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# Evidence for Noradrenergic Involvement in Mediating the FG 7142 Discriminative Stimulus

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LEIDENHEIMER, N. J. AND M. D. SCHECHTER. *Evidence for noradrenergic involvement in mediating the FG 7142 discriminative stimulus.* PHARMACOL BIOCHEM BEHAV 43(1) 77–83, 1992.—Rats were trained to discriminate the stimulus properties of the benzodiazepine receptor partial inverse agonist β-carboline-3-carboxylate acid methyl amide (FG 7142) (5.0 mg/kg) or the $\alpha_2$-adrenergic receptor antagonist 17α-hydroxyyohimban-16α-carboxylic acid methyl ester (yohimbine) (3.0 mg/kg) from vehicle in a two-lever, food-motivated operant task. These compounds have in common a β-carboline structure and anxiogenic behavioral profiles. The yohimbine discriminative stimulus was mimicked by the $\alpha_2$-adrenergic receptor antagonist idazoxan and antagonized by the $\alpha_2$-adrenergic receptor agonist clonidine, indicating that the yohimbine stimulus was mediated through the $\alpha_2$-adrenergic receptor. The anxiogenic β-carbolines FG 7142, 1,2,3,4-tetrahydro-β-carboline (THBC), and norharmane, the anxiogenic/convulsant agent pentylenetetrazole (PTZ), and two physiological stressors failed to mimic the yohimbine discriminative stimulus. In contrast, both yohimbine and idazoxan dose responsively mimicked the anxiogenic FG 7142 stimulus. The present results demonstrate that an asymmetrical generalization exists between the discriminative stimuli produced by yohimbine and FG 7142. Furthermore, these data suggest that yohimbine can produce a multicomponent discriminative stimulus, part of which may be anxiogenic in nature. The ability of $\alpha_2$-adrenergic receptor antagonists to mimic the FG 7142 cue suggests that activation of the noradrenergic system may underlie cues produced by benzodiazepine receptor inverse agonists.

Drug discrimination FG 7142 Yohimbine β-Carbolines Anxiety Norepinephrine Stimulus properties of drugs Idazoxan Rats Benzodiazepine receptors

β-CARBOLINE-3-carboxylate acid methyl amide (FG 7142) and 17α-hydroxyyohimban-16α-carboxylic acid methyl ester (yohimbine) are β-carbolines that produce anxiety. The anxiogenic effects of FG 7142 have been observed in humans (7) and in several animal models including social interaction (9), conflict (6,25,26), and exploratory (23,32) paradigms. Similarly, yohimbine has been observed to produce anxiety in man (3,4,13,20) and in both dog (29) and rodent models (11, 12,22,24).

Although FG 7142 and yohimbine are similar in structure and behavioral properties, they appear to exert their anxiogenic effects through different neurotransmitter receptor systems. FG 7142 is a benzodiazepine receptor partial inverse agonist that decreases GABAergic transmission through negative allosteric effects at the $GABA_A$/benzodiazepine receptor complex (34). The anxiogenic effects of FG 7142 are mediated at the benzodiazepine receptor, as evidenced by the ability of benzodiazepine receptor agonists (7) and antagonists (6,21) to prevent FG 7142-induced anxiety. In contrast to FG 7142, yohimbine is widely recognized as an $\alpha_2$-adrenergic receptor antagonist that increases noradrenergic transmission by blocking noradrenergic feedback at the $\alpha_2$-adrenergic presynaptic autoreceptor (1,10,31). The ability of the $\alpha_2$-adrenergic receptor agonist clonidine to antagonize the anxiogenic effects of yohimbine indicate that yohimbine-induced anxiety occurs through the $\alpha_2$-adrenergic receptor (14).

The discriminative stimulus paradigm is an operant task based upon the internal cueing properties of drugs. It has been used extensively to elucidate neuropharmacological mechanisms underlying drug action. In this paradigm, the discriminative stimuli produced by FG 7142 and yohimbine are mediated through the benzodiazepine (18) and $\alpha_2$-adrenergic (40) receptors, respectively. The FG 7142 discriminative stimulus is thought to be anxiogenic in nature based upon the generalization of the FG 7142 cue to both the anxiogenic/convulsant pentylenetetrazole (PTZ) (18) and physiological stressors (17) and the ability of FG 7142 to mimic the PTZ cue (33,35). It has been suggested that the yohimbine discriminative stimulus

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may also be anxiogenic in nature since yohimbine has been reported to mimic the PTZ stimulus (16).

