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Behavioral Effects of Chronic, Orally Administered Diuretic and Verapamil in Baboons

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TURKKAN, J. S. AND R. D. HIENZ. *Behavioral effects of chronic, orally administered diuretic and verapamil in baboons.* PHARMACOL BIOCHEM BEHAV **38**(1) 55–62, 1991.—Behavioral performances of six baboons were tested during chronic oral dosing with diuretic (hydrochlorothiazide/triamterene), a calcium channel blocker (verapamil), and a combination of the two drugs. Reaction times and color matching-to-sample performances as well as physiological measures were obtained in deoxycorticosterone acetate (DOCA)-salt baboons and in renovascular hypertensive baboons. Combined diuretic and verapamil impaired color matching to a small degree in comparison to baseline performance, while drug administered alone had no effect. Weekly systolic and diastolic blood pressures decreased maximally from baseline during the drug combination period, and were accompanied by maximal increases in serum sodium. The largest behavioral impairments during combination dosing were observed for colors that were most difficult to discriminate during baseline. Significant positive correlations were found between systolic blood pressure and color matching accuracy. No differences between the animal hypertension groups were found as a function of drug condition either in physiological or behavioral responses. Only the combination of diuretic and verapamil produced a deleterious effect on color discrimination, which suggests further study of commonly administered drug combination therapies in hypertension.

Thiazide diuretics Calcium channel blocking agents Verapamil Color discrimination Motor behavior
Renovascular hypertension DOCA-salt hypertension Blood pressure Antihypertensive agents—adverse side-effects
Nonhuman primates—baboons

SYSTEMATIC and objective laboratory data are now emerging that reveal a variety of behavioral side-effects of some standard and more recently developed antihypertensive medications both in human and animal studies (32). Because approximately 40% of hypertensive patients require combination rather than single pharmacotherapy (5), the potential exists for exacerbation of treatment side-effects. Diuretics in particular are added to antihypertensive regimens in order to overcome the reflex sympathetic stimulation and concomitant sodium and water retention often produced by antihypertensive compounds (15). Side-effects during combined antihypertensive medications with calcium antagonists, such as headache and flushing, have been occasionally reported in clinical evaluations [e.g., (41)].

Few studies have directly examined the behavioral effects of diuretics in the laboratory. A side-effect of some concern during diuretic therapy has been potassium loss; hypokalemia is known to produce muscle weakness and lethargy. Despite frequent reports of sexual impairment and fatigue, direct central effects of the diuretics have not been demonstrated (29).

The calcium antagonists have been studied more extensively in the laboratory (4, 14, 18, 40); we have reported adverse effects of the dihydropyridine calcium antagonist nifedipine on sensory discrimination and motor performances of both normotensive and renovascular hypertensive baboons during acute and chronic oral dosing (36,37). The nondihydropyridine calcium antagonist verapamil is less potent with regard to chronotropic and smooth muscle contraction properties in comparison to nifedipine and other dihydropyridine calcium antagonists (30), and has produced fewer behavioral effects in direct comparisons with nifedipine in animal studies (12). Clinically, verapamil has been shown to enhance the hypotensive effect of diuretics in controlled studies with hypertensive patients (3).

This report documents the effects of an orally administered diuretic alone, verapamil alone, and combined diuretic and verapamil on color discrimination performance, simple motor performance and choice reaction times under chronic dosing. These measures encompass the behavioral dimensions of motor activity, cognitive performance, and sensory discrimination. Physiological measures included blood pressure and serum electrolytes. Drugs were studied in baboons whose blood pressures were preexperimentally elevated, yielding low- [deoxycorticosterone acetate (DOCA)-salt] and high-renin (renovascular) associated blood pres-

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sure elevations (23). Two baboon models of hypertension were employed to allow for the possible dissociation of the behavioral effects from the pressure-lowering effects of calcium antagonist and diuretic compounds. For example, the behavioral effects of diuretics may be attributable to lowered blood pressure in DOCA-salt subjects, but not in renovascular hypertensive subjects. These models, therefore, were chosen in order to provide a model for each drug class that would be responsive to the hypotensive actions of the drugs.

