

PHARMACOKINETICS OF NITROXAZEPINE IN DEPRESSED PATIENTS

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SUMMARY

A pharmacokinetic study was done on 10 depressed patients (DSM-III-R 296.3). The patients were treated with Sintamil (R) (nitroxazepine HCl) with titrated dose from 75 mg to 225 mg for 6 weeks. Plasma levels of nitroxazepine (Sintamil (R)) and its metabolites desmethyl (D), N-oxide (N-O) and carboxylic acid (c) were estimated. Anti-depressant efficacy was judged by reduction in Hamilton Rating Depression Scale (HDRS) scores, and tolerability was monitored by reports of unwanted effects.

The overall reduction in HDRS score was about 50% by 6 weeks. The plasma levels of nitroxazepine (ng/ml) showed a rise from a mean (\pm SEM) level. 47.0 \pm 7.3 on day 1 (dose 75 mg) to 129.8 \pm 24.6 on day 7 (dose 150 mg) ($p < 0.01$) and remained steady till day 21. There were large interindividual variations. The metabolites followed a similar pattern. The HDRS score showed a steady reduction between day 14 and 42 when the levels of nitroxazepine and des-methyl metabolites were maintained between 176.5 ng/ml to 251 ng/ml.

In recent years, therapeutic drug monitoring (TDM) of tricyclic antidepressant (TCAs) has been recommended for several therapeutic situations (Preston et al., 1988; De-Oliveira et al., 1989). Besides the use of TDM in monitoring compliance and avoiding toxicity in high risk groups e. g. elderly, cardiac illness, it has also been recommended to maximise clinical response (Preston et al., 1988; De-Oliveira et al., 1989). In order to use it routinely, it is necessary to define the plasma levels at different dosage of TCAs and to correlate them with clinical response. However, it is difficult to extrapolate the western data to any population because of genetic variation in metabolism of TCAs (Preston et al., 1988; De Oliveria et al., 1989). Hence, even with well known drugs, it is necessary to study their pharmacokinetics in a population where the drug is newly introduced (Bhatia et al., 1988).

Nitroxazepine hydrochloride (Sin-

tamil (R) was introduced in India in 1982. However, its kinetics and metabolism in depressed patients could not be studied during the early clinical studies due to lack of availability of modern analytical techniques e. g. gas-chromatography, high performance liquid chromatography (Sheth et al., 1972). A limited study in healthy volunteers with radio labelled nitroxazepine in low doses (25 mg) suggested that drug metabolised differently as compared to animals. (Sheth et al., 1972). Since there were no kinetic data with doses in therapeutic range 75 mg to 225 mg, the present study was planned to estimate plasma levels of nitroxazepine and its metabolites and to judge whether any relationship could be seen between the plasma levels and antidepressant activity.

Materials and methods

Adult patients suffering from major depressive disorder (DSM-III-R 296.3)

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with a minimum score of 17 on Hamilton Depression Rating Scale (HDRS) were included in the study. Those who were already on antidepressants were included after withdrawing the drugs for at least 2 weeks. Patients who were chronic heavy smokers, or alcohol drinkers or were suffering from severe systemic disease e. g. renal failure, liver dysfunction or pregnant women were excluded from the study. Informed consent was obtained from each patient.

After an assessment of cardiovascular and other systemic status, they were hospitalised for 3 weeks and put on nitroxazepine HCl (Sintamil R) 75 mg and dose was titrated upto 100 mg once daily by day 4 and 150 mg once daily by day 7. If on day 13, HDRS score showed a reduction $>50\%$, the drug was continued in a dose of 150 mg once daily from day 14 to day 42. If the HDRS score showed a reduction $<50\%$, the dose of nitroxazepine HCl was raised to 225 mg (150 mg morning + 75 mg night) on day 14 and maintained upto day 42. The dose titration was done without waiting for the pharmacokinetic data.

Blood was also collected on days 1, 4, 7, 14, 21, 28, 35, 42 before drug and 2 hours after drug administration for estimation of drug levels. Nitroxazepine HCl (N) and its Desmethyl (D) and N-oxide (N-O) metabolite were measured in plasma by a normal-phase High Pressure Liquid Chromatography (HPLC) using standard solutions. The solutions were prepared by dissolving pure substances of N, D and N-O in 50 ml methanol and diluted to give concentrations of 1-2 mg/ml. For estimation of Carboxylic acid (C) metabolite a reverse-phase HPLC was employed with indomethacin (MSD) as internal standard. The equipment was Model 5000 liquid chromatograph (Varian USA) with a spectromonitor D variable wavelength detector (LDC/Milton

Roy) and a Model 7125 syringe loading sample injector (Rheodyne USA). The detection was done at 266 nm and the signal was monitored on a chromatopac C-R 3A (Shinadzu Japan) electronic integrator at an attenuation of 3 or 4 and a chart speed of 0.5 cm/min. Patients were not allowed to take any other drugs which could affect plasma levels of nitroxazepine and its metabolites. Plasma levels on different doses were compared by students paired 't' test.

The tolerability of nitroxazepine was judged by monitoring of baseline complaints, reports of unwanted effects measurement of pulse and blood pressure, records of ECG and assessment of haematological and liver functions. The above variables were assessed before drug and after drug on days 14, 28 and 42.

Results

Ten patients (male 6, female 4) participated in the study.

