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Intravenous amine pressor tests in healthy volunteers

Within- and between subject variances and sex differences

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Summary. The pressor effect of intravenous tyramine (TYR) and noradrenaline (NA) has been evaluated, respectively, in 157 tests in 19 healthy unmedicated subjects, and in 202 tests in 24 similar subjects, all of whom took part in ≥ 3 test sessions.

The pressor dose (PD) that raised systolic blood pressure by 30 mm Hg (PD30) ranged from 2 to 8 mg for TYR, and from 3.5 to 17 $\mu g \cdot min^{-1}$ for NA. Coefficients of variation ranged from 3 to 47% and from 6 to 38% for TYR and NA, respectively, in the intra-subject comparison. The average inter-subject variation in the TYR PD30 was 22% for 8 females and 30% for 11 males; the corresponding variation in the NA PD30 was 27% (8 females) and 26% (16 males).

While the average PD30 for NA was similar for males (10.8 µg/min) and females (10.9 µg/min), a sex-related difference was found for the PD30 of i.v. TYR: 4.4 mg for 11 males and 3.8 mg for 8 females.

Additional results from volunteers who took part in fewer than 3 pressor test sessions supported this observation; PD30 of TYR 4.6 mg in 34 males vs 3.5 mg in 21 females.

The large intra- and inter-subject variations in the i.v. TYR and NA pressor test results, and the sex difference in the systolic blood pressure response to i.v. TYR, should be considered in assessing the number and gender of subjects required in studies intended to show "significant" differences in the blood pressure response in amine pressor tests.

Key words: Amine pressor test, Tyramine, Noradrenaline; intra-, inter-subject variance, sex difference, individual response, Brofaromine, Oxaprotiline

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Amine pressor tests have been extensively used to evaluate peripheral adrenergic activity [Ghose 1980] and its interaction with such drugs as tri- and tetracyclic antidepressants [Ghose et al. 1976, Ghose 1977], and monoamine oxidase inhibitors (MAOIs) [Blackwell 1967, Pettinger et al. 1968, Simpson et al. 1984, Pickar 1981, Bieck et al. 1982, 1983, 1989]. However, information on the reproducibility and any potential sex difference in test results are scarce [Ghose 1984, Pace et al. 1988]. Data from several studies in untreated or placebo treated young, healthy, female and male subjects, who were repeatedly challenged with i.v. TYR and NA are presented here. The results are discussed with respect to the variability of the rise in systolic blood pressure between and within subjects. Sex differences in the PD30 values have also been analyzed.

Materials and methods

Subjects

In the course of several studies a total of 55 healthy volunteers, aged between 18 and 44 y (21 f, 34 m), and 57 healthy volunteers between 20 and 44 y (20 f, 37 m) participated in i.v. TYR and/or i.v. NA pressor tests.

Nineteen of the subjects between 23 and 44 y (8 f, 11 m) participated repeatedly in i.v. TYR pressor tests at least 3 times and up to 11 times. Of the healthy subjects aged 23 to 44 y (8 f, 16 m) 24 participated in NA pressor tests which were performed on 4 to 11 occasions. All 19 subjects participating in i.v. TYR pressor tests also took part in the i.v. NA pressor tests. The volunteers were not taking any medicines except for contraceptives.

21 (5 f, 16 m; 18–31 y) and 17 (4 f, 13 m; 23–31 y) of the healthy volunteers also participated in i.v. TYR and NA tests, after having been treated daily for 1–2 weeks with the specific, reversible monoamine oxidase A (MAO A) inhibitor brofaromine 150 mg/d p.o. (CGP 11 305 A). Six (5 f, 1 m, 26–29 y) of those volunteers took part in additional i.v. TYR and NA tests after having been treated daily for 10 days with the NA uptake inhibitor S-(+)-oxaprotiline 50 mg/d p.o. (CGP 12 104 A).

Before participation, each of the volunteers was found to be healthy, as determined by medical history, physical examination, routine laboratory tests (haematology, blood chemistry, urinalysis) and ECG. All volunteers were ambulant and were engaged in their usual activities. Each subject gave informed, written consent that was revocable at any time of the trial. The Ethics Committee of the Human Pharmacology Institute, CIBA-GEIGY, Tübingen, raised no objections to the design or procedures of the study.

