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BRIEF COMMUNICATION

Behavioral Performance Effects of Nifedipine in Normotensive Baboons: Single Dosing

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TURKKAN, J. S. AND R. D. HIENZ. *Behavioral performance effects of nifedipine in normotensive baboons: Single dosing.* PHARMACOL BIOCHEM BEHAV **33**(4) 923–926, 1989.—The effects of single oral doses of the calcium channel blocker nifedipine were assessed on performance of a simultaneous color match-to-sample task in three normotensive baboons. Both accuracy of color matching, and speed and latency of response were measured 30 min after administration of 0.10, 0.34, 0.57, and 1.7 mg/kg and vehicle, with each dose tested on three occasions in randomized order. Systolic and diastolic blood pressures also were measured after testing sessions. Maximal decreases in systolic blood pressures (mean of three subjects = −4.56 mmHg) were obtained after ingestion of the 0.57 mg/kg dose. Nifedipine produced dose-related changes in choice reaction times with a trend toward increased reaction times of approximately 5% obtained at 0.34 and 1.7 mg/kg. A reversal of effect was noted at 0.57 mg/kg such that smaller changes in reaction times were obtained, suggesting a lack of correlation between blood pressure and behavioral performance changes. These results indicate that nifedipine administered in single doses to patients with hypertensive crisis is unlikely to produce large impairments in these aspects of sensory and motor functioning.

Nifedipine Calcium channel blocking agents Color discrimination Choice reaction time Hypertension Blood pressure Antihypertensive agents Adverse side-effects Nonhuman primates

NIFEDIPINE is a calcium channel blocking agent with a dihydropyridine structure that has been recently recommended but not yet approved for use with hypertensive patients. Nifedipine administered orally or intravenously produces a rapid onset of hypotensive effect, with an effective duration of blood pressure decrease when administered in multiple doses (5). Nifedipine exerts its effects on blood pressure by blocking the entry of calcium into smooth muscle, and producing vasodilation and decreased peripheral vascular resistance (16). Reported side-effects of nifedipine during clinical trials have included flushing, edema, headache, dizziness, postural hypotension, fatigue, pain, and nausea (4, 9, 14, 22, 23).

The potential behavioral performance impairments that may follow from such reported adverse effects have been rarely examined in the laboratory for calcium antagonists administered alone (17). Calcium antagonists administered in single doses have impaired horizontal and vertical balancing in rodents (1,7); nifedipine in particular has also potentiated PCP- and ethanol-induced impairments of balancing performance (1,21), and blocked amphetamine-induced locomotor stimulation (6). That sensory functioning may be particularly sensitive to nifedipine is suggested by high-density calcium antagonist binding sites in the rat brain in areas such as the olfactory bulb and the molecular layer of the dentate gyrus (2), areas that have been noted to be strategic relay centers for sensory pathways (10).

We have previously reported the effects of repeated dosing with nifedipine on performance of a simultaneous color match-to-sample task in baboons (18,19). Baboons were impaired both in choice reaction times and color discrimination accuracy within one week after the onset of twice daily constant dosing. The present report follows up the previous study by examining the behavioral performance effects of single doses of orally administered nifedipine. Patients experiencing a hypertensive crisis have been administered single doses of intravenous nifedipine because of its rapid hypotensive effect (14); we have also observed rapid hypotension after single oral doses administered to hypertensive baboons (18,19).

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METHOD

Three adult male baboons *(Papio cynocephalus, hamadryas,* and *anubis)* served as subjects. The baboons ranged in weight between 26–32 kg, and were housed in individual living cages. Their previous experimental history consisted of repeated dosing with nifedipine which was terminated five months prior to the current study, and with the angiotensin-converting enzyme inhibitor enalapril two months prior to the current study. Animals had extensive training in the present color match-to-sample task.

Experimental sessions were conducted in a behavioral testing chamber with inner dimensions of $1.07 \times 1.37 \times 1.68$ m. An aluminum intelligence panel fitted at one end (46.7×48.3 cm) of the chamber contained six press-plate manipulanda (BRS) inserted into circular openings which served as both stimulus panels and response keys. The keys were configured such that the sample was centered above, and five keys were placed in a row 14 cm below the sample key and spaced equidistantly (7.6 cm center to center). Each key (diameter = 4.4 cm) was transilluminated with an IEEE stimulus projector. A food pellet dispenser (BRS) automatically delivered pellets into a food well centered below the row of five stimulus keys.

Trials began by presenting a flashing (1/sec) sample stimulus color on the sample key. A press on the sample key produced a steady sample color along with each of the 5 different choice colors presented on the choice keys simultaneously (blue, white, green, red, and yellow). A press on the choice key that matched the color of the sample key was rewarded with two 190-mg food pellets delivered automatically into the food well followed by all key lights being extinguished. A press on a nonmatching choice key was punished by extinguishing all key lights and giving a 15-sec time-out period during which no stimuli were presented and no contingencies were in effect. A 2-sec intertrial interval terminated all trials. Trials following incorrect matches repeated the sample color at the same location on successive trials until a correct match was made. Sample colors were presented according to a randomized block design, and locations of colors on the choice keys were completely randomized. Experimental sessions terminated after 1000 trials or 120 min, whichever occurred first. Animals experienced the experimental session at the same time of day (9 a.m.–5 p.m.) on the same days of the week throughout the study. Behavioral testing sessions were separated by 72 hours.