METHOD

Subjects

Six adult male baboons (*Papio cynocephalus* and *Papio anubis*) served as subjects because of: 1) their adaptability to long-term experimental conditions; 2) their similarity to man in terms of circulatory parameters such as blood pressure (BP), heart rate, clinical biochemistry, autoregulation of peripheral vasculature, and response to vasoactive pharmacological compounds [e.g., (11, 26, 38, 39)]; and 3) their similarity to man in terms of their sensory acuity [e.g., (11,17)]. Animals ranged in weight between 17–28 kg, and were housed in individual living cages. Three animals were renovascular hypertensive baboons surgically preprepared with unilateral renal artery stenosis (2-kidney, 1-clamp) at the Southwest Foundation for Biomedical Research [San Antonio, TX; see (25) for details of the surgical procedures] approximately 2½ years prior to the current study. The remaining three baboons were surgically intact and had their blood pressures preexperimentally elevated with dietary sodium and steroid administration (see below). Six animals had been administered nifedipine, and four had been administered enalapril in previous studies; the most recent period of active dosing with antihypertensive agents was 5 months prior to vehicle dosing in the current study. Water was continuously available except during daily 90-min experimental sessions; 22½-hour water intake was measured daily at 8 a.m.

Apparatus

Experimental sessions were conducted in a sound-attenuating chamber with inner dimensions of $1.07 \times 1.37 \times 1.68$ m. Two flourescent tubes covered with a translucent panel provided diffuse lighting on the ceiling of the chamber. The chamber contained a small cage fitted with a bench seat and an aluminum intelligence panel at one end (46.7×48.3 cm). Six press-plate manipulanda (BRS) were inserted into circular openings in the intelligence panel and served as both stimulus panels and response keys. The keys were configured such that one key (the sample) was centered above, and five choice keys were placed in a row 14 cm below the sample key and spaced equidistantly (7.6 cm center to center). With the animal seated on the bench, the choice keys were at eye level. All keys could be easily reached from the bench. Each key (diameter = 4.4 cm) was equipped with an IEEE stimulus projector, and could display either blue, white, green, red, or yellow colors. A computer-controlled food pellet dispenser (BRS) automatically delivered pellets into a food well centered below the row of five stimulus keys. Experimental sessions were automatically controlled and data collected with an Apple IIe computer.

Procedure

General. Baboons performed a 5-choice matching-to-sample task during which they repeatedly matched a color on a "sample" key by pressing one of five "choice" color keys. All baboons had been previously trained on this procedure. Animals were initially exposed to baseline (no drug) for 2 weeks, then diuretic alone for 2 weeks, then a combination of diuretic and verapamil for 3 weeks, then verapamil alone for 2 weeks, and then baseline (no drug). The two types of hypertensive animals were employed due to the possibility that the BP of the renovascular hypertensive animals may be insensitive to the effects of the diuretics (6). Thus if behavioral performance differences occurred, we could also assess possible correlations of these differences with changes in BP between the two types of hypertension.

Behavioral testing. Baboons were previously trained to perform a 5-choice matching to sample task composed of individual trials during which animals matched a color to a "sample" key by pressing one of five "choice" color keys. Trials began by presenting a flashing (1/s) sample stimulus color on the sample key. A press on the sample key immediately produced a steady sample color along with 5 different choice colors presented on the choice keys simultaneously (blue, white, green, red, and yellow). The sample key remained lit along with the choice keys. A press on the choice key that matched the color on the sample key was reinforced by the delivery of one 190-mg food pellet into the food well, and all key lights were extinguished. If a nonmatching choice key was pressed, all key lights were extinguished and a 15-s time-out period ensued where no stimuli were presented and no contingencies were in effect. A 2-s intertrial interval terminated all trials. Trials following incorrect matches repeated the sample color with color choices at the same locations 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. On each trial, data were recorded as to whether an animal successfully matched to a sample color among 5 color choices, and the latency and duration of responses on the sample and choice keys. Locations of correct and chosen keys were also recorded. Experimental sessions were conducted for either 90 min or 500 trials, whichever occurred first. Animals experienced behavioral testing sessions once a day Monday–Friday. Each animal was tested at the same individually assigned time of day across all conditions.

Pharmacological procedures. Normotensive baboons were administered dietary sodium chloride in the form of 5% hypertonic saline in flavored water between 7–9 a.m. daily for 8 weeks. Saline (300 ml) was combined with powdered orange drink and tap water (150 ml) and yielded a dose of 15 g NaCl/day. These animals next received steroids in the form of deoxycorticosterone acetate (DOCA) in combination with the daily sodium dose for an additional 8 weeks prior to study onset, a standard model of elevating BP in animals. This method has been previously employed with baboons (35). Filtered sesame oil (0.8 ml) containing 2.5 mg DOCA was administered IM every other day into alternating thigh muscles. The second baboon group (renovascular hypertensives) ingested 450 ml of flavored water daily without sodium throughout the protocol and did not receive DOCA injections.