Table 1. Intra- and interindividual variability of the i.v. TYR PD30 in 19 untreated or placebo-treated subjects who had participated in ≥ 3 Tyr pressor tests

Subject	Sex	Number of test 1	2	3	4	5	6	7	8	9	10	11	Mean (SD)	CV %[a]
1	male	2.0	3.0	3.0	4.3	4.0	4.0	4.3	4.0	2.5			3.4 (0.8)	24
2	male	4.0	4.5	4.5	4.0	4.0	4.5	3.7	3.0	4.0	4.0	3.7	4.0 (0.4)	11
5	male	5.0	3.7	4.0	4.5	4.5	5.0	5.5	4.5	4.5			4.6 (0.6)	12
6	male	8.0	5.0	3.0									5.3 (2.5)	47
7	male	6.0	6.0	8.0	4.3	6.0	6.0	6.0	6.0	4.5	6.0		5.9 (1.0)	17
8	male	4.5	4.3	3.7	4.0	4.0	4.5	4.5	3.7	4.0			4.1 (0.3)	8
11	male	3.3	4.0	4.0	4.5	4.0	4.0	4.5	3.7	4.0	4.0		4.0 (0.4)	9
12	male	2.3	2.0	2.5	2.3	3.0	2.7	2.0	2.0	2.5	2.8		2.4 (0.4)	15
13	male	7.0	8.0	8.0	6.0	7.0	7.0						7.2 (0.8)	10
14	male	3.0	5.0	4.0	4.5	5.0	4.0	4.0					4.2 (0.7)	17
15	male	3.0	3.0	4.0	4.5	3.0	2.5	3.0	2.0	3.0			3.1 (0.7)	24
Mean (SD) ($n = 11$)													4.4 (1.3)	18 (11)
CV %													30	
3	female	5.0	3.3	4.5	4.0	4.0	3.0	3.0	3.5	5.5	5.0	4.0	4.1 (0.9)	21
4	female	2.5	3.0	2.3	2.5	2.0	2.5	2.3	2.5	2.5	2.5		2.5 (0.3)	10
9	female	4.5	5.0	4.5	5.0	5.0	6.0	4.5	5.0	3.7			4.8 (0.6)	13
10	female	4.5	5.0	5.0	4.0	4.0	5.0	5.0	5.0	4.7			4.7 (0.4)	9
16	female	4.0	4.5	4.0	3.0	4.0	4.0	3.0					3.8 (0.6)	15
17	female	4.0	4.0	4.0	4.0	4.3	4.0	4.0					4.0 (0.1)	3
18	female	2.8	2.8	2.8	2.5	3.0	2.8	2.8					2.8 (0.2)	5
19	female	4.0	3.5	3.5	4.0								3.8 (0.3)	8
Mean (SD) ($n = 8$)													3.8 (0.8)	11 (6)
CV %													22	

[a] CV % = coefficient of variation in percent ([SD/Mean] × 100)

Table 2. Intra- and interindividual variability of the i.v. NA PD30 in 24 untreated or placebo-treated subjects who had participated in ≥ 3 NA pressor tests

