# NADOLOL (CORGARD) IN SEVERE AND RESISTANT HYPERTENSION

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## SUMMARY

*A total of 12 severely hypertensive patients were treated with a once daily dose of Nadolol. There was a drop in diastolic pressure to a mean of 105 mm Hg standing within two weeks and this was well maintained up to 12 months of therapy, the lowest diastolic pressure being 94 mm Hg standing at six months of therapy. Nadolol produced no significant side effects and bradycardia was not a problem during treatment. Of the eleven patients who were resistant to previous therapy because of various reasons all except two responded excellently. One of the non responders has real resistance to therapy and the other is non compliant.*

*Nadolol is found to be an effective once daily treatment for severe and resistant hypertension.*


## INTRODUCTION

A total of 12 patients out of 22 patients entering an open trial of Nadolol (Corgard) for a duration of 12 months were found to be severely hypertensive. They were investigated on a separate basis from the rest, the aim being to assess the efficacy of once daily Nadolol (Corgard) in the treatment of severe and resistant hypertension.

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Nadolol is a new β adrenergic receptor blocking agent that lacks intrinsic sympathomimetic activity or β receptor selectivity. It is well tolerated in large doses and has no direct myocardial depressant properties. It has a plasma half life of ten to twelve hours and this is about four times that of single doses of propranolol (Dreyfuss *et al*, 1977).

## MATERIALS AND METHOD

Twenty-two adult patients were admitted into an open trial of Nadolol (Corgard). A standing diastolic blood pressure (B.P.) of $\geq$ 115 mm Hg was taken as an indication of severe or resistant hypertension. B.P. was measured with a mercury spygmomanometer in the supine and standing positions. The systolic pressure is taken at the first phase (first Korotkoff sounds) and the diastolic pressure at the fourth phase (fourth Korotkoff sounds or muffling). Each subject had his B.P. recorded after a minimum period of 30 minutes sitting in the waiting room and 5 minutes lying on the examination couch. The raised B.P. was reconfirmed at a subsequent visit two weeks later before commencement of Nadolol therapy.

Nadolol was administered on a once daily regime in doses ranging from 40 mgs to 200 mgs. Increments in doses were made at intervals of not less than two weeks. The aim of treatment is to lower the diastolic standing B.P. to 100 mm Hg or lower without producing untoward effects in the patient. A thorough clinical examination was done from the first and subsequent visits, including fundoscopy examinations. Side effects of therapy were enquired into at every follow-up visit.

Appropriate laboratory investigations were done on commencement of the trial and during the trial itself and the changes noted. The laboratory tests included electro-

TABLE I
RESULTS OF TREATMENT

| Interval | BP ± SD mm Hg | | Average daily dose | n | 'p test' Diastolic B.P. | |
|---|---|---|---|---|---|---|
| | Supine | Standing | | | Supine | Standing |
| Initial | $\frac{169 \pm 25}{121 \pm 6}$ | $\frac{169 \pm 24}{126 \pm 12}$ | 0 | 12 | — | — |
| 2 weeks | $\frac{156 \pm 18}{102 \pm 13}$ | $\frac{152 \pm 18}{105 \pm 11}$ | 94 mgs | 12 | $< 0.01$ | $< 0.01$ |
| 3 months | $\frac{149 \pm 22}{96 \pm 9}$ | $\frac{147 \pm 24}{98 \pm 9}$ | 106 mgs | 11 | $< 0.01$ | $< 0.01$ |
| 6 months | $\frac{138 \pm 18}{91 \pm 7}$ | $\frac{139 \pm 21}{94 \pm 8}$ | 95 mgs | 11 | $< 0.01$ | $< 0.01$ |
| 9 months | $\frac{135 \pm 16}{92 \pm 6}$ | $\frac{138 \pm 20}{94 \pm 8}$ | 107 mgs | 9 | $< 0.01$ | $< 0.01$ |
| 12 months | $\frac{149 \pm 28}{94 \pm 12}$ | $\frac{149 \pm 28}{96 \pm 12}$ | 112 mgs | 9 | $< 0.01$ | $< 0.01$ |

cardiograms, chests Xrays, serum creatinine, blood urea, serum electrolytes, creatinine clearance, urine microscopy, urine culture, 24 hour collection of urine for vanillylmandelic acid (VMA) secretions and intravenous pyelogram where appropriate. At every visit careful enquiry was made into tablet taking to ensure good compliance and patient motivation assessed and encouraged.