Drugs under study were the calcium antagonist verapamil chloride (3.2 mg/kg), and the diuretic combination of hydrochlorothiazide (25 mg) and triamterene (50 mg). The potassium-sparing diuretic triamterene was added to hydrochlorothiazide in order to avoid life-threatening levels of hypokalemia. Both verapamil and the diuretic (Sigma Pharmaceuticals) were administered in powdered form: each drug was weighed and inserted into a separate piece of ¼ banana as vehicle. A double-dummy procedure was used such that two pieces of banana were always cut open and administered regardless of whether single or combined drugs were scheduled for testing. At each drug delivery, the technician observed whether complete ingestion of the two pieces of fruit occurred. On no occasion was an animal seen to reject the drug; ingestion occurred in less than 5 min.

The study consisted of consecutive phases of drug administration: a 14-day baseline (daily vehicle alone) was followed by a

14-day active dosing period with daily diuretic administered alone. Next, diuretic and verapamil were administered together during a 21-day daily dosing period ("combination drug period"), followed by a 14-day period of verapamil administered alone daily. Finally, a 14-day vehicle-alone condition ("baseline recovery") terminated the study. [A previous study had shown that when verapamil was added to ongoing diuretic treatment, more effective BP reductions occurred in hypertensive patients, compared to the reverse procedure of adding diuretic to ongoing verapamil treatment (3)].

Verapamil was administered twice daily on weekdays at a 3-h interval, and diuretic was administered once daily. During baseline and baseline recovery conditions, vehicle alone was administered twice daily. Timing of the first daily antihypertensive drug administration in relation to onset of the experimental testing session was predetermined by taking BP measurements every 10 minutes after acute administration of drugs alone and combined. Both systolic and diastolic blood pressures fell to the lowest level 30 min after a single oral dose of combined diuretic and verapamil; therefore, the sessions were set to begin at 30 min after drug (or vehicle) administration throughout the protocol. A three-hour dosing interval was chosen for practical reasons in order to maintain a constant interval between doses for the last animal tested each day, since personnel were not present to deliver a second dose late in the evening. On weekends, animals were administered drug at 9 a.m. and 3 p.m.

Blood pressure measurement. Systolic and diastolic BPs were measured by a technician certified by the American Heart Association. A small adult BP cuff (bladder dimensions 9.53×17.78 cm) was used for inflation with a mercury manometer. Baboons were first trained to extend their left arm through an opening in their home cage onto a flat shelf at heart level, and then to sit quietly during auscultatory SBP and DBP (Phase IV) measurement immediately prior to the experimental session. A continuous stream of dilute fruit sauce through a nozzle attached to the cage was used as a reinforcer during arm extension [see (33,34) for complete descriptions of training, including frequency distributions of resting BP data]. BPs were measured once a day every other day, Monday–Friday 20 min after the first daily drug dose (10 min prior to session onset). Because the technician was not blind to the drug conditions, BPs also were measured with a random-zero sphygmomanometer (Hawksley Co., Sussex, England) on a planned quasi-random schedule; these values did not differ and were, therefore, pooled.

Blood collection procedures. In order to indirectly monitor the time-course of calcium channel blockade as well as changes in electrolyte balance, venous blood was drawn at periodic intervals during the protocol for assays of serum Na^+, K^+ and Ca^{++}. Blood was sampled during ketamine sedation (5 mg/kg IM) always on a weekend day (no behavioral sessions) according to the following schedule: during the week preceding vehicle baseline, day 5 of diuretic, days 6 and 20 of combined diuretic + verapamil, day 11 of verapamil alone, and day 15 of vehicle recovery. All samples were coded and split. Serum electrolyte concentrations were measured by flame photometry in the Department of Laboratory Medicine of the Johns Hopkins Hospital.

Data collection and analysis. Three behavioral dependent variables were measured in hundredths of a sec accuracy during each trial: 1) press duration on the sample key; 2) time to select a color match on the choice keys ("choice reaction time"); and 3) total trial duration: a sum of press duration and choice reaction time plus the time to initiate the next trial on the sample key. Color matching performance was defined as the number of correct matches divided by the number presented $\times 100$ ("percent correct"), calculated across 150-trial blocks. Data were excluded from repeated trials after incorrect choices, and from trials or sessions in which there was equipment malfunction. Hypothesis testing for both behavioral and blood pressure measures was carried out with repeated measures analysis of variance for group (renovascular vs. DOCA-salt), week (11 weekly means), and within-session blocks (three medians of 150-trial units) factors, yielding a one between-group, two within-groups design for behavioral measures, and a one-between, one within-groups design for physiological measures. ANOVA for color matching data included individual animal performances to all five sample-key colors in an omnibus analysis.

