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Monoamine oxidase inhibition by phenelzine and brofaromine in healthy volunteers

The two monoamine oxidase (MAO) inhibitors phenelzine and brofaromine given for 2 to 3 weeks were compared in six volunteers. Blood pressure sensitivity to intravenous tyramine increased 2.6-fold during phenelzine (60 mg/day) and 4.8-fold during brofaromine, whereas sensitivity to oral tyramine increased more during phenelzine (15.7-fold vs 8.5-fold). After withdrawal of phenelzine, pressor sensitivity to oral tyramine returned to control values within 2 and for more than 8 weeks. Relative bioavailability of conjugated tyramine was elevated sixfold by brofaromine and 11.6-fold by phenelzine. Urinary elimination of tryptamine increased during phenelzine and brofaromine to 12.7-fold and threefold, respectively. 3-Methoxy-4-hydroxyphenylglycol (MHPG) and 3-methoxy-4-hydroxymandelic acid (VMA) excretion decreased during brofaromine significantly by 72% and 49%, respectively. The nonsignificant decrease of MHPG excretion and the increase of intravenous tyramine pressor sensitivity caused by phenelzine are significantly related. The data suggest that the selective reversible MAO-A inhibitor brofaromine has a larger therapeutic safety than phenelzine. (CLIN PHARMACOL THER 1989;45:260-9.)

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Monoamine oxidase (MAO) inhibitors were the first effective antidepressant drugs. In controlled studies they proved to be as effective as tricyclics in the treatment of typical and so-called atypical depression.[1-3] Therapy with traditional MAO inhibitors, such as phenelzine or tranylcypromine, is limited by their interaction with tyramine-containing food (hypertensive crisis, so-called cheese effect).[4] They have caused hyperthermic episodes when therapy was immediately switched to tricylic antidepressive drugs.[5] There is evidence that these serious side effects are related to the nonspecific and irreversible nature of MAO inhibition.[6]

There are two major MAO isozymes. In human beings, MAO-A acts preferentially on serotonin and norepinephrine (NE) and MAO-B deaminates preferentially phenylethylamine and dopamine. In recent years new MAO inhibitors have been developed that block MAO in a selective and reversible manner. They are expected to produce a small or no hypertensive reaction and to have a short action after withdrawal because they are easily detached from the enzyme.[3]

Brofaromine is a new reversible MAO inhibitor with a plasma half-life of about 16 hours that preferentially inhibits form A of MAO.[7-10] It is effective in the treatment of depression,[11,12] increases pressor sensitivity less and with shorter duration than tranylcypromine,[13] and influences urinary monoamine metabolites.[14] Its effects have not been compared with those of phenelzine, which binds irreversibly to both forms A and B of the MAO enzyme. A comparison is of theoretical and practical interest because of the different mechanisms of action and the expected larger therapeutic safety of brofaromine.

The aim of the present comparative, controlled study in healthy volunteers was severalfold: (1) assessment of tolerability in healthy human beings; (2) investigation of the interference with the pressor effects of intravenous tyramine, NE, and phenylephrine to see if the effects are restricted to MAO inhibition; (3) determination of the extent by which the pressor effect of oral tyramine is potentiated and the speed wherewith this

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Table I. Volunteers in the study

Volunteer	*Sex*	*Weight (kg)*	*Age (yr)*	*Acetylation*	*Hydroxylation*	*Sequence of administration*
1	M	70	20	Slow	Fast	Phen Brof
2	M	76	31	Fast	Fast	Brof Phen
3	M	74	25	Fast	Fast	Brof Phen
4	M	64	27	Unknown	Intermediate	Brof Phen
5	M	57	29	Slow	Fast	Brof Phen
6	M	71	28	Fast	Fast	Brof Phen
Mean		69	27			

Phen, phenelzine; Brof, brofaromine.

effect disappears after cessation of treatment; (4) comparison of pressor responses to oral and intravenous tyramine; (5) estimation of the relative oral bioavailability of tyramine by analysis of plasma tyramine concentrations; and (6) measurement of the effects on excretion of endogenous monoamine metabolites.

METHODS

No objections against design and procedures of the study were raised by the Ethical Committee of the Human Pharmacology Institute, Ciba-Geigy, Tübingen. The members of this committee are independent of the company and are professors of law, medicine, or theology at the Universities of Freiburg or Tübingen. Written, informed consent was obtained. Because the study was designed to measure biologic effects and not designed to be a controlled therapeutic experiment, it was not considered necessary to "blind" the subjects to their treatment.