Subject	Sex	Number of test 1	2	3	4	5	6	7	8	9	10	11	Mean (SD)	CV %[a]
1	male	13.0	10.0	10.0	13.0	13.0	14.0	12.0	12.0	16.0			12.6 (1.9)	15
2	male	8.0	8.0	9.0	9.0	10.0	9.0	8.0	9.0	8.0	7.6		8.6 (0.7)	8
3	male	7.0	10.0	10.0	10.0	12.0	9.0	10.0	11.0				9.9 (1.5)	15
6	male	13.0	11.0	13.0	8.0	13.0	14.0	10.0	15.0	13.0			12.2 (2.2)	18
7	male	7.0	4.0	6.5	6.0	5.0	5.0	4.5	8.0	9.0	4.0	4.0	5.7 (1.7)	30
8	male	16.0	13.0	14.0	16.0	12.0	16.5	13.0	17.0	14.0			14.6 (1.8)	12
9	male	14.0	14.0	12.0	6.0	10.0	12.0	8.0	10.0	7.0			10.3 (2.9)	28
12	male	16.0	14.0	15.0	17.0	14.0	16.0	16.0	15.0	15.0	15.0		15.3 (0.9)	6
13	male	11.0	13.0	11.0	7.0	11.0	15.0	14.0	11.0	9.0	11.0		11.3 (2.3)	20
14	male	12.0	14.0	14.0	16.0	14.0	14.0	15.0					14.1 (1.2)	9
15	male	13.0	13.0	11.0	14.0	10.0	12.0	14.0					12.4 (1.5)	12
16	male	6.0	4.0	7.0	7.0	7.0	6.0	5.0	12.0				6.8 (2.4)	35
20	male	8.0	8.0	8.0	9.0	7.0	8.0	8.0					8.0 (0.6)	8
22	male	9.0	14.0	13.0	9.0	9.0	9.0	11.0	10.5				10.6 (2.0)	19
23	male	11.5	11.0	9.0	14.0	12.0	12.0	14.0	15.0				12.3 (1.9)	15
24	male	8.0	14.0	6.0	10.0	5.0	5.0	9.0	12.0				8.6 (3.3)	38
Mean (SD) ($n = 16$)													10.8 (2.8)	18 (10)
CV %													26	
4	female	10.0	10.0	17.0	6.0	11.0	13.0	7.0	16.0	8.0	14.0	14.0	11.5 (3.6)	31
5	female	8.0	8.0	11.0	7.0	7.0	7.0	11.0	4.0	3.5	8.0		7.5 (2.5)	33
10	female	17.0	10.0	16.0	14.0	17.0	15.0	15.0	16.0	17.0			15.2 (2.2)	14
11	female	12.0	13.0	14.0	14.0	15.0	10.0	15.0	14.0	15.0			13.6 (1.7)	13
17	female	12.0	10.0	12.0	9.0	15.0	11.0	10.0					11.3 (2.0)	18
18	female	10.0	10.0	8.0	9.0	11.0	8.0	9.0					9.3 (1.1)	12
19	female	6.0	7.0	6.0	7.0	7.0	7.0	7.0					6.7 (0.5)	7
21	female	9.0	10.0	12.0	17.0								12.0 (3.6)	30
Mean (SD) ($n = 8$)													10.9 (2.9)	20 (10)
CV %													27	
Total Mean (SD) ($n = 24$)													10.9 (2.8)	19 (10)
CV %													26	

[a] CV % = coefficient of variation in percent ([SD/Mean] × 100)

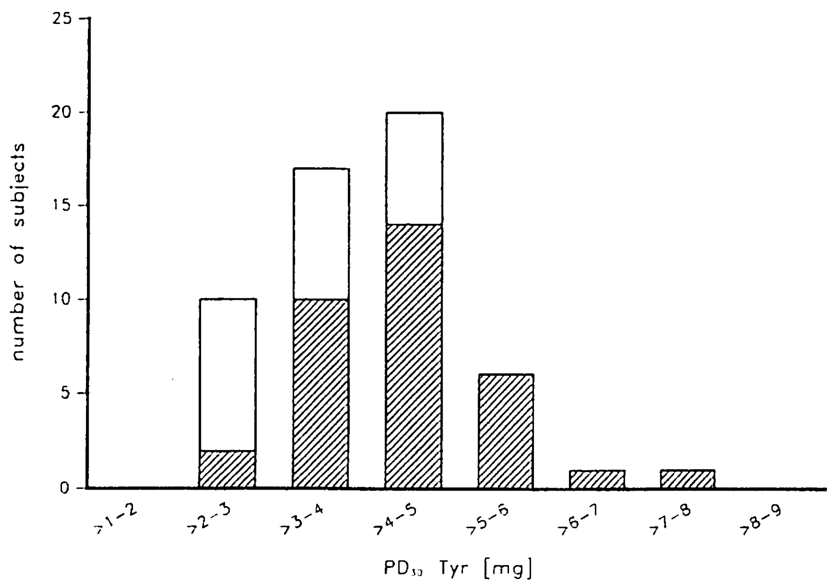

Fig. 1. The mean i. v. dose of Tyr [mg] required to produce a quantal blood pressure response ≥ 30 mm Hg (PD30) in 55 individuals (21 females, 34 males) in 234 i. v. pressor tests. ☐ female (mean: 3.5 (0.7), $n = 21$) ▨ male (mean: 4.6 (1.1), $n = 34$)

