

CONTROLLED TRIAL WITH BRINERDIN — A NEW ANTIHYPERTENSIVE

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Summary

A double-blind study on 40 ambulant, mild to moderate hypertensive patients aged from 35-67 years showed that Brinerdin is an effective anti-hypertensive agent. After a dose-adjustment period and a 3-week wash-out the patients were randomised into 2 groups each on active drug and placebo respectively. Regular physical and laboratory examinations were made.

The Brinerdin group showed a highly significant fall in blood pressure. In all cases the fall was gradual without sudden fluctuation (see graph). By comparison the placebo group showed only insignificant changes in blood pressure. At the effective dosage of 1-3 tablets daily there were no untoward side-effects. As with all saluretic drugs some patients tended to have slightly raised uric acid levels.

Introduction

Dihydroergocristine is a hydrogenated alkaloid of ergot. As such, it reduces vascular tone through the vasomotor centre, exerts a peripheral adrenosympathicolytic action and has a mild central sedative effect. Clopamide is a salidiuretic. The properties of reserpine in producing a gradual fall of blood pressure are well-known.

Each tablet of Brinerdin contains:

dihydroergocristine	0.5mg
clopamide	5.0mg
reserpine	0.1mg

Objectives of the study

The objectives of this study were:

1. To evaluate the effect of Brinerdin in reducing blood pressure
2. To determine its effects on subjective symptoms of hypertension
3. To confirm its safety by assessment of the incidence and type of side effects and by laboratory investigations.

Method

A double-blind technique was employed using a preliminary adjustment period. 40 ambulant patients suffering from mild to moderate hypertension were selected for the study. Of these, 32 completed the study within the date-line set for evaluation. 3 patients dropped out during the trial.

The remaining 8 patients finished the trial later but the computerised programming for evaluation had already been completed. Analysis of the additional data showed a decrease of 50% on values above not in any way alter the overall results of the trial.

Adjustment period

During the first 4 weeks of the study patients were given increasing doses of Brinerdine until the effective dose for each patient was determined. For the purpose of the trial an effective lowering of the blood pressure was considered to have

been achieved when the diastolic pressure showed a decrease of 5% on values above 90mm.Hg. There were 2 drop outs during this period.

Wash-out period

The period of adjustment was followed by a wash-out phase of 3 weeks during which all patients received placebo.

Double-blind period

Finally the patients were randomised into 2 equal groups of 15 patients each taking active drug and placebo respectively for 6 weeks. The third drop-out from the group on active drug occurred during this phase.

Evaluations

Throughout the study blood pressure readings were taken at weekly intervals in the standing, sitting and supine positions. The values recorded in each case were the mean of 2 separate readings. The same technique was applied in reading the pulse rate.

Accompanying symptoms of hypertension — such as headache, dyspnoea, dizziness and vertigo, insomnia, fatigue, anxiety and depression — were evaluated. In order to determine whether Brinerdin causes any biochemical disturbances the following laboratory investigations were carried out at the beginning and end of the adjustment period after 3 weeks of the double-blind phase and at the end of the trial:

1. Haemoglobin estimation
2. Full blood count
3. Blood urea
4. Serum electrolytes (sodium, potassium and chlorides)
5. Blood cholesterol
6. Uric acid.

Results

Of the 29 patients evaluated statistically 14 had been placed on Brinerdin during the double-blind phase while 15 received placebo.

The Brinerdin group consisted of one patient who was classified a severe hyper-

tensive, 8 who had moderate hypertension and 5 with mild hypertension. In the placebo group 7 were classified as moderate hypertensives and 8 as mild hypertensives. There were no patients with renal complications in either group. The duration of the condition varied from 0-8 years with a mean of 3 years. Ages ranged from 35-67 and there was a family history of hypertension in 10 cases. The effective dose of Brinerdin established during the initial adjustment period varied from 1-3 tablets per day.

Adjustment period

During this period a highly significant lowering of blood pressure was achieved ($p < 0.001$). The mean fall in systolic pressure was 35mm.Hg. while the mean fall in diastolic pressure was 19mm.Hg. 2 patients were taken off Brinerdin early during this period. One patient was proved to have had a myocardial infarction prior to starting treatment with Brinerdin. Another patient, who suffered for many years with chronic diarrhoea from ulcerative colitis complained of coldness and dizziness after taking the tablet

Wash-out period

During the wash-out period blood pressure readings showed a significant rise ($p < 0.001$) towards previous levels. At the end of this phase the mean systolic pressure had risen by 29mm.Hg. and the mean diastolic pressure showed an increase of 16mm.Hg.