Subjects

The study was done in six healthy male subjects (Table I) aged 20 to 31 years (mean 27 years) who weighed 57 to 76 kg (mean 69 kg). All subjects were shown to be healthy by medical examination that included physical status, hematology, blood chemistry, urinalysis, and ECG. Hydroxylator and acetylator phenotype was determined.[15,16] The test persons were not allowed to take any other drugs starting 2 weeks before the trial. The intake of tyramine-rich food and alcohol was not permitted during the study. All volunteers were ambulatory and carried out their usual activities.

Dosage regimen

With a drug-free interval of at least 2 weeks between the first and second courses, the following oral treatment schedules were applied: (1) During the first course all subjects except volunteer 1 received daily for 14 days 150 mg brofaromine hydrochloride (50 mg t.i.d.; CGP 11 305 A; Ciba Geigy AG, Basel, Switzerland). The dosage was chosen because daily administration of 100 to 150 mg brofaromine exerted a definite antidepressant effect in patients with endogenous depression (Schiwy W, unpublished results). (2) During the second course the subjects took phenelzine sulfate tablets (Nardil) for 3 weeks in weekly increasing doses of 30 mg (15 mg b.i.d.), 45 mg (15 mg t.i.d.), and 60 mg (30 mg b.i.d.).

In volunteer 1 the sequence of the two treatment courses was reversed. He had a treatment-free interval of 3 months between the last dose of phenelzine and the first dose of brofaromine.

Procedures

Pressor tests. Before, at the end of each treatment period, and several times after phenelzine, three types of pressor tests were done by experienced physicians on three consecutive test days with full resuscitative measures available. The volunteers rested on a bed at a comfortable temperature. ECG obtained from three precordial leads was monitored throughout the test periods. The test was started after 30 minutes of bed rest to allow for equilibration of blood pressure (BP). To reverse an excessive rise in BP, phentolamine (Regitine) was available to be administered by intravenous infusion (50 mg) in isotonic saline solution. An indication for phentolamine was given when (1) the systolic BP rose by more than 60 mm Hg or beyond 180 mm Hg, (2) the heart rate (HR) fell below 40 beats/min (3) pathologic ECG changes developed, or (4) subjects complained about severe headache or other serious side effects. Phentolamine was infused at a rate and dose guided by fall in BP and HR achieved.

On the first test day, intravenous pressor tests[17] were done in fixed sequence: tyramine was administered by bolus intravenous injections, whereas NE and phenylephrine were infused with an infusion pump via a cannula in an antecubital vein. The dosage was elevated

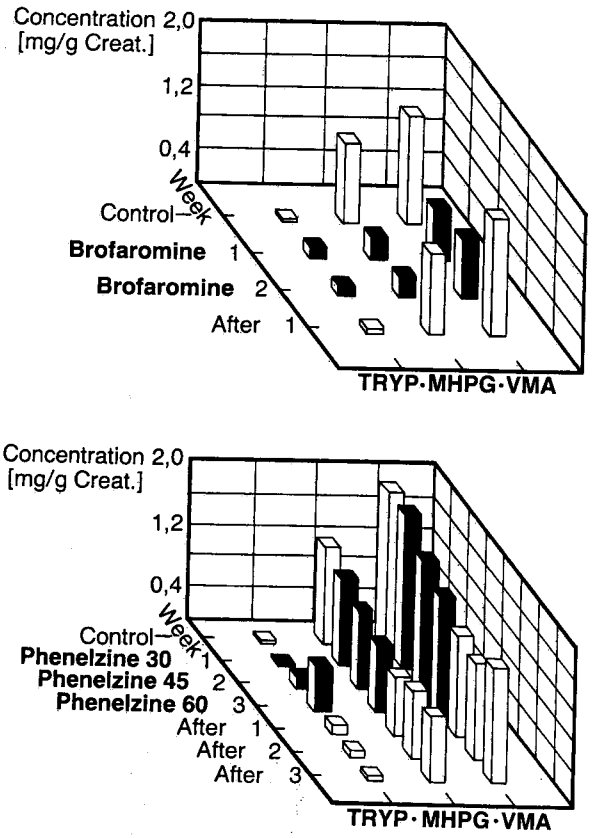

Fig. 1. Urinary excretion (mg/gm creatinine) of tryptamine (TRYP), MHPG, and VMA before, during, and after treatment of six subjects with brofaromine and phenelzine.

by stepwise increases in the infusion rate. BP was recorded at ½- or 1-minute intervals with an automatic hemodynamometer (Boso BC 40, Bosch, Jungingen, West Germany). After BP had returned to normal or reached steady state (three consecutive equal readings of systolic BP), the next dose of amine was given until an increase of at least 30 mm Hg (PD_{30}) was reached.