Probability levels less than 0.05 were considered significant. The more conservative Huynh-Feldt probability levels were used to control for violations of sphericity due to repeated measures. Post hoc tests compared means of treatment conditions when the overall F values were significant; comparisons to baseline or to postdrug recovery employed only the final (2nd) weeks of these conditions.

RESULTS

Preexperimental and Baseline Conditions

After 8 weeks of DOCA-salt administration, SBP of the surgically intact baboons increased from (mean ± SD) 117(±9) mmHg during resting conditions to 131(±18) ($t=2.47$, $p=0.06$). DBP increased from 71(±15) to 76(±16) mmHg ($t=5.5$, $p<0.05$). BP of the surgical renovascular baboons was stable during this period, and averaged 157(±13)/102(±18) mmHg during vehicle baseline. Behavioral performances during baseline did not differ between baboon groups: Average (±SD) matching to sample performance ranged between 97.19(±2.6; yellow) and 99.76(±0.2; green) percent correct. Baseline average (±SD) press duration, choice reaction time and trial durations were 32.2(±20.8), 808.7(±137.7), and 1681.3(±147.4) msec, respectively.

Experimental Blood Pressure Effects

Figure 1 shows mean SBP as a function of drug condition for both renovascular (top panel) and DOCA-salt (bottom panel) groups. SBP but not DBP changed significantly across drug conditions, $F(4,16)=8.87$, $p=0.001$. Differential changes in SBP according to group were not significant, as evident in a comparison of panels A and B in Fig. 1. Daily SBP pooled across animals decreased maximally during the combination condition by approximately 9 mmHg; SBP during the combination and verapamil alone conditions were significantly different from baseline ($p<0.05$). SBP returned to baseline levels during the baseline recovery period ($p<0.05$ in comparison to the combination condition).

Color Discrimination

Changes in accuracy were significant for main effects of drug condition when all colors were pooled in the analysis, $F(10,280)=3.64$, $p<0.05$. Main effects of group or session block were not obtained. Maximal decreases in average color performance were obtained during the combination condition; peak decreases based on weekly changes ranged between -0.08 to -12.16 percent correct across six animals (average across animals and drug combination weeks $=-2.81$ percent change). Figure 2 (top panel) shows mean percent correct matching scores for an average of the five colors, and illustrates a significant decrease in color matching during the second and third weeks of combination dosing in comparison both to baseline vehicle and to postdrug recovery (both $p<0.05$). Diuretic or verapamil alone conditions were not significantly different from baseline or postvehicle conditions, and were

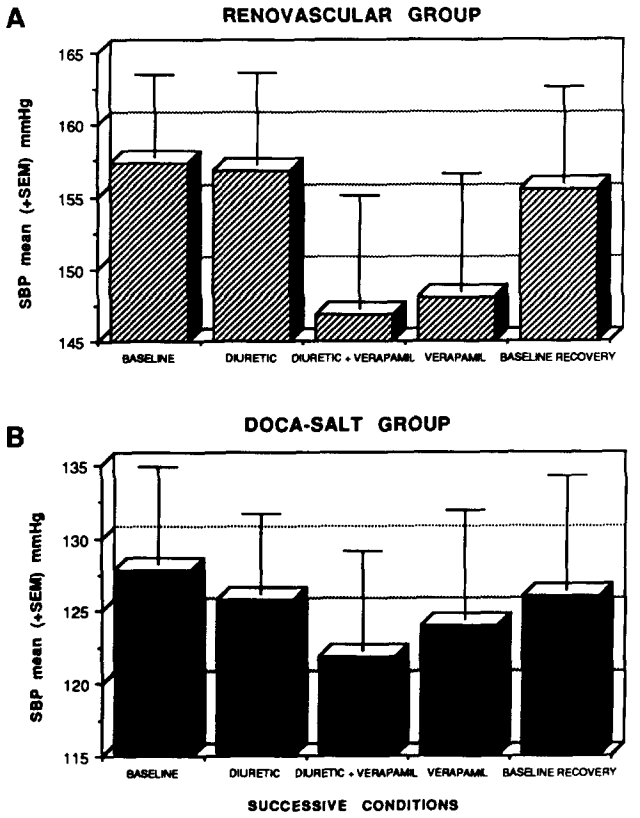

FIG. 1. Systolic blood pressure (mean + SEM) as a function of successive experimental conditions for renovascular baboons (A) and DOCA-sodium baboons (B). Each data point is averaged over all days per condition, and over three animals. Normal, resting SBP of the baboon is approximately 115 mmHg.

