

## EFFECTS OF NITROXAZEPINE ON DIASTOLIC BLOOD PRESSURE IN MILD HYPERTENSIVE PATIENTS - A SHORT TERM CLINICAL STUDY

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**Abstract:** In a double blind short term clinical study, nitroxazepine has been found to be superior over placebo in reducing the diastolic blood pressure in mild hypertensive patients. In short term open clinical trial design nitroxazepine (25 mg PO, HS) has been found to be superior and better tolerated than diazepam (5 mg PO, HS). In open clinical trial design, nitroxazepine (25 mg PO, HS) reduced the diastolic blood pressure to the target level (100 mm Hg and less) effectively controlling the uncontrolled hypertensive patients receiving maintenance dose of beta blockers. There was no such beneficial effect in patients receiving maintenance doses of other antihypertensive drugs (pilot study). Adverse drug reactions like disturbed sleep in one, uneasiness in 3, palpitation in one and dryness of mouth in one patient have been observed.

**Key words:** diastolic blood pressure  
nitroxazepine

clinical trial  
ADR

### INTRODUCTION

Nitroxazepine (NTXZ) and its active metabolites in humans possess antidepressant, anxiolytic and mild sedative activity (1, 2). NTXZ has been reported to cause reduction in mean blood pressure (BP) marginally in 41% of test subjects (174 out of 424) suffering from depression (3).

Present study was undertaken to explore the antihypertensive effect of NTXZ in mild hypertensive patients using minimal dose (25 mg, PO HS) Vs placebo in double blind, Vs diazepam (5 mg, PO HS) and in illcontrolled hypertensives on beta blockers in open clinical trial design. Diastolic blood pressure (DBP) was taken as main parameter.

### METHODS

After excluding the patients having raised blood urea, arrhythmia, IHD, conduction defects, postural hypotension, bronchial asthma, jaundice, altered liver function tests, 46 fresh

adults of essential mild hypertension and 24 known hypertensives taking maintenance doses of antihypertensive drugs were included and divided in groups as follows :-

Gr A - Double blind study Vs placebo (n=30). Active drug/glucose filled and supplied in capsules of similar size, shape and colour, labelled as Cap P and D

Gr A1 (n=15) received Cap P from day 1 to 14; 1 cap HS

Gr A2 (n=15) received Cap D from day 1 to 14; 1 cap HS

Gr B - Open clinical trial.

B 1 - (N=16) received tab diazepam - 5 mg HS PO: x 7-14 days.

B 2 - Non responders from B1 group (DBP more than 96 mm Hg) NTXZ after a washout period of 7 days (dose 25 mg PO HS) for 14 days.

Gr C- Antihypertensive drugs + NTXZ - Open trial design:

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After pilot study to identify responders to NTXZ while continuing the maintenance doses of other antihypertensives which these patients were taking, 15 ill controlled patients on beta blockers (Atenolol, Tenolol, Propranolol) were included.

BP was recorded in sitting posture, on same arm, using same sphygmomanometer, by the same physician, during the same day spell, initially daily for 7 drug free days, followed weekly to see persistent target DBP effect, if any. Prior approval of Ethical Committee and written consent of patients was taken after informing benefits and side effects. Target DBP was aimed less than 96 mm Hg for Gr A and B while 100 or less for Gr C. Mean DBP was calculated for 5 days each upto 14 days (drug treated). Mean DBP of 7 drug free days was taken as control while DBP on day - 0 served as individual control.

Statistical analysis for significance of the observed values done by applying paired 't' test.

## RESULTS

In Gr A 1, 7 out of 15 patients receiving Cap 'P' (NTXZ) showed significant reduction in DBP compared to GrA2, treated with Cap 'D' (glucose). The responders from Gr A 1 showed persistent target effect upto 6-8 weeks even after withdrawal, making crossover difficult. Remaining patients of Gr A 1, 2 showed no significant change in DBP.

In Gr B1, 7 out of 16 patients (diazepam treated) completed 14 days therapy, and 1 out of these 7 showed reduction in DBP, Other 9 complained side effects like daytime sedation, lathargy and uneasiness hence requiring stoppage of drug. Thus total nonresponders (n=15) after a washout period of 7 days, were given NTXZ (Gr B 2) & 7 out of these showed reduction in DBP (Table I). Two patients (Gr "B2") were dropped due to ADR i.e disturbed sleep and palpitation.

In pilot study for Gr. C patients receiving tab adelphane (1 OD), aldomet (½ BD), aldomet

TABLE I : Effects of Nitroxazepine on DBP (see text for groups).

Sr No.	Groups	n	DBP on days (Mean ± SEM)						% red. DBP (range)	
			1-7 to 0	0	1-5	6-10	11-14	14		
1.	A1	R	7	100.14±0.78	100.85±0.83	91.57±1.23***	89±2.08**	89.57±2.55**	90±2.04	6-16
		NR	8	101±0.80	100.75±0.79	97.75±0.72	99.37±0.49	99.62±0.96	98.87±0.53	1-2
2	A2	NR	15	98.66±0.51	99.3±0.48	95.3±1.32*	98±0.32	98.66±0.11	99±0.22	
	B1	R	1	97	96	92	92	92	90	4
		NR	15	98.93±0.48	100±0.51	98.11±1.39	96.75±1.59	97.5±1.81	98±2.22	0-3
4	B2	R	7	98.57±0.62	99.14±0.71	90.85±1.92**	84±1.64**	83.14±1.77***	83.71±2.02***	8-16
		NR	8	97.62±0.70	98.5±0.79	82.12±2.58	96.62±0.75*	100.5±0.00	100.5±0.50	
5	PILOT	ad	3	102	103.33	93.33	97.66	100.5	100	
		ald	2	103	105	103	103.5	104	105	
		ale	2	111	115	111.2	114	112	112	
		BB	2	103	102	92	91.5	93.5	91	
6	C	R	15	104.54±0.93	104.54±0.93	94.36±1.33**	92±1.36**	92.09±1.46**	92.18±1.98**	4-10

R=Responders, NR=Non-responders, ad-adelphane, ald-aldomet, alen-aldomet+envas, BB-beta blocker

\*P < 0.05; \*\*P < 0.01; \*\*\*P < 0.001 comparing column (1) Vs (3) (4) (5) and (2) Vs (6).

+ envas in maintenance doses, none showed significant reduction of DBP with addition of NTXZ. 3 patients complained of uneasiness and one had dryness of mouth.

Gr C patients who were already taking beta blockers showed reduction in DBP (target level) with addition of NTXZ.

The DBP change was 4-10%. 2 patients who were taking atenolol (50 mg, OD), after addition of NTXZ, required reduction of the dose of atenolol to 25 mg. In 1 patient atenolol was stopped, since NTXZ alone was effective.

### DISCUSSION

In this study (Gr A1, B2) we have observed reduction in DBP to the target level with NTXZ in 46% (14 out of 30), which is closer to reported 41% reduction in mean BP (3). Small rise of 2 mm seen in 3 out of 30, while 13 showed no

changes, may not restrict the use of NTXZ in mild hypertension. Since the onset of CNS effects of NTXZ have been reported to be before the end of second week, initial reduction in DBP in first 7 days along with additive effect with beta blocker (mainly atenolol) may be due to its cardiodepressant action reported in animal studies (4). This is possibly added in second week to sedative and anxiolytic action of NTXZ and its metabolites.

The authors conclude that NTXZ is antihypertensive, effective in mild hypertension.

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