On the second test day, oral tyramine tests were done in the morning after a 12-hour fasting period. Tyramine capsules (tyramine hydrochloride) were ingested with 100 ml water while the subject was sitting. The initial dose in untreated volunteers was 200 mg and in treated subjects 12 mg tyramine HCl. BP and HR were monitored every 3 minutes. The dose of tyramine was increased stepwise tailored to each subject until the PD_{30} was reached. After each dose, BP and HR were recorded for 1 hour or until an effect had disappeared.

Tyramine kinetics. On the third test day the PD_{30} of tyramine found on the previous day or a lower dose (in case of previous phentolamine administration) was given to study tyramine kinetics. Tyramine capsules were given as a single oral dose with 100 ml water to the fasted subjects at 8 AM. BP, HR, and ECG were monitored as described before. Blood was drawn from an antecubital vein for tyramine analysis at the following times: 0, ¼, ½, ¾, 1, 1¼, 1½, 1¾, 2, 2¼, 2½, 2¾, 3, 3½, 4, 4½, 5, 5½, 6, 6½, and 7 hours. Plasma was prepared immediately and samples were frozen at −20° C until analysis.

Assessment of unwanted effects

The state of well-being was rated by each volunteer daily during the entire study on 17-stage scales and evaluated with a special computer program. The subjective sleep quality was assessed on a four-score rating scale (KUSTA).[18] Also, unwanted effects were recorded spontaneously.

Urinary amine metabolites

Twenty-four-hour urine samples were collected daily in 2 L bottles containing 40 ml 20% sodium hydrogen sulfite solution. Total volume was measured and aliquots of 10 ml were kept frozen at −20° C until analysis. The urinary excretion of total 3-methoxy-4-hydroxyphenylglycol (MHPG), 3-methoxy-4-hydroxymandelic acid (VMA), and tryptamine was determined with specific methods. MHPG was measured with capillary GC,[19] tryptamine by fluorometric detection after HPLC separation,[20] and VMA by electrochemical detection after HPLC separation (Bieck PR and Kowolik E, unpublished results). Urinary creatinine was determined by the standard Jaffe reaction in a Beckman Creatinine Analyzer 2 (Beckman Instruments, Inc., Fullerton, Calif.).

Plasma tyramine

Unconjugated tyramine. One milliliter plasma containing 3-methoxytyramine as internal standard was precleaned by adsorption on a Bond-elut C^{18} column (Bond Optics Inc., Lebanon, N.H.). After washing with 2 ml water, tyramine was eluted with 3 ml methanol. The recovery from the Bond-elut C^{18} column was 78% for tyramine and 84% for 3-methoxytyramine. Methanol was evaporated with a stream of nitrogen at 30° C and the residue dissolved in 200 µl 0.1 mol/L NaH_2PO_4 (pH 2.0). After extraction with 200 µl ethyl acetate, 50 µl of the aqueous phase was injected into the HPLC system. Tyramine was detected by electrochemical detection (Bioanalytical Systems, Inc., West Lafayette, Ind.) at 0.90 V. The limit of quantitation was 5 ng/ml. The coefficient of variation was 6.9% or less (n = 18; triple determination).

Conjugated tyramine. Conjugated tyramine in plasma was hydrolyzed by treating 0.5 ml plasma with