Out of these 22 patients, 12 or 55 percent satisfied the criteria of severe and/or resistant hypertension. The standing diastolic B.P. ranged from 115 mm Hg to 150 mm Hg. The standing systolic pressure ranged from 140 mm Hg to 230 mm Hg. The patients comprised five females and seven males; divided into eleven Malays and one Indian, of age range between 35 years and 67 years. None had any contra-indications to β-blockade therapy. A total of eleven patients had been on other anti-hypertensives before, including diuretics, Methyldopa, other β-blockers and Prazocin. Weaning from previous medications to Nadolol was attempted in all cases. At various intervals a once daily dose of a diuretic was added; other antihypertensives were added when necessary. Paired t tests were used to calculate statistical significance.

## RESULTS

Out of the twelve patients in the severe and resistant group, two had renal hypertension as proven by blood urea, serum creatinine, creatinine clearance and the intravenous urogram. Five patients had previous accelerated hypertension and two had previous toxaemia of pregnancy. No patient had a previous stroke or myocardial infarction. One patient was regarded to be in acute hypertensive crises requiring hospital admission when first seen. His clinical features and management will be discussed in this paper (Case history No. 1).

Table I gives the results of treatment. The mean initial B.P. (in mm Hg ± Standard Deviation) was standing $\frac{169 \pm 24}{126 \pm 12}$ mm Hg, supine $\frac{169 \pm 25}{121 \pm 6}$ mm Hg. Within 2 weeks of treatment the B.P. dropped to $\frac{152 \pm 18}{105 \pm 11}$ mm Hg standing and $\frac{156 \pm 18}{102 \pm 13}$ mm Hg lying. Seven out of the twelve patients responded with a standing diastolic B.P. to 100 mm Hg or less. Test of significance showed this to be significant at the $p < 0.01$ level. The average daily dose of Nadolol used was 94 mgs.

On the third month of treatment one patient dropped out because of side effects. The result on the remaining eleven showed a mean B.P. of $\frac{147 \pm 24}{98 \pm 9}$ mm Hg standing and $\frac{149 \pm 22}{96 \pm 9}$ mm Hg supine. Eight out of the eleven

patients had an excellent response with diastolic standing B.P. to 100 mm Hg or less. Test of significance compared to initial values, showed this to be significant at the $p < 0.01$ level. The average daily dose was 106 mgs.

At six months therapy, data on eleven patients showed mean B.P. at $\frac{139 \pm 21}{94 \pm 8}$ mm Hg standing and $\frac{138 \pm 18}{91 \pm 7}$ mm Hg supine. Ten out of eleven patients had a standing diastolic B.P. of 100 mm Hg or less. Test of significance showed this to be significant at the $p < 0.01$ level, compared to initial values. The average daily dose was 95 mgs.

At nine months therapy, two more patients dropped out for various reasons. Data on the remaining nine showed a mean B.P. of $\frac{138 \pm 20}{94 \pm 8}$ mm Hg standing and $\frac{135 \pm 16}{92 \pm 6}$ mm Hg supine. Seven of the nine showed excellent response, the remaining two had a standing diastolic pressure of 105 mm Hg. Test of significance showed the p level to be $< 0.01$. The average daily dose was 107 mgs.

At twelve months therapy, data on the remaining nine patients showed a mean B.P. of $\frac{149 \pm 28}{96 \pm 12}$ mm Hg standing and $\frac{149 \pm 28}{94 \pm 12}$ mm Hg lying. Seven of the nine showed good response. Test of significance showed p at $< 0.01$ level. The average daily dose being 112 mgs. However two patients continued to show poor response. Their cases will be discussed below (Case histories No. 2 and 3).

Fig. 1 illustrates the drop in standing diastolic pressure from pretreatment to that at various intervals after treatment with Nadolol.