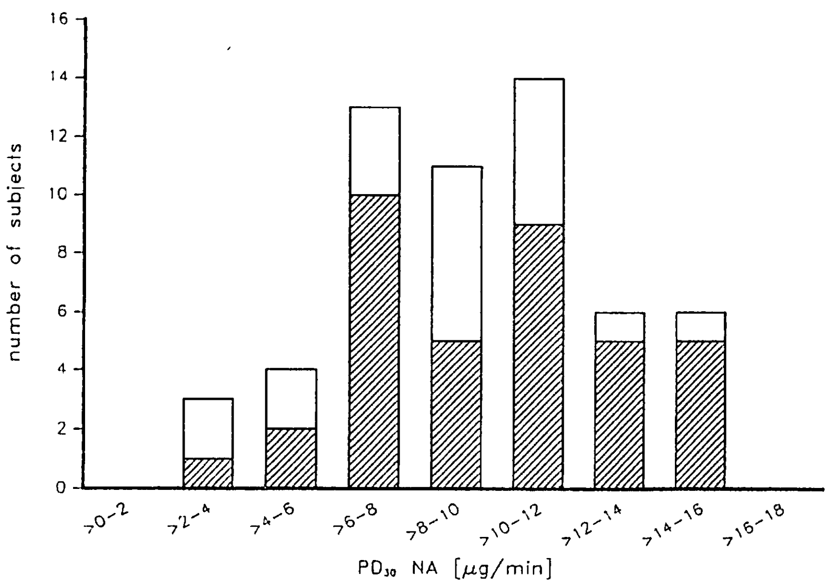

Fig. 2. The mean i. v. dose of NA [µg/min] required to produce a quantal blood pressure response of ≥ 30 mm Hg (PD30), determined in 57 individuals (20 females, 37 males) in 276 i. v. pressor tests. ☐ female (mean: 9.0 (3.4), $n = 20$) ▨ male (mean: 10.0 (3.2), $n = 37$)

Intravenous amine pressor tests

Tests were performed in the morning after a 12 h fast. The test subject rested on a bed at a comfortable room temperature. The ECG obtained from three precordial leads (V1, V4 and V6) was monitored on a Hellige Servocard 132 (Hellige, Freiburg, FRG) throughout the test period. Systolic blood pressure and heart rate were recorded every 30 s (TYR) or 60 s (NA). Blood pressure was measured with an automatic haemodynamometer (Boso BC 40, Boso Digimat C; Bosch, Jungingen, FRG). Heart rate was taken from the ECG.

The test was started after 30 min rest in bed to permit stabilisation of the blood pressure. The dose of amine was increased up to an amount which produced a rise in systolic blood pressure of at least 30 mm Hg (PD30). Blood pressure and heart rate were recorded until the effect had disappeared. Through an indwelling cannula (butterfly® -21 or Abbocath®-T 20G) isotonic saline was infused slowly into an antecubital vein. Rising bolus doses of TYR (1 mg–8 mg) were injected over 15 s via a three-way stopcock, and the transient increase in blood pressure was recorded. The dosage was increased until the PD30 was reached. After returning to the basal blood pressure, NA in isotonic saline was infused in rising doses from 2–17 µg·min⁻¹ (Infusomat® II); Braun, Melsungen, FRG). The infusion rate of NA was increased after obtaining three consecutive, equal blood pressure readings until the PD30 was reached.

Calculations and statistical analysis

The amount of amine (mg TYR or $\mu g \cdot min^{-1}$ NA) required to increase systolic blood pressure by at least 30 mm Hg was calculated as the Pressor Dose 30 (PD30). Means and standard deviation (SD) are given. The coefficient of variation was calcuated as CV [%] = (SD/mean)*100.