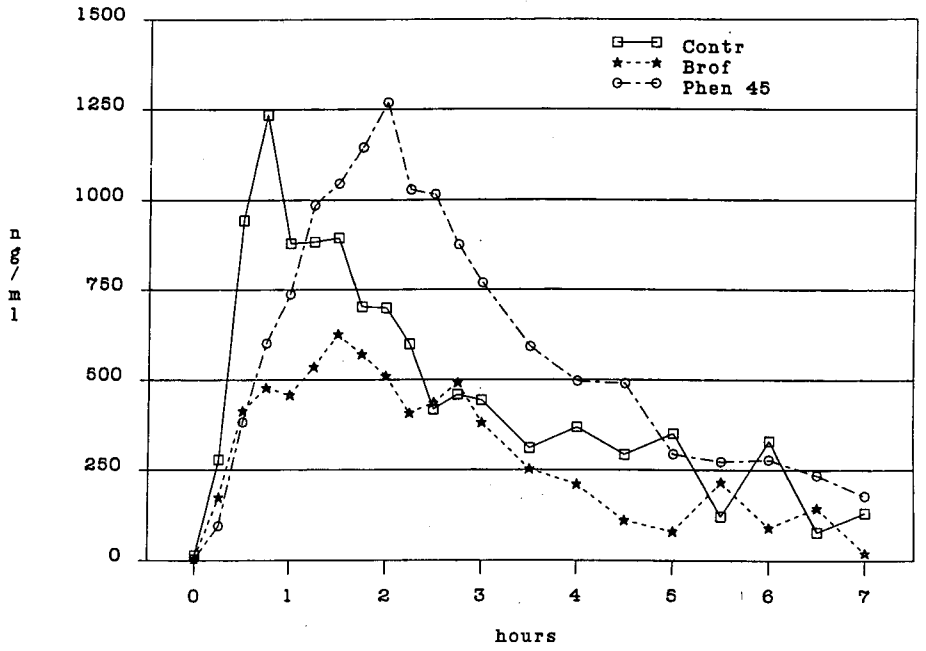

Fig. 2. Mean plasma concentrations of conjugated tyramine in six subjects after oral tyramine load. Controls *(Contr)*: 421 ± 110 mg, brofaromine *(Brof)*: 54 ± 17 mg; phenelzine, 45 mg/day *(Phen 45)*: 60 ± 15 mg. For visual purposes the SD values are not depicted. Coefficient of variation (SD/mean · 100) ranged between 29% and 85% (controls), 15% and 77% (brofaromine), and 15% and 68% (phenelzine).

a mixture of 10 μl glucuronidase plus sulfatase (Sigma Chemical Co., St. Louis, Mo., G 0876) for 16 hours at 37° C. Plasma containing 3-methoxytyramine as internal standard was precleaned by adsorption on a Bond-elut C^{18} column as described above. Twenty microliters was injected into the HPLC system. Tyramine was detected with either fluorometric detection at 197/300 nm or ultraviolet detection at 223 nm.

Calculations

The urinary concentrations of MHPG, VMA, and tryptamine were calculated as milligrams per gram of creatinine. Changes of the urinary elimination of these metabolites during treatment were expressed as percentage of the pretreatment values.

To express the change of sensitivity to tyramine (PD_{30} ratio), the control dose (no MAO inhibitor = PD_{30} control) was divided by that obtained during MAO inhibitor administration (PD_{30} MAOI): PD_{30} ratio = PD_{30} control/PD_{30} MAOI.

From plasma concentrations of tyramine the AUC(0-7) was calculated by the linear trapezoidal rule. The AUC was normalized by dividing by the tyramine dose given (AUC_{spec}). The relative bioavailability was calculated: AUC_{spec} (MAOI)/AUC_{spec} (control).

Means ± SD are given. Differences were tested by ANOVA and a posteriori test (Dunnett *t* test). Correlations were calculated with linear regression analysis.

RESULTS

Tolerability. All volunteers tolerated both treatments well. Brofaromine and phenelzine did not influence BP, HR, or blood chemistry. However, they were not entirely free from causing unwanted effects. Brofaromine caused a mean weight loss of 0.6 kg, probably because of decreased appetite. The weight did not change during phenelzine treatment. All volunteers slept less well during brofaromine. Amount and quality of sleep were reduced starting 2 days after the beginning of treatment. First there were no sleep disturbances during phenelzine, but they appeared after withdrawal between days 1 and 9. Activity scores decreased slightly in volunteers during brofaromine and in two subjects during the daily dose of 30 and 45 mg phenelzine.

Endogenous urinary amine metabolites

Brofaromine (Fig. 1). Tryptamine excretion increased 2.7-fold (from 0.056 to 0.153 mg/gm creatinine; $p < 0.05$) during brofaromine. It returned to control values within the first week after treatment was

Table II. Kinetic parameters of conjugated tyramine during MAOI treatment in six subjects

	Tyramine load (mg)	*AUC(0-7) ([ng/ml] · hr)*	*$AUC(0\text{-}7)_{spec}$ ([ng/ml] · hr · mg^{-1})*	*Relative bioavailability*
Control	421 ± 110	2991 ± 1159	9.4 ± 3.7	
Brofaromine	54 ± 17	1961 ± 311	49.1 ± 14.4‡	6.0 ± 2.6
Phenelzine 30	115 ± 34	1890 ± 364	23.6 ± 12.0	2.7 ± 1.2
Phenelzine 45	60 ± 15	3960 ± 668	89.1 ± 31.8†	11.3 ± 6.2
Phenelzine 60	30 ± 7	2326 ± 763	121.5 ± 77.0†	11.6 ± 9.1
(n = 4)				

Data are means ± SD.
Tyramine was administered as tyramine HCl.
†$p < 0.01$; ‡$p < 0.05$, a significant difference from those of the control group.