In the present study, we employ the discriminative stimulus paradigm to examine: a) the anxiogenic nature of the yohimbine discriminative stimulus; b) the similarities between yohimbine and FG 7142 cues; c) the possible involvement of the noradrenergic system in mediating the FG 7142 stimulus.

## METHOD

### *Subjects*

Experimentally naive, male Sprague-Dawley rats purchased from the Zivic-Miller Laboratories (Allison Park, PA), weighing between 125–250 g at the beginning of the experiment, were individually housed and maintained on a 12L:12D cycle (light on 0600–1800 h) in a room kept at temperatures between 20–22°C. They received water ad lib and a daily rationing of commercial rat chow to maintain their weight at approximately 85% of the weight expected to be attained by rats at the same age fed ad lib.

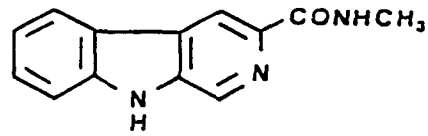
### *Apparatus*

Twelve standard rodent operant chambers (Lafayette Instruments Corporation, Lafayette, IN) were used as the experimental space. Each chamber contained two levers situated 7 cm apart and 7 cm above a grid floor. A food receptacle was located 2 cm above the grid floor, midway between the two levers. Each operant chamber was enclosed in an unlit, sound-attenuated cubicle with an exhaust fan for ventilation. Solid-state programming equipment (Med Associates, E. Fairfield, VT), located in an adjacent room, was used to control and record discrimination sessions.

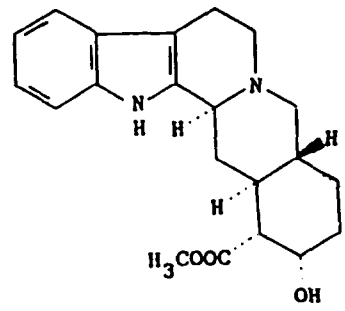
### *Training Procedure*

Rats were previously trained to discriminate the interoceptive properties of FG 7142 (5.0 mg/kg, IP) from a Tween vehicle (17,18). A second group of rats ($n$ = 12) was trained to discriminate yohimbine (3.0 mg/kg, IP) from a saline solution. FG 7142, yohimbine, or vehicle injections were administered 30 min prior to the discrimination session. The structures of these two $\beta$-carbolines are presented in Fig. 1.

A detailed protocol of the training procedure has been reported (18). Briefly, rats were trained to discriminate the interoceptive effects of drug vs. vehicle in a two-lever, food-motivated operant task. The reinforcement schedule was set at a fixed ratio of 10 (FR 10), that is, 10 injection-appropriate lever responses yielded one reinforcement (45-mg Noyes pellet). Daily training sessions were conducted until animals had made 400 injection-appropriate responses and, thus, received 40 reinforcements. Training sessions were conducted once per day according to the following 2-week training schedule: YOH, V, V, YOH, YOH; V, YOH, YOH, V, V. The lever that accumulated 10 responses (presses) first in the session was considered to be the "selected" lever for that session. The training schedule was repeated until each rat achieved two 10-session training periods in which 8 of 10 consecutive training sessions resulted in injection-appropriate responding (18). Data collection began when all animals had fulfilled this criterion. Once discriminative criterion was attained, the discrimination training regiment was limited to every other day to ensure and maintain discriminative performance to the training conditions. Between these "maintenance" sessions, generalization and antagonism experiments were performed (a test session was conducted every other day). If during generalization and antagonism testing an animal's maintenance session performance fell below the 80% injection-appropriate criterion required for discriminative training, the animal continued through maintenance/testing sessions; however, its data was excluded from the experiment. Once the animal's maintenance performance returned to criterion level, subsequent data from that animal was included in the experiment.




FG 7142




yohimbime

FIG. 1. Structures of FG 7142 and yohimbine.