The systolic pressures recorded drops at the all phases of treatment. However paired t tests could not demonstrate a consistent satisfactory p level of $\leq 0.05$ during some phases of therapy.

Nadolol tends to produce bradycardia, though this is not excessive. No patient developed bradycardia necessitating change of dose or medication.

Two patients developed eczematous reactions; one refused to take Nadolol after that, the other had a past history of eczema on other β-blocking medication. One patient had mild postural hypotension which dis-

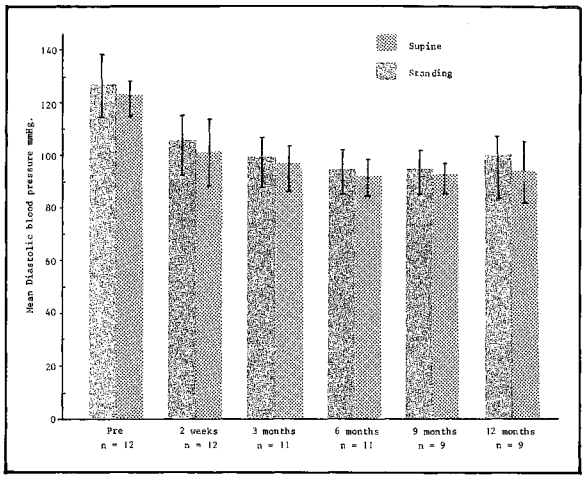


**Fig. 1 Mean Diastolic B.P. pre and at various intervals of treatment with Nadolol.**

appeared after dose adjustments. One patient felt very sleepy initially but this disappeared spontaneously after the first two weeks. The side effects were mainly seen within the severe and resistant group. The mild and moderate group of hypertensive did not report similar side effects. Two patients in the severe group were resistant to treatment, one was thought to be due to true resistance (Case history No. 2) and the other possibly due to non compliance (Case history No. 3).

Eleven of the twelve patients reported poor compliance on their previous therapy due to side effects, multiplicity of dosage regimes and the many tablets they have to consume daily. At the end of the trial 10 of these patients had excellent compliance.

**Case History No. 1**

The patient M.R.M.S. aged 67 years retired planter, was referred because of one month's history of tiredness, fatigue and nocturia x 5-6/night. He was a known hypertensive for 6 years, and defaulted about 1½ months before being seen. Examination revealed B.P. of 190/135 mm Hg supine taken twice, at two hour intervals, early hypertensive retinopathy, and puffy face. Rectal examination showed a very large prostate. Other systems were normal. Urine examination showed numerous pus cells, few red blood cells and culture gave a mixed growth. Serum creatinine was at 150 umol/L. Nadolol 200 mgs was started with Lasix 40 mgs daily. Within 24 hours the B.P. dropped gradually to 150/100 mm Hg, well maintained till time of discharge. On follow-up at the clinic the B.P. was 150/95 mm Hg standing and lying.

**Case History No. 2**

The patient, a 56 year old Malay, working as a boilerman with the Railway board, had a known history of hypertension for the last 12 years. He had two past admissions for accelerated hypertension. There was no other past history of any significance. Presently he complained of occasional headaches. His father, mother and older brother were hypertensive. He smoked 10-15 cigarettes per day and was non alcoholic. Examination revealed an obese man, B.P. supine 170/130 mm Hg, standing 170/140 mm Hg, fundoscopy showed grade 2 changes of A-V nipping and silver wiring of arteries. Other systems were normal. Investigations could not show any cause for his hypertension. His medications include Methylolopa, Oxyprenolol, Nitrazepam, Bendrofluozide and Guanethidine, despite which his B.P. remained persistently high. Nadolol 80 mgs daily, with hydrochlorothiazide was substituted for all these medications. Within two weeks of treatment the B.P. went down to 180/110 mm Hg supine, 180/120 mm Hg standing. Within the next three months the B.P. went up gradually to 180/120 mm Hg supine and 180/130 standing. Prazocin 1 mg B.D. was added. This seemed to help and B.P. at 6 months showed a drop to 160/100 mm Hg supine and 170/105 mm Hg standing. He developed mild eczema on Nadolol but had a past history of eczema on other β-blockers and agreed to continue taking the drug because of easy dosage regime. At 12 months therapy the B.P. had gradually increased to 200/120 mm Hg supine and standing. Laboratory data on this patient continued to be normal. He was thought to be resistant to treatment and another agent substituted.