Table III. Increase of tyramine pressor sensitivity (PD_{30} ratio) during MAOI treatment in six subjects

	Tyramine P.O. (mg)	*PD_{30} ratio*	*Tyramine IV (mg)*	*PD_{30} ratio*	*NE IV (μg · min^{-1})*	*PD_{30} ratio*	*PE IV (μg · kg^{-1} · min^{-1})*	*PD_{30} ratio*
Control*	475 ± 120		4.6 ± 1.3		7.8 ± 2.3		1.6 ± 0.6	
Brof	55 ± 19†	8.5 ± 1.3	1.0 ± 0.2†	4.8 ± 1.3	2.6 ± 0.8‡	2.9 ± 0.9	0.6 ± 0.2†	3.0 ± 1.7
Phen 30	127 ± 49†	4.0 ± 0.8	4.3 ± 2.2	1.2 ± 0.5	6.8 ± 3.3	1.3 ± 0.6	1.4 ± 0.6	1.2 ± 0.3
Phen 45	60 ± 15†	8.4 ± 2.8	2.7 ± 0.8‡	1.8 ± 0.6	7.3 ± 1.9	1.1 ± 0.4	1.3 ± 0.5	1.3 ± 0.6
Phen 60	33 ± 11†	15.7 ± 6.1	1.9 ± 0.4†	2.6 ± 1.1	7.5 ± 3.3	1.2 ± 0.7	1.2 ± 0.7	1.7 ± 0.7

PE, phenylephrine; Phen, phenelzine; Brof, brofaromine.
Tyramine was administered as tyramine HCl.
*Mean of two pressor tests for each subject.
†$p < 0.01$; ‡$p < 0.05$, a significant difference from those of the control group.

stopped. Total MHPG excretion was decreased significantly ($p < 0.01$) (from 1.15 mg/gm creatinine) by 69% during the first week and 72% during the second week of brofaromine. It returned to control values rapidly after treatment was stopped. Urinary excretion of VMA mirrored the changes of MHPG.

Phenelzine (Fig. 1). During the two higher doses of phenelzine, tryptamine excretion increased 3.1-fold ($p < 0.05$) and 12.7-fold ($p < 0.01$) (from 0.047 to 0.146 and 0.597 mg/gm creatinine). Tryptamine was still about twice normal (no significant difference) in the second week after phenelzine was stopped. A small reduction of MHPG excretion (maximally −28%) was observed during phenelzine (60 mg/day, third week) and in the week after discontinuation of phenelzine (−39%). Again, the excretion of VMA mirrored that of MHPG. All changes of MHPG and VMA during phenelzine were statistically not significant.

Relative bioavailability of tyramine

In several volunteers, concentrations of unconjugated tyramine after tyramine load were not measurable or were below the limit of quantitation (5 ng/ml). The concentrations of unconjugated tyramine, expressed as AUC(0-7), before and during MAO inhibition ranged between 1% and 3% of total tyramine measured in plasma. Therefore relative bioavailability was calculated from the amounts of conjugated tyramine in plasma. Fig. 2 shows comparatively the mean concentrations of six subjects in the untreated state after a mean PD_{30} of 421 mg tyramine HCl, during brofaromine after a mean PD_{30} of 54 mg tyramine HCl, and during phenelzine after a mean PD_{30} of 60 mg tyramine HCl. Maximal concentrations (C_{max}) were reached earlier (¾ hour) in control subjects than during MAOI treatment (1½ and 2 hours). C_{max} values were in a concentration range of 630 to 1270 ng/ml, despite eightfold and sevenfold lower oral pressor doses of tyramine during MAOI treatment. From the AUC values of conjugated tyramine was calculated a significant sixfold increase of relative bioavailability during brofaromine and a nonsignificant 2.7-fold to a significant 11.6-fold increase of relative bioavailability during phenelzine (Table II).

Oral tyramine pressor test

The oral PD_{30} of untreated volunteers (calculated as mean of two pressor tests) amounted to 475 ± 120 mg tyramine HCl (Table III). The PD_{30} decreased significantly to 55 mg on day 12 of brofaromine treatment.