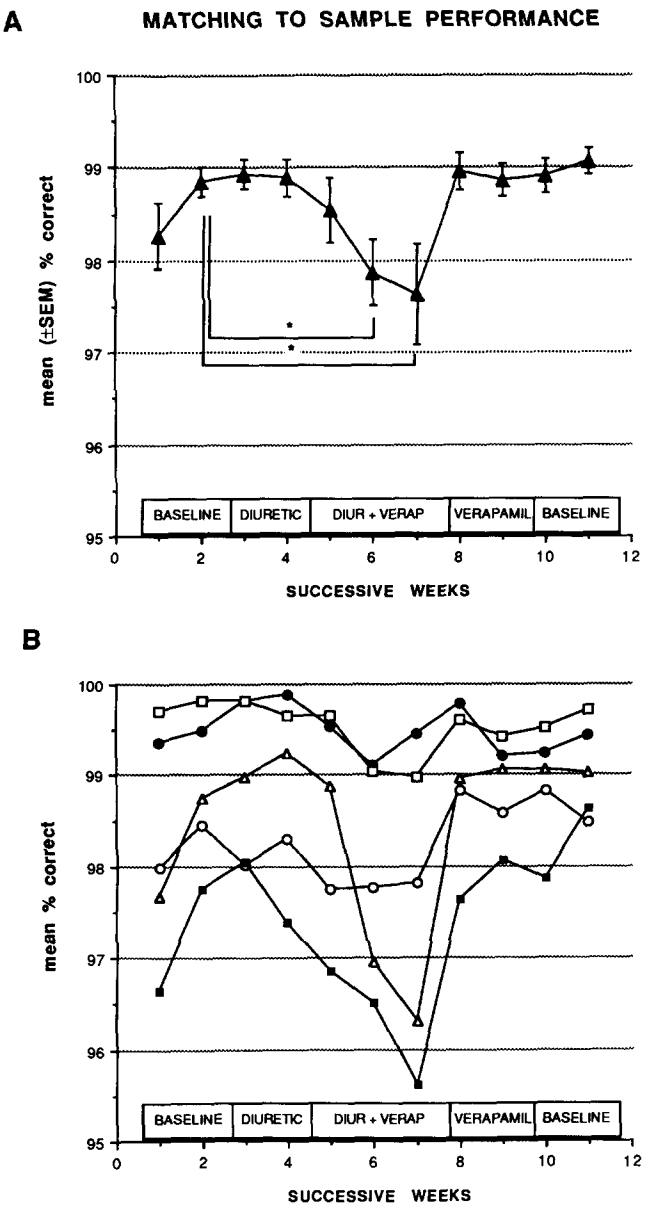

FIG. 2. Color matching-to-sample performance (percent correct) as a function of successive weeks. (A) Pooled colors. Each data point is averaged (±SEM) over 5 experimental sessions, over 6 animals, over five sample-key colors. *$p<0.05$ after post hoc comparisons. (B) Sample-key hue as a parameter. Each data point is a median of 450 trials, averaged over 5 experimental sessions and over 6 animals. Experimental conditions are shown on the abscissae of both panels. □: green; ●: blue; ○: white; △: red; ■: yellow.

not different from each other. There were no within-session trends.

Figure 2 (bottom panel) illustrates separate functions for each of the five colors across experimental weeks. Color discrimination during the drug combination period was particularly impaired for sample-key hues that produced more matching errors during baseline: yellow, white, and red matching accuracies were weakest during baseline, and were impaired to the greatest degree during the drug combination condition. Pearson r correlation between baseline accuracy and change in accuracy was significant for the first week of the drug combination condition [Pearson r ($df = 13$ employing all session blocks as coordinates) $= 0.548$, slope of linear regression (β) $= 0.44$]; both r and β were significant at $p<0.05$.

Figure 3 compares mean percent correct of the matching-to-sample performance with mean SBP's across drug conditions, showing the relationship between color matching accuracy and SBP. During the diuretic alone condition there were no trends in SBP or matching accuracy. During the subsequent drug combination condition, decreases both in SBP and color matching accuracy occurred within the first 5 days of dosing. The relationship between SBP and matching accuracy was weaker during the verapamil alone phase, where matching accuracy returned to baseline levels but SBP remained below baseline. Both functions returned to baseline levels during baseline recovery. A Pearson r correlation based on daily coordinate pairs of SBP × color matching accuracy (mean across colors) was significant at $p<0.05$ [Pearson r ($df = 28$) $= 0.445$].