**Case History No. 3**

Patient No. 3 is a Malay housewife, aged 44 years. She had several admissions for toxaemia of pregnancy in the past and had been on various treatments, including Methyldopa, Oxyprenolol and Chlorothiazide. She complained of occasional neck pain and headaches. There is no significant family history. She is a nonsmoker and does not consume alcohol. Examination showed a B.P. of 160/120 mm Hg supine and standing. Other systems were normal. All laboratory investigations were within normal limits. She is a poor clinic attender and noncompliance was suspected. All the medications concerned were stopped and Nadolol 80 mgs substituted. Within two weeks the B.P. dropped to 140/95 mm Hg supine and standing. However within three months the B.P. climbed up to 170/120 mm Hg supine and standing and patient admitted to not taking medications regularly. The situation continued with the patient taking the medication on and off as reflected by varying B.P. responses. At 12 months therapy the B.P. was still at 160/105-110 mm Hg supine and standing. Non-compliance was regarded to be the cause of her apparent resistance to Nadolol therapy.

## DISCUSSION

There has been new interests lately in the use of oral medications for severe and resistant hypertensives. It was first noted by Strangaard *et al* (1973) that rapid reduction of B.P. may have deleterious effects on cerebral blood flow causing cerebral ischaemia leading to permanent neurological deficits. These were subsequently supported by Ledingham and Rajagopalan (1979) who reported a series of ten cases, four of whom subsequently died, another four having permanent neurological damage. They conclude that the high B.P. should only be reduced cautiously in a matter of 18-48 hours and a drastic drop in B.P. should not be the aim of treatment. Ghose (1979) showed that accelerated hypertension could be effectively and safely reduced by oral labetalol.

In this group of severe and resistant hypertensives oral Nadolol was the main mode of therapy. Four such patients required additional treatment including low doses of Prazosin (minipress) and diuretics. It is interesting to note that Nadolol was effective in all the cases, thus agreeing with Ghose that oral treatment with a β blocker (an α and β blocker in Ghose's series) could be effectively given for severe hypertension. Case history No. 1 is an example.

The blood pressure response could be seen within two weeks of treatment. Seven out of twelve (58 percent) responded with a standing diastolic pressure of 100 mm Hg or less. This was well maintained at three, six, nine and twelve months of therapy. The tests of significance showed a highly significant level of $p < 0.01$. The mean daily dose at 2 weeks was 94 mgs and it varied between 106 mgs to 112 mgs between three to twelve months of therapy.

Four patients complained of side effects to therapy. In one case Nadolol had to be withdrawn as the patient refused to take Nadolol after developing a rash on her thighs. She had been on Nadolol for two weeks and had a satisfactory drop in standing diastolic pressure. No other withdrawal of therapy occurred. The other case had a history of developing eczematous rash even on other β-blockers but agreed to continue treatment because of easy dosage regime. The side effects in the other two cases were mild and transient.

Two cases were found to be resistant to Nadolol (Case histories 2 and 3). One was due to noncompliance, as she had a record of being a poor clinic attender and admitted to not taking the medications regularly.

It is not fully understood how — β-blockers reduce hypertension. Buhler *et al* in 1972 proposed that they act through an inhibition of renin secretion and this was supported by Menard *et al* in 1976. Stokes *et al* in 1974 could not show any correlation between renin activity and drug effect. However β-blockers could also act through the central nervous system, the baroreceptors and through its effects on the cardiac output. Nadolol has been shown to increase the renal blood flow (Hollenberg, *et al*, 1979). Increasing the renal blood flow will help in maintaining renal function and reduction in blood pressure. Resistance to β-blockers may be due to differing levels of receptiveness or the number of adrenergic receptors between various patients. However this could not be substantiated by data in this study. Compliance was improved in ten out of eleven patients that were on other antihypertensives before. In conclusion this study demonstrated the effectiveness of once daily Nadolol for severe and resistant hypertensives.

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