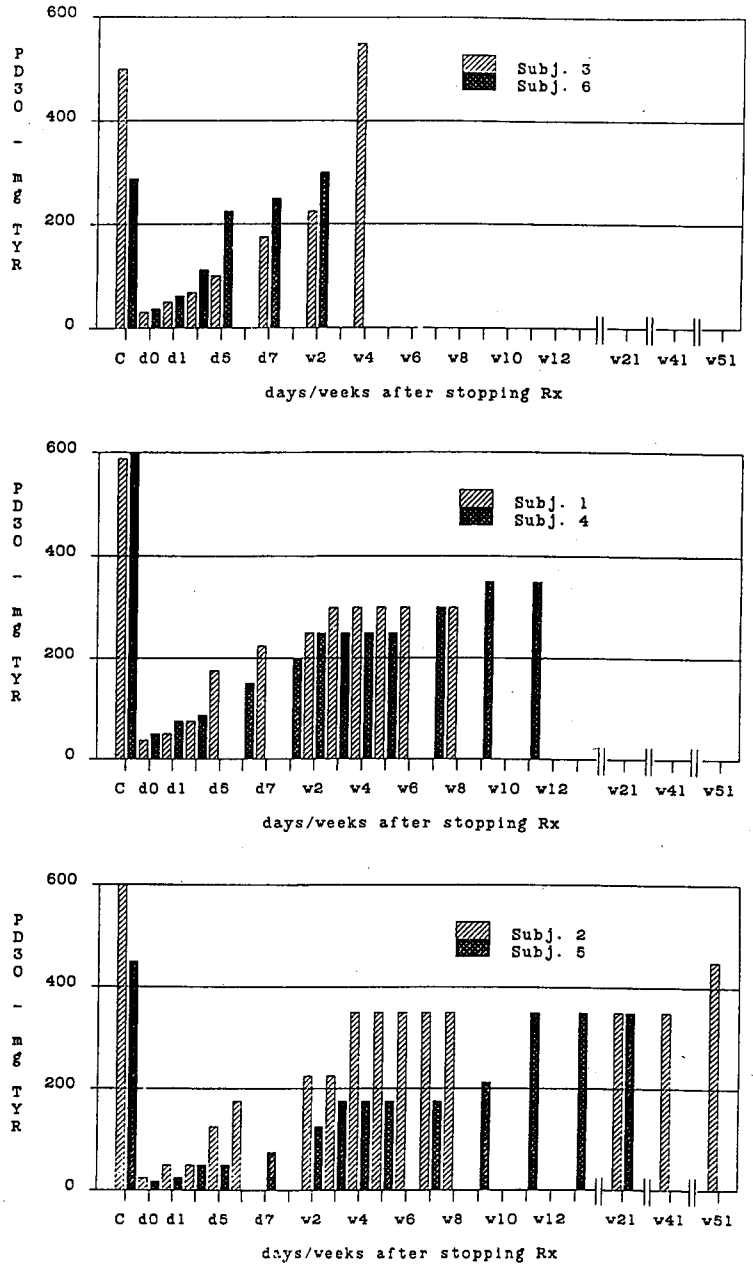

Fig. 3. Normalization of oral tyramine (TYR) pressor sensitivity after subchronic treatment *(Rx)* with weekly increasing doses of phenelzine (30, 45, and 60 mg/day), PD_{30} = mg tyramine to increase the systolic BP by 30 mm Hg or more. *Upper panel,* recovery within 2 to 4 weeks; *middle and lower panels,* no normalization within 11 to 51 weeks.

This corresponds to a PD_{30} ratio of 8:5. During phenelzine, PD_{30} values decreased in a dose-dependent manner to 127, 60, and 33 mg. This means there was an increase of pressor sensitivity (PD_{30} ratio) of fourfold (difference not significant), 8.4-fold ($p < 0.01$), and 15.7-fold ($p < 0.01$). After cessation of phenelzine treatment the PD_{30} returned very slowly to control values (Fig. 3). Fig. 3 shows individual time courses of recovery after phenelzine. Subject 6 reached his early PD_{30} within 2 weeks and subject 3 within 4 weeks. The other four volunteers continued to have a low PD_{30} for 8 to 11 weeks. In subject 2 an increased pressor sen-

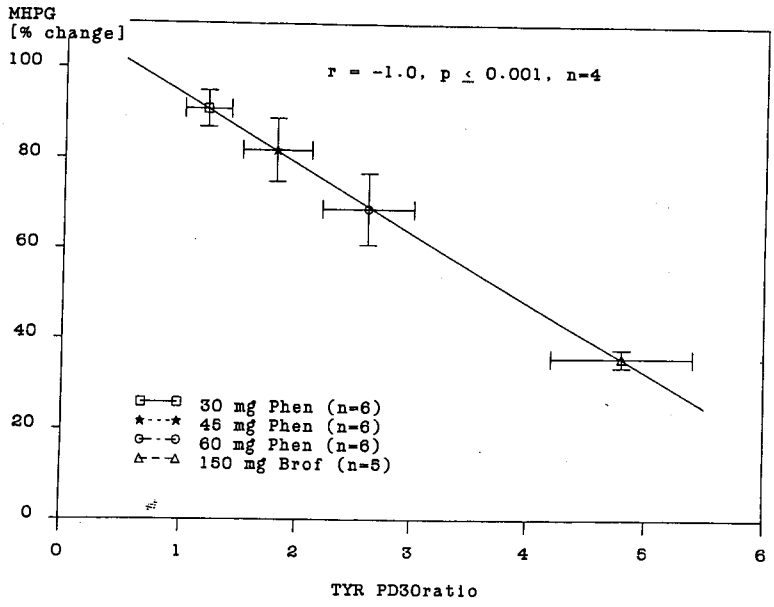

Fig. 4. Dose-response effect of phenelzine *(Phen)* and brofaromine *(Brof)* on relationship between IV tyramine pressor sensitivity and urinary MHPG excretion (mean ± SE of six subjects).

sitivity (1.3-fold) was found 51 weeks after treatment was stopped.