### *Generalization Experiments*

Generalization tests were conducted in FG 7142 and yohimbine-trained rats every other day (between drug and vehicle maintenance days). Generalization test drugs were administered such that each drug dose was tested twice, once following a drug maintenance (DM) day and once following a vehicle maintenance (VM) day according to the following schedule: DM, test drug dose 1, VM, test drug dose 1; DM, test drug dose 2, VM, test drug dose 2, etc. This counterbalancing was used to control for any possible residual influence from the previous maintenance day. Thirty minutes following administration of test drugs, rats were placed into the discrimination chamber and immediately removed, without receiving reinforcement, after accumulating 10 responses on one of the levers. Animals were not reinforced on test days to preclude training to the test compound. Responses on both drug and vehicle levers were recorded and subsequently used to calculate the quantitative measurement (see the Measurements and Statistics section below).

### *Antagonism Experiments*

Rats were coadministered the training/test drug and antagonist drug prior to being placed into the discrimination chamber. Rats were then placed into the discrimination chamber and, upon emitting 10 responses on one of the levers, were

removed without receiving reinforcement. Antagonism testing was counterbalanced between maintenance days as in generalization testing. Test drug doses and treatment times were determined from the literature. All antagonists were administered 30 min prior to the discrimination session except Ro 15-1788, which was administered 15 min before the session.

*Novelty and Foot-Shock Experiments*

Exposure to novelty or foot-shock has previously been shown to produce an interoceptive cue (17). For novelty experiments (17), rats were injected with vehicle and placed into the modified operant chamber for 20 min, during which time no shocks were delivered. They were removed after 20 min and placed into the operant chambers used for discrimination sessions. After making 10 responses on either lever, rats were removed without receiving reinforcement and returned to their home cages. Unlike the drug testing experiments, which were counterbalanced between maintenance sessions as described below, novelty experiments (by definition) were conducted only once per rat. This was necessary to preclude habituation to novelty (17). Foot-shock experiments were conducted in a similar manner except a mild foot-shock (0.2 mA, 160-ms duration, 330-ms interval) was delivered during the 20-min period in the modified operant chamber (shockbox) (17).

*Measurements and Statistics*

The data collected in the drug discrimination session are expressed as both quantal and quantitative measurements, each measurement providing an indication of lever preference prior to any reinforcement. The quantal measurement is the percentage of rats selecting the drug lever as their "selected" lever, that is, the first lever to be pressed 10 times. The quantitative measurement is the number of responses on the drug lever divided by the total number of responses on both the drug and vehicle levers at the time that the tenth response is made on either lever. This fraction is expressed as a percentage. Unlike the (all-or-none) quantal measurement, the quantitative measurement accounts for responses on both the selected and unselected levers, thus providing a relative measure of the magnitude, as well as the direction, of lever preference. In addition, parametric statistics may be performed on the quantitative data. The advantages of using both types of measurements have been previously discussed (36).

A test or novel drug was considered to generalize to the training drug if quantal responding following administration of that drug was equal to, or greater than, 80% on the drug lever. This criterion was based upon the criterion for establishing acquisition of the training drug cue, that is, 80% or greater responding on the drug-appropriate lever. For generalization testing, the standard deviations for the quantitative measurements reflect the deviation between the counterbalanced test sessions.

For antagonism testing, each dose of antagonist was tested twice in each rat, once following a vehicle maintenance day and once following a drug maintenance day. For each rat, the quantitative scores from the two antagonism test sessions were averaged. Likewise, individual quantitative scores were averaged from the drug maintenance sessions. These individual quantitative scores from the antagonism test sessions and drug maintenance sessions were then tested for differences between group means. Data in which more than one dose of antagonist was used was subjected to a repeated-measures analysis of variance (ANOVA) followed by a posthoc Scheffe' test to determine significant differences between treatment means, $p < 0.05$. If only one dose of antagonist was used, the data was subjected to a one-tailed, paired $t$-test, $p < 0.05$.

*Drugs*

Drugs used in these experiments were obtained from the following sources: yohimbine, pentylenetetrazole, clonidine, and norharmane (Sigma Chemical Co., St. Louis, MO); FG

