Effects of clonidine and hydrochlorothiazide on the cardiovascular response to mental stress in adolescent hypertension

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Summary
1. The effects of clonidine and hydrochlorothiazide on the cardiovascular responses to mental stress were compared in 29 adolescents with essential hypertension.
2. Clonidine therapy was associated with lower diastolic pressures, heart rate and noradrenaline in response to mental stress. By contrast, hydrochlorothiazide resulted in the reduction of systolic pressure only. The mental stress testing produced a greater absolute diastolic pressure response and higher plasma noradrenaline on hydrochlorothiazide therapy.
3. Juveniles with essential hypertension may be more sensitive to central control of blood pressure and more resistant to diuretics.
4. The reduced diastolic pressure and heart rate response to central stimuli during clonidine therapy may be related to decreased adrenergic activity, as indicated by lower plasma noradrenaline.

Key words: clonidine, hydrochlorothiazide, mental stress, noradrenaline.

Introduction
The hyperkinetic cardiovascular state of borderline hypertension has been well described [1]. Studies which have evaluated the cardiovascular response to centrally mediated stimuli have demonstrated a similar cardiovascular hyperresponsivity in adolescents with borderline hypertension [2]. Furthermore, it has been recently reported that adolescents with borderline hypertension and a strong family history of hypertension have a greater risk for progression to fixed hypertension [3]. This progression rate is higher than that described in older populations with borderline hypertension. Thus the phase of hypertension emerging in adolescence appears to be more sensitive to centrally mediated environmental stimuli. The purpose of this study was to compare the effects of clonidine and hydrochlorothiazide on the cardiovascular response to mental stress in hypertensive adolescents.

Methods
Adolescents with documented essential hypertension were invited to participate in a treatment programme. All participants were between 13 and 19 years of age and had blood pressure measurements consistently above the 95th percentile [4] for over 3 months. The first phase in the treatment programme was placebo therapy consisting of one tablet twice daily for 4 weeks. During the placebo phase, mental stress testing was performed by previously described methodology [2]. During the mental stress procedure blood pressure and heart rate measurements were obtained by Arteriosonde (Roche) with the subject rested (30 min) in the supine position. After determination of baseline blood pressure and heart rate, the subjects performed difficult mental arithmetic for 10 min, followed by a recovery phase. Blood pressure and heart rate
measurements were obtained at 1 min intervals throughout the test. Blood specimens were obtained through an indwelling butterfly needle after the rest period before stress, and immediately on completion of stress. These samples were assayed for plasma catecholamines [5].

After the placebo phase, all adolescents who had blood pressure beyond the 95th percentile and who demonstrated over 80% compliance with placebo were randomly allocated double blind to one of two treatment groups. Adolescents who were assigned to clonidine therapy included 12 males and two females with a mean age of 16-0 years. Mean pretreatment values for this group were weight 78 kg, height 170 cm, casual seated systolic blood pressure 146 mmHg, diastolic pressure 96 mmHg and heart rate 85 beats/min. Those adolescents assigned to hydrochlorothiazide therapy included nine males and six females and the mean age of the group was 15-0 years. Mean pretreatment measurements of this group were weight 76 kg, height 168 cm, casual seated systolic blood pressure 145 mmHg, diastolic pressure 97 mmHg and heart rate 80 beats/min. These values reflect close matching of the two treatment groups.

The clonidine treatment group began active therapy at a low dose of 0-1 mg twice daily. The hydrochlorothiazide treatment group began low dose therapy at 25 mg twice daily. Treatment goals were blood pressure reduction to the 90th percentile or less. After 12 weeks' therapy, those adolescents who did not achieve blood pressure treatment goals proceeded to high dose therapy consisting of clonidine 0-2 mg twice daily or hydrochlorothiazide 50 mg twice daily. Mental stress testing was repeated at 16-18 weeks of therapy. After 24 weeks’ total therapy the medication was tapered and discontinued, with further treatment determined on an individual basis. Changes in casual seated blood pressure and heart rate in the two treatment groups were evaluated by a paired t-test. The difference in cardiovascular response to mental stress after therapy was analysed by a two-way analysis of variance.

Results

Placebo therapy resulted in a systolic pressure reduction of less than 2 mmHg in both groups. No diastolic pressure reduction occurred in either group on placebo therapy. On low dose active therapy, the clonidine treated group had a significant reduction in systolic pressure (10 mmHg; \( P < 0.05 \)), diastolic pressure (7 mmHg; \( P < 0.01 \)) and heart rate (10 beats/min; \( P < 0.01 \)). Low dose therapy in the hydrochlorothiazide treated group resulted in a significant reduction only in systolic pressure (6 mmHg; \( P < 0.05 \)). The diastolic pressure reduction of 3 mmHg was not significant. Four clonidine treated adolescents remained on low dose therapy and 10 proceeded to high dose (0-02 mg twice daily). At completion of 24 weeks of total active therapy the clonidine treatment group had a significant reduction in mean systolic pressure (136 mmHg; \( P < 0.025 \)), diastolic pressure (88 mmHg; \( P < 0.001 \)) and heart rate (75 beats/min; \( P < 0.01 \)). All hydrochlorothiazide treated adolescents proceeded to high dose therapy (50 mg twice daily). At completion of the programme significant reduction was achieved in systolic pressure (135 mmHg; \( P < 0.01 \)) only. The diastolic reduction to 92 mmHg was not significant and no change occurred in heart rate.