Three dependent variables were measured in hundredths of a sec accuracy during each trial: Press duration on the sample key, latency from sample color onset to a response on the choice keys ("choice reaction time"), and the latency to the next trial initiation ("trial latency"). These values were also summed for total trial duration. For reaction time measures, medians were obtained for consecutive blocks of 50 trials. Color matching performance was defined as the number of correct matches in a session divided by the number presented, $\times 100$ for each of five colors across consecutive 50-trial blocks. Data were not included from repeated trials after incorrect choices. For the purpose of hypothesis testing, within-session trials were further averaged across thirds of the session (time blocks).

In order to measure hypotensive response to nifedipine, blood pressure (BP) was measured with the standard American Heart Association auscultatory procedure in awake animals. From 2–3 BP measurements were taken on each measurement occasion; these values were then averaged (see Turkkan *et al.*, 1989, for a complete description of training, with frequency distributions of blood pressure displayed). BPs were measured immediately after the daily session at 2½ hours postdrug.

Oral nifedipine doses were used that approximated the clinical doses and conditions under which this drug is normally administered. Doses studied were 0.10, 0.34, 0.57, and 1.7 mg/kg, and vehicle. Powdered drug (Sigma, St. Louis) was weighed and inserted into ¼ banana as vehicle. On no occasion was an animal seen to reject the vehicle + drug; ingestion occurred in less than 5 min. The rate but not the extent of nifedipine bioavailability has been shown to be slightly diminished by small meals in human volunteers (15). Doses were administered according to a randomized block design where the five doses (vehicle and four active doses) were randomized within blocks, and each block was repeated three times. Animals experienced individually randomized schedules. We have obtained maximal hypotensive effects in these normotensive baboon subjects of approximately 5 mmHg within 30 min after ingestion of single oral doses of nifedipine (18,19).

In our earlier study with repeated dosing (18,19), the highest dose of nifedipine (0.57 mg/kg twice daily) produced smaller behavioral impairments. In order to determine whether this finding resulted from dose-ordering effects, the present study randomized the dose order among subjects. Also, the nifedipine dose was increased over doses previously studied.

Analyses of variance on behavioral measures and systolic and diastolic blood pressures were conducted for dose, time block (for behavioral measures only), and session No. of each dose as factors. Each color was entered into an individual analysis for matching to sample accuracy. Number of trials per session, and minutes/session also were analyzed. We report here standard probability levels, and also the more conservative Huynh-Feldt probability levels which control for violations of sphericity due to repeated measures. Standard errors are reported with mean values where appropriate. Post hoc comparisons of active dose means versus vehicle means were performed using Dunnett's test where significant main effects were obtained.

RESULTS

Nifedipine produced dose-related decreases in systolic BP, $F(4,8) = 4.46$, $p = 0.035$, Huynh-Feldt $p = 0.08$ (Table 1); diastolic BP was not significantly changed. Systolic BP decreased maximally by 4.56 (± 1.63) mmHg and diastolic blood pressure increased by 1.44 (± 2.54) mmHg at 0.57 mg/kg. Total daily water intake was not changed by nifedipine.

Nifedipine also produced dose-related changes in choice reaction times, $F(4,8) = 5.83$, $p = 0.017$, Huynh-Feldt $p = 0.0972$ (Table 1). Choice reaction times tended to be increased by nifedipine, although individual comparisons with vehicle were not significant. Choice reaction time was maximally increased by an average of 3.04 (± 0.58) hundredths/sec after the 0.34 mg/kg dose. Figure 1 shows the dose-effect functions for an average of three animals (light grey bars): slowing of choice reaction time was greatest at 0.34 and 1.7 mg/kg in comparison to vehicle, with all animals showing a reversal at 0.57 mg/kg.

Examination of changes in trial durations within sessions showed that two out of three animals diverged from vehicle performance levels in the second half of the daily two-hour sessions, while the third animal diverged from vehicle performance levels early in the session. Statistical analysis did not find these effects to be significant. Press duration, trial latency, and matching to sample accuracy (Table 1) were not significantly changed by nifedipine.