Double-blind period

One patient in the Brinerdin group dropped out of this phase because of epigastric pain. However this pain had persisted during the placebo wash-out period and was later proved to be due to cholecystitis.

The 14 patients on Brinerdin again showed a highly significant fall in blood pressure. From a mean value of 184.3/110.7/mm.Hg. in the sitting position at the end of the wash-out period readings fell to a mean of 149.3/96mm.Hg. This fall becomes even more significant when the values reached at the end of the trial

are compared with those found when the study began. The mean value recorded in both groups at the initiation of the trial and at the end of each phase are to be found in the following table.

In all cases in the Brinerdin group the fall in blood pressure during the double-blind phase was gradual without

the objective findings and the subjective assessment by the physician.

Side effects

The 3 drop-outs in the trial have already been described.

During the entire duration of the trial other side effects encountered were short-

Mean Blood Pressure Readings in Sitting Position (mm.Hg.)

Group	Initiation of trial	End of adjustment period	End of wash-out period	End of double-blind period
Brinerdin	189.67/114.67	150/93.67	184.33/110.67	149.27/96.06
Placebo	184.67/110.67	157/92.67	172.67/107.67	168.4/105.8

any marked fluctuations (see graph). By comparison the 15 patients who received placebo during this phase of the trial showed only insignificant changes in blood pressure.

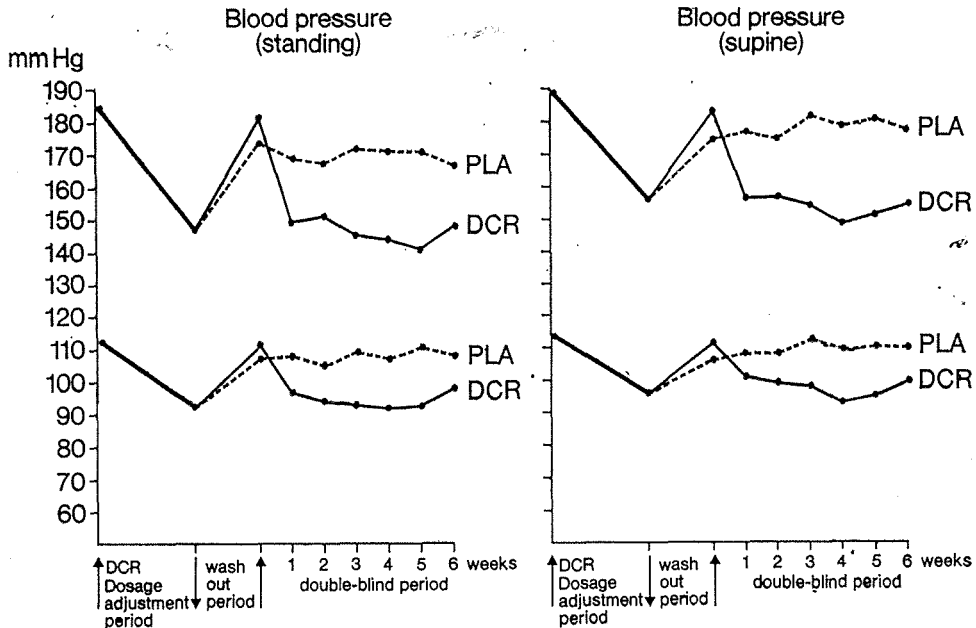
The pulse rate observations during the study showed no appreciable change and the accompanying symptoms of hypertension were too mild and infrequent to be evaluated.

There was good correlation between

lived and never severe enough to stop medication.

Ten patients taking Brinerdin showed elevated uric acid levels at the end of the study. The mean value for this group rose from 4.98mg/100ml (3.2-8.0) at the beginning of the trial to 6.29mg/100ml (4.4-11.2) at the 10th week.

In the placebo group 6 patients also finished the study with high uric acid levels.



All the other laboratory values investigated remained within physiological limits for all patients. No hypokalaemia was observed.

Conclusion

The study demonstrates that at a dosage of 1-3 tablets per day Brinerdin is an effective anti-hypertensive agent. In all cases comparison with placebo showed a highly significant difference in favour of Brinerdin. Subjective side effects show a

low incidence and are not of a serious nature. There is, however, a tendency towards the production of raised uric acid levels but this is a known consequence of saluretic drugs.

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