Results

Over several studies, the pressor effects of i. v. TYR and NA have been evaluated in 157 and 202 pressor test sessions, respectively. The large range of TYR PD30 values in individ-

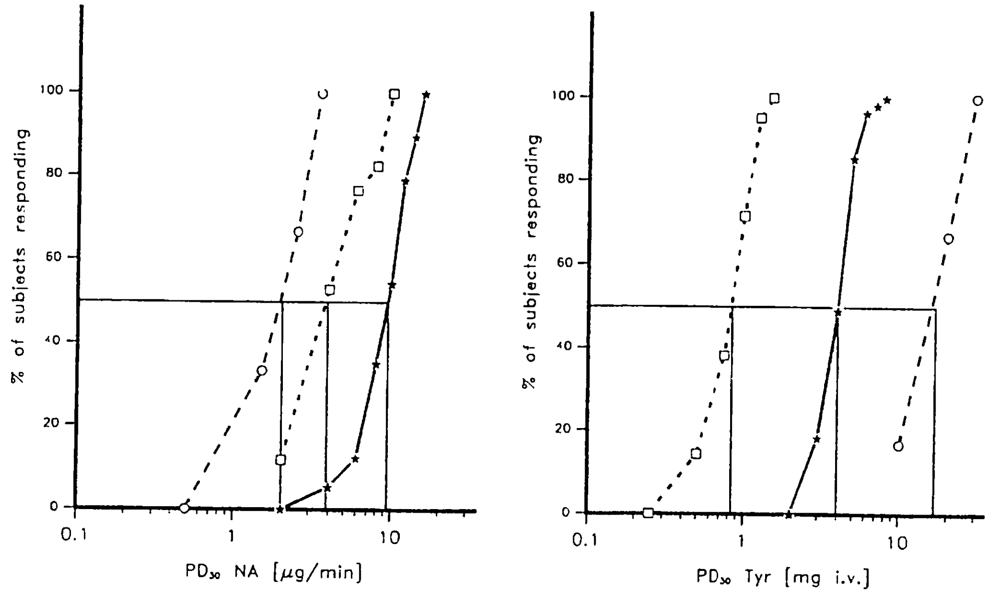

Fig. 3. Cumulative frequency distribution of PD30 values for NA and TYR in unmedicated subjects, on Day 10 of treatment (25 mg b.i.d. p.o.) with the NA uptake inhibiting compound S-(+)-oxaprotiline (CGP 12104 A), or on Days 7–14 of treatment (150 mg daily p.o.) with the MAO A inhibitor brofaromine (CGP 11305 A)
—*— unmedicated NA ($n = 57$), TYR ($n = 55$)
--O-- S-(+)-Oxaprotiline, NA and TYR ($n = 6$ each)
---□--- Brofaromine, NA ($n = 17$), TYR ($n = 21$)

ual subjects is shown in Table 1. The lowest PD30 for TYR was 2.0 mg and the highest was 8.0 mg. The intraindividual variation, expressed as the coefficient of variation (CV%), ranged from 3 to 24%, and in 13 out of 18 volunteers it was in the range between 3 and 15%. One subject, in whom the smallest number of only 3 tests had been performed, showed the highest variation of 47% (volunteer 6). The range of mean intra-subject PD30 values was wider (2.4–7.2 mg), the group mean PD30 value (SD) was slightly higher (4.4 (1.3) mg) and the CV values were higher (18 (11)%) in the 11 males than in the 8 females (range 2.5–4.8 mg; mean (SD) 3.8 (0.8) mg; CV 11 (6)%).

The corresponding data for NA are summarized in Table 2. The PD30 values in different subjects ranged from 3.5 to 17 µg·min^{-1}. The intraindivudal CV% was between 6 and 38%; 17 out of 24 volunteers showed values between 5 and 20%, and in 7 volunteers the CV lay between 25 and 40%. The range of mean intra-subject PD30 values, the group mean PD30 values and CV% values were not different in 16 males (range 5.7–15.3 µg·min^{-1}; mean (SD) 10.8 (2.8) µg·min^{-1}; CV 18 (10%) and 8 females (range 6.7–15.2 µg/min; mean (SD) 10.9 (2.9) µg·min^{-1}; CV 20 (10)%).