A comparison of average increases in choice reaction time of the present study with a previous study involving repeated dosing with nifedipine is illustrated in Fig. 1, which shows that the largest increases in choice reaction time were produced by nifedipine at 0.34 mg/kg during both single (% of vehicle dose) and repeated (%

TABLE 1

MEAN BEHAVIORAL PERFORMANCE AND BLOOD PRESSURE LEVELS FOR VEHICLE AND FOUR DOSES OF NIFEDIPINE PO

Dose (mg/kg)	Trial Duration Mean	SE	Choice Reaction Time* Mean	SE	Press Duration Mean	SE	Trial Latency Mean	SE	% Correct Matching† Mean	SE	Systolic BP (mmHg)‡ Mean	SE	Diastolic BP (mmHg) Mean	SE
Vehicle	160.01	3.95	75.63	6.41	4.86	1.59	79.53	9.27	98.68	0.53	115.56	8.55	65.45	5.12
0.10	153.82	6.55	76.30	6.61	4.95	1.46	72.58	5.37	98.44	0.73	115.22	8.18	66.78	5.34
0.34	166.26	8.65	78.67	6.68	5.02	1.85	82.58	10.86	98.72	0.67	113.22	11.00	67.33	6.68
0.57	160.05	3.90	75.68	6.82	4.71	1.53	79.67	9.30	99.06	0.19	111.00	9.03	65.67	7.42
1.70	164.52	10.12	78.14	6.86	4.60	1.45	81.77	6.88	98.52	0.61	111.78	9.24	65.45	8.10

All values averaged over three subjects.
*Significant main effect of dose; $p=0.017$. Individual comparisons with vehicle not significant.
†Average of white, blue, green, red, and yellow.
‡Significant main effect of dose; $p=0.035$. Individual comparisons with vehicle not significant.

of vehicle baseline; dark columns) dosing. Both studies also show a reversal in choice RT impairment at the 0.57 mg/kg dose.

DISCUSSION

The present results show that nifedipine administered orally in single doses in a clinical dose range tends to increase choice reaction time and decreases systolic blood pressure in normotensive baboon subjects, without affecting color discrimination accuracy. Nifedipine is known to rapidly decrease peripheral vascular resistance when administered in single doses (14), and further decreases in arterial blood pressure have been observed after constant daily dosing both in hypertensive humans (12), and in our previous study with renovascular hypertensive baboon subjects

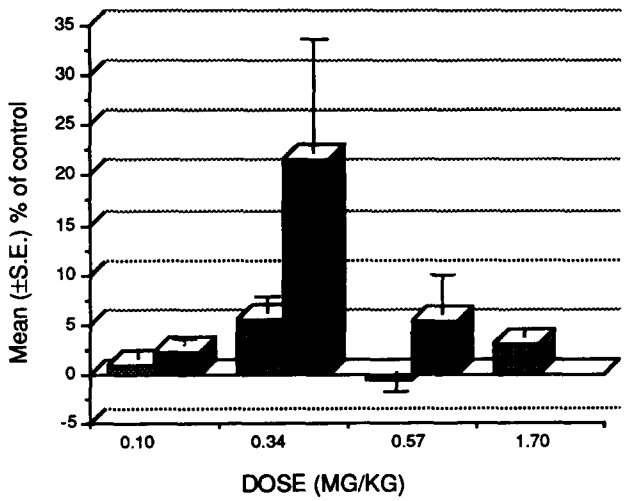

FIG. 1. Dose effects of single and repeated dosing with nifedipine (PO) on choice reaction time. Columns for single dosing (light shading) are % of vehicle response averaged over three sessions at each dose, averaged over three baboon subjects. Columns for repeated dosing (dark shading) are % change from predrug baseline for days 12–14 of twice daily dosing, averaged over the same three baboon subjects. For comparability of data, only the first 450 trials of each session were compared across the two studies. (Data from repeated dosing derived from Turkkan and Hienz, in press.)

(18,19). The hypotensive effects of nifedipine were not, however, found to be correlated with the behavioral performance impairments observed during repeated dosing [cf. also (1)]. In the present study as well, maximal hypotensive effects and maximal increases in choice RTs were not observed at the same doses. Further, the use of higher doses than those previously studied did not markedly increase the behavioral effects observed. As we and others (11, 18, 19) have previously observed, the dose-effect function of nifedipine's hypotensive and behavioral effects does not appear to be steep.

In a previous study (18,19), marked increases in choice RT and impairments in color matching accuracy were obtained following three days of constant oral dosing with nifedipine. This is in contrast to the present study, where smaller changes were observed for the same subjects. The differences in degree of impairment may be attributable to the differences between single and repeated dosing. A potential mechanism underlying this difference is suggested by a study with healthy human volunteers in which residual nifedipine was eliminated more slowly after repeated (longer than 7 days) oral administration (13). It should be noted, however, that healthy human volunteers receiving single oral doses of nifedipine (0.15 mean mg/kg) have reported adverse side-effects of headache and dizziness within 120 min after ingestion (4). Relatedly, nimodine, another dihydropyridine calcium antagonist, has produced EEG changes in healthy human volunteers after single dosing (8). Of some interest was the finding that although effects on reaction time were smaller after single doses, the dose-effect functions after single and repeated dosing were similar (Fig. 1). In both dosing conditions, effects on choice RT were greatest following 0.34 mg/kg.

These data have implications for emergency treatment of hypertensive crises with nifedipine (14), and for side-effects that may be expected on the first day of medication for longer-term treatment of hypertension. Although dihydropyridine binding sites have been identified in rat brain and nifedipine has modulated the behavioral effects of alcohol (21) and amphetamines (1) in the rat, significant adverse effects on nonhuman primate visual and motor performances are not evident after single doses as have been obtained with other antihypertensive medications (17).

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