Serum Electrolytes

Significant changes in both serum calcium, $F(4,16) = 3.60$, $p = 0.028$, and serum sodium, $F(4,16) = 13.40$, $p<0.0001$, occurred as a function of drug condition (Fig. 4); group differences

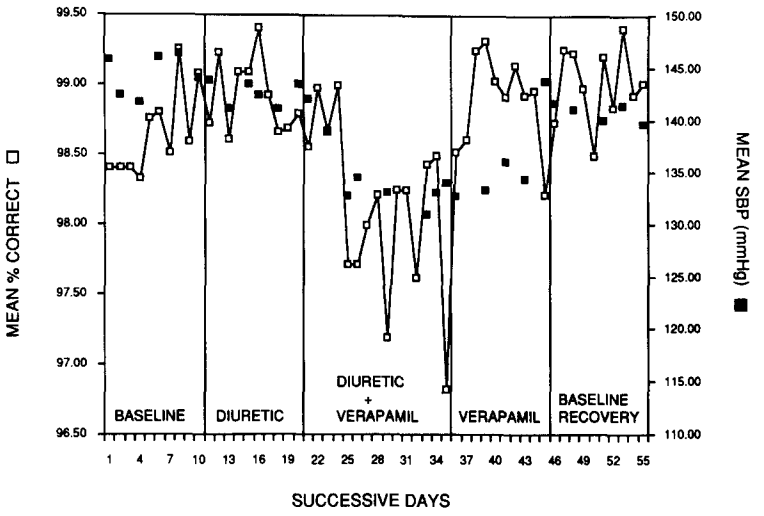

FIG. 3. Color matching-to-sample performance (mean percent correct) as a function of successive experimental sessions (left ordinate, open points) plotted with SBP (mean mmHg) as a function of successive measurements (once every 2 days; right ordinate, filled points). Each data point is averaged over six animals.

were not obtained. Serum calcium (upper panel) was elevated during all active drug conditions by approximately 0.50 mEq/l in comparison to baseline. After the verapamil alone period, serum calcium levels declined during baseline recovery ($0.10>p>0.05$).

Serum sodium (lower panel) was not significantly changed during diuretic alone in comparison to the first baseline period, but was significantly lower than the baseline recovery period (-3 mEq/l, $p<0.05$). Serum sodium was significantly elevated during the drug combination and the verapamil alone conditions (by approximately $+3$ mEq/l) in comparison to levels during the first baseline period ($p<0.05$).

Serum potassium was higher across all drug conditions for the DOCA-salt animals (mean $\pm$SD $= 3.80 \pm 0.11$) in comparison to the renovascular hypertensive animals [3.32 ± 0.12; $F(1,4) = 8.79$, $p = 0.04$]. Significant changes in serum potassium as a function of drug condition were not obtained, nor was there a group $\times$ drug condition interaction.

Psychomotor Response

Trial duration, $F(10,40) = 4.21$, $p<0.05$, changed significantly across drug conditions; post hoc means comparisons were not, however, significant. Group differences in trial duration were not obtained. Sample-key press duration remained stable across conditions.

Choice reaction times decreased systematically across consecutive study conditions, $F(10,40) = 8.26$, $p = 0.0001$, from a mean ($\pm$SD) of 798.0($\pm$35.0) ms during the second week of baseline, and reached the lowest point during baseline recovery (725.5 $\pm$ 25.0 ms), indicating progressive improvement in speed of performance across study weeks regardless of drug condition. Choice reaction time means during drug combination, verapamil alone, and baseline recovery conditions (but not during diuretic alone) all were significantly lower than baseline ($p<0.05$). Group differences in choice reaction times were not obtained; within-session trends were not significant.

DISCUSSION

The results of this study show that diuretic or verapamil alone produced no changes in color matching accuracy, whereas the combination of verapamil and diuretic impaired matching accuracy to a small degree within the first week of administration, which was maintained until the combination was discontinued. Those hues that were the most difficult to discriminate during baseline were also the most impaired by the drug combination. Decreases in matching accuracy were accompanied also by decreases in SBP and displayed a similar timecourse.