The frequency distributions of the mean individual PD30s of TYR and NA in a population of 55 and 57 healthy young subjects are shown in Figs. 1 and 2. In addition to the 19 and 24 volunteers with ≥3 pressor tests sessions, whose data were evaluated for intra-subject variance, the two histograms also include data from volunteers of similar age and health state who participated in fewer than 3 pressor test sessions.

The distribution of the NA PD30 values appeared to be of Gaussian type and showed no major difference between males and females (mean of 37 males 10 (3.2) µg·min^{-1} vs mean of 20 females 9 (3.4) µg·min^{-1}). However, TYR PD30 values seemed not be equally distributed and to show a shift to higher doses in males: mean of 34 males 4.6 (1.1) mg vs mean of 21 females 3.5 (0.7) mg (significantly different: $p < 0.01$).

Examples of drug effects are shown in Fig. 3. The MAO A inhibitor brofaromine shifted the frequency distribution curves to the left, both for TYR and for NA. In contrast, the NA uptake inhibitor S-(+)-oxaprotiline shifted the NA curve to the left and the TYR curve to the right.

Discussion

NA shows a clear, dose-dependent relationship between the infusion rate (µg·min^{-1}) and the increase in systolic blood pressure. The dose-related response to TYR was more predictable and more reliable when TYR was administered as a bolus injection. This observation, recently confirmed by the methodical work of PACE et al. [1988], led to the procedure of infusing NA and rapidly injecting TYR in all our i.v. pressor tests [Bieck et al. 1982, 1983, 1989].

The degree of intra-subject variability was similar for both i.v. catecholamine tests.

Fifteen out of 19 subjects, who had taken part both in TYR and NA i.v. pressor tests, showed similar sensitivity towards both catecholamines. Three volunteers seemed to be more sensitive to TYR than to NA, and one subject seemed more sensitive to NA than to TYR.

The 4-fold range of PD30 for TYR (2–8 mg), and the 5-fold range of PD30 for NA (3.5–17 µg·min^{-1}), in drug-free young healthy subjects reflects the well known inter-individual difference in sensitivity to catecholaminergic compounds. This might be influenced by such factors as the varying tone of the sympathetic nervous system, varying numbers of adrenergic receptor sites and pharmacokinetic differences in volunteers. For ethical reasons human pharmacological investigations deal with relatively small numbers of healthy young people. They are mostly designed as placebo controlled cross-over studies. Therefore, the "pre-study" intrasubject variance of the parameters chosen for the subsequent evaluation of drug effects is important. In addition to the expected extent of drug induced changes in the PD30 values, the variance estimate of the PD30 of pressor amines is the major determinant of the number of volunteers necessary in studies designed to show a "significant" drug effect. Pace et al. [1988] reported sample size calculations in this context.

The gender of the volunteers should also be taken into consideration, at least in TYR pressor tests. Ghose et al. [1976] pointed out that male volunteers on average needed more TYR than females in order to produce an increase in the systolic blood pressure of 30 mm Hg. In that study, the mean PD30 for TYR was 6.5 mg for men ($n = 4$) and 4.7 mg for women ($n = 6$, $P < 0.10$). This observation has now been confirmed by our data showing a significant difference between sexes in the PD30 values of TYR.

Presentation of "normal" mean individual PD30 values as a cumulative frequency distribution results in S-shaped curves for both NA and TYR (Fig. 3). An MAO A inhibitor, such as brofaromine, shifts the curves for both pressor amines to the left, thereby signalling higher sensitivity to these pressor amines of subjects during treatment with a MAO A inhibitor. Drug-induced changes, exemplified here by data after treatment with the NA-uptake inhibitor S-(+)-oxaprotiline (CGP 12104 A), shifted the TYR curve to the right, indicating decreased sensitivity of the subjects to the indirect acting sympathomimetic TYR. However, the NA curve was shifted to the left, which suggests increased sensitivity to the direct acting sympathomimetic NA.

In comparison with many "normal" data from a large number of untreated volunteers, even data from only six volunteers made these drug-related changes stand out very clearly.

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