidil (Ranchoff & Bergeld, 1985; Vanderveen *et al.*, 1984; DeVillez, 1985; Feinstein, 1985). Some subjects showed 'minor' ECG changes (Olsen *et al.*, 1985, 1986). No controlled studies have as yet been reported using quantitative echocardiography to assess more accurately possible cardiac effects of topical minoxidil.

We hypothesized that sufficient minoxidil

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does reach the systemic circulation to cause cardiac effects during chronic therapy. The objective of the present study was therefore to evaluate changes in LV anatomy and function as assessed by echocardiography during long-term treatment with topical minoxidil *vs* placebo using a double-blind, randomized design for two parallel groups.

Methods

Thirty-five men, age 18–49 years, with early, progressive, premature thinning of the scalp hair (male pattern baldness) were entered into the study. Subjects were otherwise healthy as judged by history, physical examination and routine laboratory screening. Main exclusion criteria were any evidence of cardiac disease, a technically unsatisfactory echocardiogram, or the possibility of non-compliance. Subjects were asked to continue their regular dietary and physical activity habits. Written informed consent was obtained from all subjects. Twenty subjects (age 30 ± 1.4 years and B.S.A. 1.95 ± 0.02 m^2) were randomized to minoxidil and 15 subjects (age 32 ± 2.1 years and B.S.A. 1.90 ± 0.04 m^2) to placebo.

Following baseline measurements, subjects were randomized to either topical minoxidil solution 2% (propylene glycol, alcohol, water and minoxidil) or placebo solution (propylene glycol, alcohol and water) using a double-blind, randomized, two-group parallel design. Each application consisted of 1 ml, using a calibrated dropper and spread around over the scalp, beginning at the balding vertex. Applications were made twice daily (morning and night). The total daily dose of minoxidil amounted therefore to 40 mg. Cardiovascular assessment was performed at baseline, and at 3 and 6 months of follow-up. These assessments were performed by the same research assistant in a quiet, temperature-controlled room at the same time of the day (usually in the afternoon) to avoid possible diurnal variations in the measurements. Subjects were placed semi-supine and a BP cuff and ECG electrodes applied. Blood pressure (by Roche Arteriosonde 1226) and heart rate (from the ECG) were measured every 5 min for the first 20 min and then every 2 min for 10 min. An echocardiogram was obtained between 20–30 min of rest. Subsequently each subject stood for 5 min with blood pressure and heart rate measured at 1, 2 and 5 min. Echocardiograms were obtained using a Picker Echoview System 80C, with a 2.25 MHz, 13 mm diameter, medium-focus transducer in conjunction with a Honeywell strip-chart recorder, as recently described (Leenen *et al.*, 1987). Parameters of LV anatomy and function were measured or calculated as described previously (Leenen *et al.*, 1987).

Results are expressed as mean ± s.e. mean. Statistical analysis was performed by analysis of variance for repeated measure, looking at drug and time effect. This assessment was performed on the changes from baseline; the primary comparison of interest obviously being the between-group comparison (Fleiss, 1986). No significant time differences or time-drug interactions were observed for any of the parameters. $P < 0.05$ was considered significant.

Results

Blood pressure and heart rate (Table 1)

At baseline, the two groups had comparable systolic and diastolic BP and heart rate, both supine and standing. During the 6 months of follow-up, BPs for the placebo and minoxidil groups showed minor variations with no significant differences between the groups. Supine and standing heart rate tended to decrease over time in the placebo group, but not in the minoxidil group. The differences between the two groups were significant ($F = 4.0$, $P = 0.05$) for standing heart rate, but not supine heart rate ($F = 2.9$, $P = 0.09$).

LV anatomy and function (Table 2)

At baseline, parameters of LV anatomy and function did not differ significantly between groups. LV wall thickness remained unchanged during the study in both groups. LV mass showed a small but significant ($F = 3.9$, $P = 0.05$) increase in the minoxidil group *vs* the placebo group.

LV end-diastolic volume did not change in the placebo group, but increased in the minoxidil group. The difference between the two groups was highly significant ($F = 7.2$, $P = 0.008$). LV end-systolic volume did not change significantly.

Cardiac output decreased in the placebo group but increased in the minoxidil group, resulting in a significant ($F = 8.2$, $P = 0.006$) difference between the two groups of about 0.75 l min^{-1} at 3 and 6 months of follow-up.

Body weight remained unchanged during the study in both groups (Table 2).

Table 1 Changes in supine and standing blood pressure and heart rate during chronic treatment with topical minoxidil or placebo in men with early male pattern baldness.