Because color discrimination was not impaired during the diuretic alone or verapamil alone dosing periods, one can conclude that only the combination of these agents produced a deleterious effect on the animals' ability to match to a simultaneously presented sample color. Verapamil has been reported to synergize the effects of other drug classes both in animal studies and in clinical investigations. For example, verapamil has potentiated PCP-induced decreases in maze efficiency (24) and rotorod performance (4) in rodents. In clinical investigations, chronic dosing with verapamil has inhibited the metabolism of simultaneously administered antipyrine (1) and carbamazepine (27), leading in the latter study to dangerous levels of neurotoxicity in epileptic patients. In the present study, verapamil may have inhibited the metabolism of hydrochlorothiazide during the combination dosing period, since decreases in serum sodium levels were reversed. It remains unclear, however, how inhibited metabolism of these drugs may have impaired color discrimination. While neither drug has been reported to have direct sensory effects during oral administration, studies have shown that sensory functioning may be particularly sensitive to calcium antagonists: high-density calcium antagonist binding sites have been located in the rat brain in areas such as the olfactory bulb and the molecular layer of the dentate gyrus (7), areas that are strategic relay centers for sensory pathways (22). Related more peripherally to visual sensory functioning, there have been clinical case reports of eye pain and blurred vision during chronic dosing with the calcium antagonist nifedipine (8), and experimental evidence in rabbits that topical verapamil increases ocular pressure (2). If metabolism of verapamil was inhibited in the presence of diuretic, such sensory effects may have been potentiated.

Another possibility is that the drug combination adversely af-

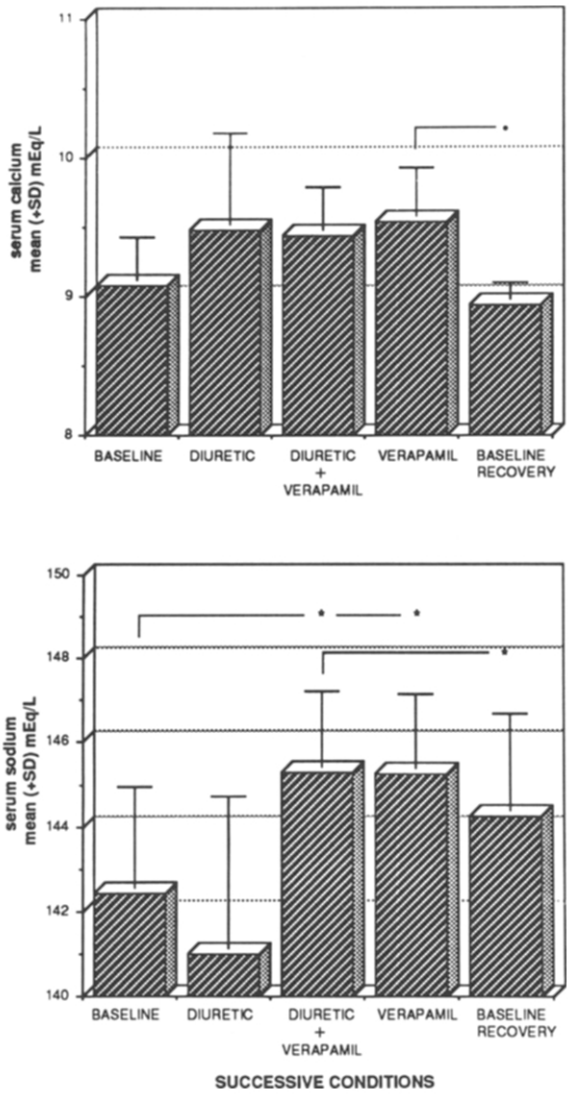

FIG. 4. Mean (+SD) serum calcium (upper panel) and serum sodium (lower panel) as a function of successive experimental conditions. *$p<0.05$; •$0.10>p>0.05$ for post hoc comparisons between means. Data points for the diuretic + verapamil condition are an average of two sampling occasions, averaged over six animals. For all other conditions, each data point is based on one sampling occasion averaged over six animals.

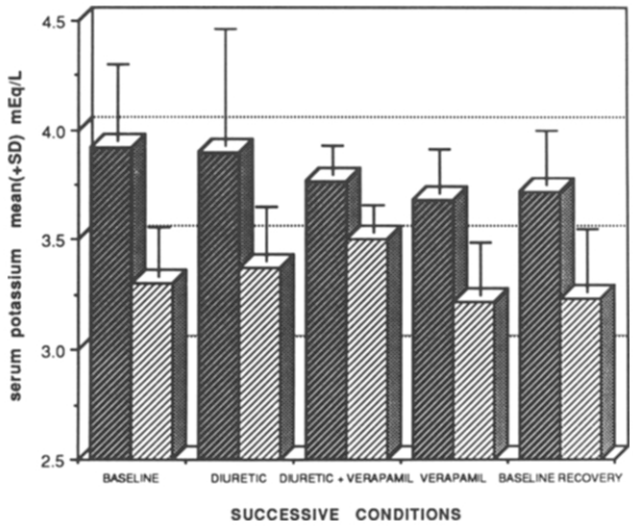

FIG. 5. Mean (+SD) serum potassium as a function of successive experimental conditions for renovascular baboons and DOCA-salt baboons. Data points for the diuretic + verapamil condition are an average of two sampling occasions, averaged over three animals. For all other conditions, each data point is based on one sampling occasion averaged over three animals. Heavily shaded bars: DOCA-salt, N=3; lightly shaded bars: renovascular, N=3.