TABLE 1

GENERALIZATION EXPERIMENTS IN RATS TRAINED TO DISCRIMINATE YOHIMBINE

| | | % Responding on the Yohimbine Lever | | |
|---|---|---|---|---|
| Treatment | Dose (mg/kg) | Quantal | Quantitative (±SD) | $n$ |
| Vehicle | – | 4.2 | 7.6 (6.2) | 12 |
| Yohimbine | 0.5 | 41.7 | 42.8 (12.7) | 12 |
| | 1.0 | 54.2 | 50.3 (8.5) | 12 |
| | 2.0 | 66.7 | 64.8 (10.0) | 12 |
| | 3.0 | 87.5 | 78.8 (10.2) | 12 |
| Idazoxan | 2.5 | 50.0 | 48.8 (14.4) | 10 |
| | 5.0 | 65.0 | 67.9 (27.6) | 10 |
| | 10.0 | 88.9 | 84.1 (16.5) | 9 |
| FG 7142 | 5.0 | 4.1 | 23.1 (2.1) | 12 |
| | 10.0 | 45.8 | 49.9 (1.1) | 12 |
| | 15.0 | 25.0 | 36.2 (10.3) | 12 |
| THBC | 5.0 | 33.3 | 34.3 (15.2) | 12 |
| | 10.0 | 33.3 | 36.7 (11.0) | 12 |
| | 15.0 | 25.0 | 29.8 (26.2) | 12 |
| Norharmane | 5.0 | 5.6 | 17.4 (13.0) | 9 |
| | 10.0 | 31.3 | 36.5 (6.3) | 8 |
| PTZ | 20.0 | 36.4 | 37.2 (6.0) | 11 |
| Clonidine | 0.2 | 22.2 | 35.6 (6.2) | 9 |
| | 0.3 | 50.0 | 50.3 (8.6) | 9 |

1742 (Schering AG, Berlin, West Germany); CGS 9896 (CIBA-GEIGY, Summit, NJ); 1,2,3,4-tetrahydro-β-carboline (THBC) (Aldrich Chemical Co., Milwaukee, WI); idazoxan (Reckitt & Coleman Pharmaceutical Division, N. Humberside, UK). FG 7142, CGS 9896, and Ro 15-1788 were suspended in a 2% Tween-80 solution (Sigma) by sonification. Other drugs were dissolved in distilled water. The HCl salt of THBC was prepared by dissolution of THBC in absolute ethanol and acid, followed by recrystalization at 4°C.

## RESULTS

### *Experiments in Yohimbine-Trained Rats*

Results of yohimbine dose–response experiments and generalization testing are presented in Table 1. The yohimbine discriminative stimulus was dose responsive in the dose range of 0.5–3.0 mg/kg yohimbine. A 3.0-mg/kg dose of yohimbine produced quantal and quantitative responses of 87.5 and 78.8(10.2)%, respectively. In generalization studies, the $\alpha_2$-adrenergic receptor antagonist idazoxan (2.5–10.0 mg/kg) dose responsively mimicked the yohimbine discriminative cue, with the highest dose of idazoxan resulting in quantal and quantitative responding of 88.9 and 84.1(16.5)%, respectively, on the yohimbine lever. In contrast, the β-carbolines FG 7142 (5.0–15.0 mg/kg), THBC (5.0–15.0 mg/kg), and norharmane (5.0–10.0 mg/kg) failed to produce yohimbine-appropriate responding. In addition, the anxiogenic/convulsant PTZ (20.0 mg/kg) did not mimic the yohimbine discriminative stimulus. A higher dose of PTZ (30.0 mg/kg) was also tested; however, seizures were observed at that dose. The $\alpha_2$-adrenergic receptor agonist clonidine (0.2–0.3 mg/kg) also failed to mimic the yohimbine cue. Behavioral disruption precluded testing at higher doses of clonidine. Exposure of yohimbine-trained rats to the stressors novelty and foot-shock produced predominantly vehicle-appropriate responding (Table 2).

Results of clonidine antagonism experiments in yohimbine-trained rats are shown in Table 3. Coadministration of the 3.0 mg/kg training dose of yohimbine with clonidine (0.05–0.3 mg/kg) produced a U-shaped antagonism relationship, with maximal antagonism occurring at a 0.2-mg/kg dose of clonidine. At this dose, quantal and quantitative responding was 45.9 and 49.1(5.9)%, respectively. This antagonism was significantly different from the yohimbine control, $p < 0.05$.

### *Experiments in FG 7142-Trained Rats*

In FG 7142-trained rats, both yohimbine and idazoxan produced dose-responsive generalizations to the FG 7142 discriminative stimulus (Table 4). The highest dose of yohimbine (9.0 mg/kg) tested resulted in quantal responding of 83.3% on the FG 7142 lever. Quantal responding of 92.9% on the FG 7142 lever was observed following administration of a 10.0-mg/kg dose of idazoxan.