Intravenous pressor tests (Table III)

At the end of brofaromine treatment the sensitivity to intravenous tyramine (PD_{30} ratio) increased significantly (4.8-fold). During daily treatment with 30, 45, and 60 mg phenelzine the PD_{30} ratio increased from 1.2 to 1.8 and 2.6. However, only the change after the largest dose was significantly different from that of control values. Pressor sensitivity to NE increased 2.9-fold during brofaromine but did not change significantly during phenelzine. Pressor sensitivity to phenylephrine increased threefold ($p < 0.01$) during brofaromine and 1.7-fold (difference not significant) during the highest daily dose of phenelzine (60 mg/day).

Comparison of pressor sensitivity to oral and intravenous tyramine

From Table III the PD_{30} ratios after oral and intravenous tyramine can be compared. The increase of pressor sensitivity during MAOI treatment is always larger after oral tyramine: 1.8-fold (8.5 vs 4.8) during brofaromine and from 3.3-fold (4.0 vs 1.2) and 4.7-fold (8.4 vs 1.8) to sixfold (15.7 vs 2.6) during increasing doses of phenelzine.

DISCUSSION

Although phenelzine is the major MAOI used in the United States, its effects have not been evaluated in healthy subjects by combined application of several methods. Only such a combined approach permits significant conclusions about time course and extent of MAO inhibition in human beings.[21] However, from single clinical reports it is known that phenelzine has a long duration of action. Significant hypertensive reactions happened to intravenous amphetamine 16 and 19 days after discontinuation of 90 mg/day phenelzine.[22] Platelet MAO-B activity returns to predrug levels 1 to 2 weeks after stopping phenelzine, and plasma MAO activity takes more than 6 weeks to return to baseline.[23] The pharmacodynamic effects of brofaromine (formerly CGP 11 305 A) have repeatedly been shown to be of short duration in human beings.[9,12,13]

The quickly appearing effect of brofaromine on sleep could be the result of an interaction with rapid eye movement (REM) sleep.[11] The missing influence on sleep during phenelzine and the small "rebound effect" can be explained by using low clinical doses.[24]

There were striking differences between the two MAO inhibitors regarding the influence on urinary monoamine excretion patterns. Excretion of endogenous tryptamine was enhanced thirteenfold in the third week of phenelzine treatment and remained elevated for 2 to 3 weeks after the drug was stopped. Our results are in accordance with an earlier report on phenelzine showing a maximal eightfold increase of tryptamine excretion.[23] More recently we found that the irreversible MAO-A inhibitor clorgiline enhanced tryptamine excretion threefold, which is similar to that of brofar-

omine. However, it remained elevated for 2 to 3 weeks after stopping treatment (Bieck PR, Mühlbainer B, Antonin KH, unpublished results). Therefore the larger and longer-lasting effect of phenelzine on tryptamine seems to be related to the nonselective and irreversible MAO inhibition.

Urinary MHPG and VMA, the deamination products of endogenous NE, were not significantly decreased during phenelzine. However, pretreatment levels were not reached during 3 weeks after stopping treatment. In contrast, brofaromine diminished urinary MHPG and VMA sharply and significantly and this effect disappeared immediately after discontinuation of the drug. These results suggest that MAO-A inhibition is achieved rapidly and reversibly by brofaromine but not by the nonspecific irreversible MAO inhibitor phenelzine. Phenelzine differs from brofaromine by an approximate selectivity ratio to MAO-A of 2 versus 3000.[25] The low ratio apparently is opposed by cumulative irreversible inhibition of the MAO-A isozyme activity. This is supported by the finding that phenelzine given in larger daily doses of 60 mg/day for 3 to 4 weeks reduced urinary MHPG in 12 patients with depression by about 50%.[26]

During inhibition of tyramine deamination to *p*-hydroxyphenylacetic acid by MAOI, the second essential pathway of its inactivation (i.e., conjugation) is used increasingly. Therefore the measurement of conjugated tyramine can be used to compare the relative potency of pharmacologically different MAOI drugs.[27] The relative bioavailability of conjugated tyramine increased maximally elevenfold after phenelzine and sixfold after brofaromine (Table II). This can be explained by inhibition of both isozymes A and B of MAO and lack of substrate competition with the irreversible inhibitor phenelzine.