	Baseline	*Changes from baseline* + 3 *months*	+ 6 *months*	
Systolic BP (mm Hg)				
Supine				
Placebo	122 ± 3	−1 ± 2	−1 ± 2	
Minoxidil	119 ± 3	+1 ± 1	+1 ± 2	
Standing for 5 min				
Placebo	121 ± 4	+4 ± 2	−1 ± 2	
Minoxidil	124 ± 3	0 ± 2	0 ± 2	
Diastolic BP (mm Hg)				
Supine				
Placebo	78 ± 2	+1 ± 2	0 ± 2	
Minoxidil	75 ± 2	+3 ± 2	+1 ± 1	
Standing for 5 min				
Placebo	84 ± 2	+1 ± 2	+2 ± 2	
Minoxidil	85 ± 2	+3 ± 1	+2 ± 2	
Heart rate (beats min^{-1})				
Supine				
Placebo	58 ± 2	−3 ± 2	−4 ± 2	$P = 0.09$
Minoxidil	61 ± 2	−1 ± 1	−1 ± 2	
Standing for 5 min				
Placebo	77 ± 3	−5 ± 3	0 ± 3	$P = 0.05$
Minoxidil	76 ± 3	+1 ± 2	+4 ± 3	

Values represent means ± s.e. mean (n = 20 for minoxidil group, n = 15 for placebo group).

Discussion

The present study demonstrates that chronic use of topical minoxidil is associated with statistically significant cardiovascular effects. For the placebo group, the within-group changes are as expected with time during placebo treatment. Compared with placebo, minoxidil caused average increases in heart rate by 3–5 beats min^{-1}, LV end-diastolic volume by 6–8 ml and in cardiac output of 0.75 l min^{-1}. Moreover, LV mass increased by 5 g m^{-2}. BP did not change during chronic use. These changes are qualitatively similar to those occurring following long-term administration of minoxidil to normotensive rats: increases in LV internal diameter and in LV mass, but no change in BP (Tsoporis & Leenen, 1988). It appears that during chronic use of topical minoxidil, sufficient minoxidil is being absorbed to persistently increase cardiac volume load. An arterial vasodilator such as minoxidil may increase cardiac volume load by sodium and water retention, increasing sympathetic activity to the heart and veins, or by causing redistribution of blood from the peripheral to the central compartment. Body weight did not change over a period of 6 months, but this represents a very inaccurate index of intravascular volume.

In the subjects on topical minoxidil, the change in cardiac output varied from a small decrease to a clear increase (up to 3 l min^{-1} increase). This variation in the cardiac responses to topical minoxidil may relate to several factors. For example, compliance was not evaluated in the present study and non-compliance may therefore partly explain absence of responses in some of the subjects. In addition, inter-individual variation may exist for absorption of topically administered minoxidil into the blood-stream as well as for responsiveness of the cardiovascular system to minoxidil. Plasma minoxidil obviously would have been of help but was not measured.

The above described cardiac effects of topical minoxidil have potential clinical implications. Patients with coronary artery disease may be

Table 2 Changes in LV anatomy and function during chronic treatment with topical minoxidil or placebo in men with early male pattern baldness.

	Baseline	*Changes from baseline* + 3 months	+ 6 months	
LV wall thickness in diastole (septum + posterior wall, mm)				
Placebo	17.6 ± 0.4	−0.1 ± 0.1	−0.1 ± 0.1	
Minoxidil	17.5 ± 0.3	0.0 ± 0.1	+0.1 ± 0.1	
LV mass (g m^{-2})				
Placebo	111 ± 5	−1 ± 1	−2 ± 2	$P = 0.05$
Minoxidil	112 ± 3	+2 ± 2	+3 ± 2	
LV end-diastolic volume (ml)				
Placebo	145 ± 8	0 ± 2	−3 ± 3	$P = 0.008$
Minoxidil	158 ± 5	+6 ± 2	+5 ± 3	
LV end-systolic volume (ml)				
Placebo	42 ± 3	0 ± 1	−2 ± 2	
Minoxidil	47 ± 2	−1 ± 1	0 ± 1	
Cardiac output (l min^{-1})				
Placebo	5.99 ± 0.40	−0.38 ± 0.30	−0.56 ± 0.29	$P = 0.006$
Minoxidil	6.68 ± 0.23	+0.37 ± 0.19	+0.16 ± 0.25	
Body weight (kg)				
Placebo	76.0 ± 2.5	+0.1 ± 0.5	−0.1 ± 0.4	
Minoxidil	78.2 ± 1.8	−0.0 ± 0.3	−0.1 ± 0.3	

Values represent means ± s.e. mean (n = 20 for minoxidil group, n = 15 for placebo group).

exposed to increased cardiac work if treated with topical minoxidil; in susceptible patients this may aggravate ischaemic symptoms. Previous studies have not reported any cardiac signs or symptoms, except for 'minor' ECG changes (Olsen *et al.*, 1985, 1986). However, these studies were all performed in healthy subjects, excluding patients with cardiovascular diseases. Safety in patients with coronary artery disease has not as yet been demonstrated.

The clinical significance of the cardiac effects of chronic treatment with topical minoxidil in otherwise healthy subjects is more difficult to evaluate. Chronic increases in cardiac output up to 0.5–1 l min^{-1} are as such unlikely to be detrimental for a healthy heart. However, similar to our observations in normotensive rats (Tsoporis & Leenen, 1988), the chronic volume overload was associated with a small increase in LV mass. Long-term studies will be needed to assess whether the LV mass will progressively increase over years of chronic treatment with topical minoxidil. If so, there would be another reason (Anderson, 1984; Levy *et al.*, 1987) for concern regarding the safety of topical minoxidil.

In conclusion, chronic treatment with topical minoxidil does cause systemic cardiovascular effects, of which the clinical relevance clearly needs to be established.

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