TABLE 2

DISCRIMINATIVE RESPONDING IN YOHIMBINE-TRAINED RATS FOLLOWING EXPOSURE TO STRESSORS

| | % Responding on the Yohimbine Lever | | |
|---|---|---|---|
| Treatment | Quantal | Quantitative (±SEM) | *n* |
| Novelty | 10.0 | 18.5 (27.5) | 10 |
| Foot-shock (0.2mA) | 20.0 | 32.1 (21.7) | 10 |

## DISCUSSION

In the present study, the yohimbine discriminative stimulus generalized to the $\alpha_2$-adrenergic receptor antagonist idazoxan but failed to generalize to the β-carbolines FG 7124, THBC, and norharmane, the anxiogenic/convulsant PTZ, and two physiological stressors. The yohimbine cue was partially antagonized by the $\alpha_2$-adrenergic receptor agonist clonidine. In contrast, the FG 7142 discriminative stimulus was dose responsively mimicked by both yohimbine and idazoxan.

The stimulus effects of yohimbine have been previously investigated (2,38,40). The yohimbine discriminative stimulus generalized to the $\alpha_2$-adrenergic receptor antagonist piperoxane (2) and was antagonized by the $\alpha_2$-adrenoceptor antagonist clonidine (40), indicating that the yohimbine cue is related to enhanced noradrenergic transmission. The generalization of yohimbine to the $\alpha_2$-adrenergic receptor antagonist idazoxan here is consistent with the above studies and also with data showing that the idazoxan discriminative stimulus generalizes to yohimbine (28). The ability of clonidine to only partially antagonize the yohimbine cue in the present study, however, is inconsistent with the study of Yang et al., who demonstrated that clonidine produced a complete blockade of the yohimbine cue (40). The discrepancy between these results may be due to that fact that a higher dose of yohimbine was used in the present study to establish discriminative control. Thus, it is possible that high doses of clonidine would be required to completely antagonize the yohimbine stimulus. Testing with higher doses of clonidine, however, were precluded by behavioral disruption.

It has been suggested that the yohimbine stimulus may be anxiogenic in nature based upon the ability of yohimbine to mimic the PTZ cue, a cue believed to be based upon the anxiogenic properties of PTZ (15). The ability of the benzodiazepine receptor anxiolytic diazepam to antagonize the yohimbine discriminative stimulus further supports the anxiogenic nature of the yohimbine cue (2,40). The anxiogenic basis of the yohimbine stimulus was further investigated in the present study. The anxiogenic β-carbolines FG 7142, THBC (27,30), and norharmane (27) failed to mimic the yohimbine cue. Furthermore, the yohimbine stimulus did not generalize to either PTZ or two physiological stressors (novelty and foot-shock) previously shown capable of substituting for the anxiogenic FG 7142 cue (17,18). These data indicate that the predominant cue underlying the *yohimbine-controlled* discrimination is not anxiogenic in nature.

Although yohimbine-trained rats failed to generalize to FG 7142, FG 7142-trained rats generalized to yohimbine. Since the FG 7142 cue is believed to be based upon the anxiogenic properties of FG 7142 (17,18), these results suggest that in *FG 7142-controlled* discrimination yohimbine can produce an anxiogenic discriminative stimulus. It has been suggested that yohimbine may produce anxiogenic effects via an inverse agonist activity at the benzodiazepine receptor since yohimbine has a micromolar affinity for this receptor (16). However, the anxiogenic effects of yohimbine have since been demonstrated to be independent of benzodiazepine receptor activation (22).

Alternatively, yohimbine may produce an anxiogenic stimulus mediated through the $\alpha_2$-adrenergic receptor. To examine this possibility, idazoxan, a compound that produces a discriminative stimulus selectively mediated by the $\alpha_2$-adrenergic receptor (28), was tested in FG 7142-trained rats. Similar to yohimbine, idazoxan dose responsively mimicked the FG 7142 cue. It is unlikely that the generalization of FG 7142 to idazoxan represents a nonspecific generalization since FG 7142 does not generalize to all compounds capable of producing discriminative stimuli (18,19). Thus, it appears that yohimbine