The results of the mental stress testing in the two treatment groups before therapy (during placebo) and on active pharmacological therapy are presented in Fig. 1. In both treatment groups the baseline systolic pressure was lower on active therapy. However, the systolic pressure response to mental stress was the same on active therapy in both treatment groups. In the clonidine treated group, the diastolic pressure response at baseline, stress and recovery was significantly lower on active therapy (\( P < 0.01 \)). In the hydrochlorothiazide treated group the diastolic pressure response was higher on active therapy. The heart rate response pattern to stress was significantly lower with active therapy in the clonidine treated group (\( P < 0.01 \)). In the hydrochlorothiazide treated group the heart rate response to stress was lower but this change was not significant.

Pretreatment baseline plasma noradrenaline levels were similar in the clonidine treated group (223 pg/ml) and in the group to receive hydrochlorothiazide (225 pg/ml). On therapy the baseline plasma noradrenaline decreased in the clonidine treated group (166 pg/ml) and increased in the hydrochlorothiazide treated group (282 pg/ml). The difference in baseline values on therapy is significant (\( P < 0.05 \)). Post-mental stress levels of plasma noradrenaline was also similar in the two groups before therapy: clonidine 261 pg/ml, hydrochlorothiazide 236 pg/ml. During therapy the post-stress plasma noradrenaline decreased in the clonidine treated group (204 pg/ml) and increased in the hydrochlorothiazide treated group (313 pg/ml). The difference between the two groups in stressed plasma noradrenaline values on therapy is significant (\( P = 0.02 \)).
Stress response in adolescent hypertension

Fig. 1. Cardiovascular response to mental stress, presented for the two treatment groups. The response before active treatment is depicted by continuous lines representing the mean values with SEM represented by the shaded areas. The response on active therapy is depicted as the broken line for mean values with the diagonal areas representing SEM. B, baseline values; R, recovery values. On clonidine therapy the diastolic response and heart rate response are significantly lower ($P < 0.01$).

Discussion
All participants in the treatment phase were clearly hypertensive. They had not responded to non-pharmacological manoeuvres, such as dietary salt reduction and weight control. All adolescents included in this report remained hypertensive after 4 weeks of placebo treatment. The change in casual seated systolic pressure was less than 2 mmHg in either group and no change in diastolic pressure occurred with placebo. Investigators were blind as to which of the active treatments each patient received. One adolescent in the clonidine therapy group complained of dry mouth and drowsiness at the higher dose. No other side effect symptomatology was expressed which permitted identification of the treatment. To further preclude the possibility of investigator bias the mental stress testing was performed with the stressor blinded to the response.

The results indicate that clonidine significantly reduces casual blood pressure at low dose (0.1 mg twice daily) in adolescents with hypertension, whereas hydrochlorothiazide significantly reduces only systolic pressure even at the higher dose of 50 mg twice daily. However, neither drug appeared to alter the systolic pressure response to mental stress. As demonstrated, the systolic pressure response was similar before and on treatment in both groups, although the baseline was lower. The effect of the centrally acting agent on the mental stress response was a significant reduction in diastolic pressure response and heart
rate response to stress. These changes corresponded with lower plasma catecholamine levels. In the diuretic treated group the heart rate response was not significantly lower, the diastolic pressure response was somewhat higher, and plasma catecholamine levels were higher on treatment.

The hyper-responsiveness to mental stress observed in adolescents with mild hypertension resembles the hyperkinetic cardiovascular state of borderline hypertension. Previous studies have demonstrated a form of impaired neurogenic activity in borderline hypertension [6, 7]. This hyperkinetic state may be associated with increased sympathetic activity or a combination of reduced parasympathetic and increased adrenergic activity [8, 9].

Our subjects all had blood pressures beyond the borderline range for age. On the basis of age and duration, the hypertensive adolescents in this study represent an early phase of essential hypertension. At this stage of hypertension subjects were more sensitive to the effects of centrally acting agents in blood pressure control and were more resistant to diuretic effect. The reduced diastolic pressure and heart rate response to environmental stimuli on clonidine therapy may be related to decreased adrenergic activity as expressed by lower plasma catecholamines.

References