The mean pre-drug HDRS was 31.2 and it dropped to 15.5 (50% reduction) by day 42. As none of the patients showed $>50\%$ reduction in HDRS by day 13, all of them received 225 mg of nitroxazepine between day 14 and 42 for 4 weeks.

Plasma Levels of Nitroxazepine and its Metabolites (Table-1)

As there were large variations in 0 hr. values of plasma levels of N and its metabolites, only 2 hour values have been included in the analysis. The plasma levels of N showed a significant rise ($p < 0.01$) from a mean level of 47.0 mg/ml on day 1 (dose 75 mg) to 129.8 mg/ml on day 7 (dose 150 mg) and remained fairly steady till day 21 and dropped to 97.0 ng/ml by day 42. Metabolite D also showed an increase from 29.6 ng/ml on day 1 to 62.1 ng/ml on day 7 ($p < 0.01$) and showed a similar pattern

TABLE I—Plasma Levels (ng/ml.) of Nitroxazepine and its Metabolites in Patients (N=10) (Mean+SEM)

Day	Nitroxazepine	Desmethyl	N-O	Carboxylic acid
1	47.0+7.3	29.6+3.1	40+3.3	398.9+45.4
4	53.4+14.9	42.4+5.9	43.0+6.3	474.9+83.7
7	129.8+24.6	62.1+8.7	68.6+15.7	577.9+94.9
14	117.5+25.4	75.1+10.5	70.6+15.7	560.7+90.5
21	132.8+14.7	118.5+13.8	86.9+8.4	770.2+86.9
28	106.0+28.9	93.5+13.9	61.6+14.2	472.7+80.6
35	96.3+19.1	86.9+9.1	61.7+15.6	602.2+97.3
42	97.0+18.7	79.4+8.6	60.9+14.0	617.0+102.1

thereafter, N-O and C metabolite also showed a significant rise by day 7 ($p < 0.05$). There were large inter individual variations in the plasma levels. However, there was no significant difference between the levels of N and its metabolites on day 21, 28, 35 and 42.

Relation between efficacy and plasma levels

It was difficult to correlate the HDRS reduction and plasma levels because of small number of patients and large interindividual variations. However, until day 13 when the dose titration was up to 150 mg reduction in HDRS was 19.7%. Later on, the HDRS scores dropped steadily over 4 weeks when steady levels of N and its metabolites were maintained.

Tolerability of Nitroxazepine

The drug was well tolerated and there were no drop-outs due to severe unwanted effects. The heart rate did not show any significant alterations. The supine and standing B. P. did not show any orthostatic hypotension even at a dose of 150 mg and above. There was no

significant change in PR, QRS and QTC intervals on ECGs taken after nitroxazepine. Haematological and liver functions before and after N did not show any significant abnormalities.

Discussion

The present study showed that nitroxazepine is an effective antidepressant showing a reduction of 50% in HDRS score. The drug was well absorbed in depressed patients and showed a dose dependent rise in plasma levels. The plasma levels were comparable to those observed in healthy volunteers with single dose of nitroxazepine of 75 and 150 mg. (Bhatia *et al.*, 1988). The plasma levels on nitroxazepine 150 mg were about twice as high as on 75 mg ($p < 0.01$). Nitroxazepine was metabolised extensively and showed rising levels of desmethyl, N-oxide and carboxylic acid metabolites over a period of 6 weeks.

The plasma levels of nitroxazepine and its metabolites showed a high interindividual variation. The variation is similar to that observed with other TCAs which show 10 to 30 fold variations in

plasma levels (Preston et al., 1988; De Oliveira et al., 1989) and could be due to differences in metabolism of TCAs. The total level of nitroxazepine and its metabolite desmethyl are in the range of 176.5 ng/ml to 251 ng/mg (meg/l) at the optimum and commonly used effective dose of 150 mg. There are relatively less number of studies of TCAs levels in Indian patients. However, the range of levels of N and D is comparable to the therapeutic levels of imipramine and desimipramine of between 150 to 300 meg (Preston et al., 1988; De Oliveira et al., 1988). At the optimum dose of 150 mg, the HDRS score also showed improvement suggesting that these levels are necessary for optimum therapeutic response.

The study also suggested that HORS scores are reduced by a single dose of nitroxazepine. Although, nitroxazepine has a short plasma half-life, the metabolites, desmethyl and carboxylic acid have long half-life of 8 and 15 hours respectively (Bhatia et al., 1988). Animal studies have shown that all the metabolites desmethyl, N-oxide and carboxylic have antidepressant activity (Nagarajan, 1972). It appears that the antidepressant activity seen with a single dose of drug is not only due to nitroxazepine but also due to its metabolites. It may be necessary to measure all the metabolites while judging therapeutic levels.

In conclusion, the present study has shown that nitroxazepine is well absorbed and metabolised in depressed patients into active metabolites. The doses of 150 mg and beyond, show plasma levels comparable to therapeutic levels with other TCAs and also show antidepressant efficacy. As suggested for other TCA, rapid titration of nitroxazepine dose to 150 mg might improve efficacy (Preston et al., 1988; De Oliveira et al.,

1989). However this needs to be confirmed by a special clinical and pharmacokinetic study incorporating rapid titration of dose based on plasma levels of nitroxazepine and its metabolites.

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