TABLE 3

ANTAGONISM OF THE YOHIMBINE DISCRIMINATIVE STIMULUS BY CLONIDINE

| Treatment | Dose (mg/kg) | % Responding on the Yohimbine Lever | | n |
|---|---|---|---|---|
| | | Quantal | Quantitative ( ± SEM) | |
| Yohimbine | 3.0 | 87.0 | 79.2 (6.1) | 12 |
| Yohimbine + Clonidine | 3.0 | | | |
| | 0.05 | 83.3 | 77.7 (1.1) | 12 |
| | 0.1 | 95.9 | 79.5 (7.1) | 12 |
| | 0.2 | 45.9 | 49.1 (5.9)* | 12 |
| | 0.3 | 75.0 | 65.0 (11.7) | 12 |

*Significantly different from yohimbine control, $p < 0.05$.

may produce an anxiogenic discriminative stimulus in FG 7142-controlled discriminations based upon its ability to enhance noradrenergic transmission.

The generalization of the FG 7142 cue to the $\alpha_2$-adrenergic receptor antagonists in the present study suggests that inverse agonist cues may be dependent upon activation of the noradrenergic system. Several reports are consistent with this possibility. Takada et al. (37) obtained similar preliminary results in rats trained to discriminate the inverse agonist $\beta$-CCE. In $\beta$-CCE-trained rats, generalization occurs to both yohimbine and the $\alpha_2$-adrenergic receptor selective antagonist piperoxane. In another study, the benzodiazepine receptor inverse agonist 6,7-dimethoxy-4-ethyl-$\beta$-carboxamide (DMCM) has been demonstrated to potentiate the yohimbine discriminative stimulus via benzodiazepine receptor activation (40). The dependence of inverse agonist cues upon activation of the noradrenergic system is consistent with the noradrenergic hypothesis of anxiety. This hypothesis proposes that activation of the noradrenergic system increases anxiety, while a dampening of noradrenergic transmission is associated with anxiolysis. This theory has received much support and been extensively reviewed (5).

In addition to behavioral evidence for an interaction between the $GABA_A$/benzodiazepine receptor complex and the noradrenergic system, neurochemical studies support this association. The benzodiazepine receptor inverse agonist DMCM has been demonstrated to increase norepinephrine turnover in several brain regions (42) and increase norepinephrine release from presynaptic terminals (41). Furthermore, the locus coeruleus, the major noradrenergic nucleus in the brain, is under inhibitory control of the $GABA_A$ receptor (8), the subtype of GABA receptor modulated by benzodiazepine receptors.

In the present study, an asymmetrical generalization is observed between the yohimbine and FG 7142 cues, that is, FG 7142-trained rats generalize to yohimbine whereas yohimbine-trained rats do not generalize to FG 7142. Asymmetrical generalizations in the discriminative stimulus paradigm have been noted to occur between compounds of differing specificities (19,39). It is possible that in yohimbine-trained rats the yohimbine discriminative stimulus may result from activation of the entire noradrenergic system. However, only part of the noradrenergic system may be associated with anxiety-related behaviors. Therefore, administration of FG 7142 to yohimbine-trained rats would reproduce only a part of the yohimbine cue and generalization would, thus, fail to occur. This hypothesis would also explain the lack of generalization of yohimbine-trained rats to stressful environmental manipulations in this study. Conversely, the generalization of the FG 7142 discriminative stimulus to both yohimbine and idazoxan may depend upon the ability of these compounds to activate the part of the noradrenergic system associated with anxiety.

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TABLE 4

GENERALIZATION EXPERIMENTS WITH YOHIMBINE AND IDAZOXAN IN RATS TRAINED TO DISCRIMINATE FG 7142

| Treatment | Dose (mg/kg) | % Responding on the FG 7142 Lever | | n |
|---|---|---|---|---|
| | | Quantal | Quantitative ( ± SD) | |
| Vehicle | – | 0 | 11.2 (5.6) | 9 |
| FG 7142 | 5.0 | 88.9 | 78.7 (4.5) | 9 |
| Yohimbine | 3.0 | 38.9 | 46.7 (1.1) | 9 |
| | 6.0 | 61.1 | 55.1 (15.0) | 9 |
| | 9.0 | 83.3 | 68.8 (1.8) | 9 |
| Idazoxan | 5.0 | 35.7 | 39.1 (5.2) | 7 |
| | 7.5 | 50.0 | 50.0 (10.0) | 7 |
| | 10.0 | 92.9 | 72.9 (1.1) | 7 |

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