The pressor sensitivity to tyramine differs largely with the type of administration. Injected systemically, tyramine reaches the peripheral adrenergic neurons where MAO-A is generally inhibited. Pickar et al.[28] showed that pressor sensitivity changes to intravenous tyramine caused by three different MAO inhibitors were highly correlated with decreases in plasma MHPG. They suggested that measuring MHPG might be a useful index of in vivo MAO-A inhibition. We compared urinary MPHG excretion with tyramine pressor sensitivity. Because of the small changes of MHPG excretion after phenelzine (not the individual correlations between increase of sensitivity to intravenous tyramine and percent decrease of MHPG excretion), the four treatment conditions pooled show an excellent correlation (Fig. 4; $r = -1.0$).

Only the highest dose of phenelzine enhanced pressor sensitivity to intravenous tyramine significantly (Table III). The increase was about half of that seen during brofaromine administration. This could be the result of reaching a "threshold" dose only after prolonged treatment. Such "threshold" doses of phenelzine to yield disproportionally greater effects have been suggested earlier for platelet MAO inhibition, increase of urinary tryptamine excretion, and suppression of REM sleep.[23,24]

The change in intravenous tyramine pressor sensitivity by brofaromine has been ascribed mainly to its specific MAO-A–inhibiting properties.[9] It has been speculated that antidepressant therapy with MAO inhibitors leads to an increase in noradrenergic "efficiency" (e.g., by decreasing presynaptic reuptake of NE).[29] Such a hypothesis could explain the increased sensitivity to NE found in this study during treatment with brofaromine and in a previous one during therapy with tranylcypromine.[30] The small change of pressor sensitivity to intravenous phenylephrine after both MAO inhibitors reflects that this amine is also metabolized by deamination but that it does not release NE.

The potentiation of oral tyramine by brofaromine is only 1.8-fold that of intravenous tyramine. For phenelzine this difference, in dosages that also significantly increase relative bioavailability, is fivefold to sixfold. These results can be explained by a dual mechanism of MAO inhibition. Aside from their MAO-A–inhibitory effects in the adrenergic neuron, both drugs inhibit MAO in the gastrointestinal tract. There is a significant correlation ($n = 16$; $r = 0.68$; $p < 0.01$) between the relative bioavailability of conjugated tyramine and the increase of oral tyramine pressor sensitivity (PD_{30} ratio).

Extent and duration of oral tyramine pressor sensitivity differs largely between both drugs. The maximum oral tyramine PD_{30} ratio of 15.7 after phenelzine returned to control values in a biphasic manner. Taken individually, the early sensitivity was reached by only two subjects within 2 to 4 weeks. Four subjects did not reach their control PD_{30} values during the time of observation. In one subject, oral tyramine sensitivity was still enhanced 51 weeks after phenelzine treatment was stopped. In contrast, the enhancement of oral tyramine pressor sensitivity after brofaromine was smaller (PD_{30} ratio of 8.5) and early sensitivity is known to be reached within 1 week.[13]

Recovery from the effects of an irreversible inhibitor will depend on the turnover rate of MAO and inhibitory concentrations. The turnover rate of MAO is tissue dependent, and half-lives for recovery of 2½ to 3½ days and 10 to 13 days have been reported for rat liver and brain.[31] Recovery from the effects of a reversible MAO

inhibitor depends mainly on the rate of drug clearance from tissues.[32]

The biphasic normalization of pressor sensitivity after phenelzine could be explained by the different tissue-dependent turnover rates of MAO. Because of the faster turnover of gastrointestinal MAO,[31] first-pass metabolism of tyramine is inhibited for a shorter time (early recovery phase). Both indexes of MAO-A inhibition, decrease of MHPG/VMA, and tyramine pressor sensitivity returned to normal very slowly over several weeks. This suggests that irreversible neuronal MAO inhibition is long-standing (second recovery phase).

Two kinetic properties of phenelzine could also account for the long-lasting pharmacodynamic effects. First, it has been suggested that the drug or active metabolite(s) may inhibit its own metabolism in liver and other tissues, causing drug accumulation. Second, a maximum of 80% of an administered dose was recovered even when given to chronically treated patients.[33] The authors suggest that irreversible binding might account for the remaining balance of the dose.

In conclusion, brofaromine compared with phenelzine has the advantage of causing a smaller and shorter lasting increase of oral pressor sensitivity to tyramine.

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