fected attentional processes. In such a case, however, one might predict changes in choice reaction times as well. For example, in a previous study of normotensive baboons during chronic oral dosing with the dihydropyridine calcium antagonist nifedipine, increases in matching errors were obtained, and, moreover, were accompanied by increases in choice reaction times (37). This finding stands in contrast to the present results in that verapamil, a papaverine-derivative calcium antagonist, did not impair any behavioral performances when administered alone even though blood pressure decreases were similar to those obtained previously with nifedipine. In a comparison of 16 calcium antagonists, Grebb (14) found that nifedipine but not verapamil blocked amphetamine-induced locomotor stimulation. Clinically, verapamil has been associated with fewer complaints of headache and flushing than has nifedipine, which is a stronger vasodilator (21).

The fact that diuretic combined with verapamil led to increases in matching errors while speed of psychomotor response was unaffected suggests that the animals were not sedated during combination dosing. The potential existed for the development of hypokalemia with attendant muscle weakness and lethargy during diuretic treatment, but hypokalemia generally was not observed. (Notably, although one renovascular animal's serum potassium dropped to clinical "panic" levels, with serum potassium at 2.90 mEq/l during baseline recovery, his behavioral performance levels remained stable and high.) Choice reaction times were not differentially changed by the drug conditions; the progressive decreases in reaction times across study weeks undoubtedly reflected learned increases in motor coordination that have been previously observed in these animals during extended dosing with vehicle alone (37). The dissociation of choice reaction performance and color discrimination performance was particularly evident during combination dosing in that response speed was high, but accuracy was low.

An overall relationship between BP and behavioral performance, specifically color discrimination, was evident. Orthostatic (postural) hypotension is one mechanism by which a fall in BP may modulate task performance, and has occurred frequently during antihypertensive treatment with attendant complaints of dizziness from hypertensive patients (10). Conscious monkeys, unlike quadrupeds such as dogs and cats, have shown characteristics of orthostatic hypotension similar to humans when administered alpha-adrenergic and ganglionic blockers (28). However, tests of orthostatic hypotension in hypertensive patients administered verapamil (13), as well as tests in patients with congestive heart failure administered diuretic combined with the calcium channel blocker felodipine (20) have been negative. It is unlikely that the BP decreases obtained during combination dosing elicited orthostatic hypotension, since BP was not returned to pre-DOCA-salt levels nor was BP of the renovascular baboons returned to normal levels. The failure to find changes in reaction times also supports this conclusion.

Similar to our findings with nifedipine and also noted for other drug classes (16), weak baseline performances such as the yel-

low-white discrimination were particularly impaired during drug dosing. Such performances under weak stimulus control, and performances that are complex or recently acquired may be differentially sensitive to lower doses of antihypertensive medications than those used here [cf. (31)]

The physiological profile of the baboon subjects was markedly similar to cardiovascular and electrolyte profiles displayed by human hypertensive patients. For example, the renovascular baboons displayed lower levels of serum potassium throughout the protocol and their BP responses were relatively insensitive to diuretic treatment in comparison to the DOCA-salt animals (23). Also, predictable by the actions of calcium antagonists in preventing transmembrane Ca^{++} uptake (9), chronic oral dosing with verapamil produced a small increase in serum calcium levels of both baboon groups of the same magnitude as shown by human hypertensive patients (3). These findings, in addition to the expected decreases in serum sodium during diuretic treatment, suggest that baboons closely simulate the physiological responses of humans and provide a excellent model to test the psychopharmacological actions of antihypertensive agents.

BP was elevated preexperimentally by two different methods in order to produce selective BP decreases under the mechanistically different hypotensive agents administered (19). This aim was achieved during diuretic dosing in that BP of the DOCA-salt baboons decreased while BP of the renovascular hypertensive animals was not affected (6,35). Diuretics administered alone, however, did not affect color discrimination or psychomotor responses of either group. Also, the small BP difference between the groups did not allow conclusions regarding correlations between behavioral and BP changes during diuretic alone. BP of the two groups responded similarly during all other drug conditions, again precluding speculation as to whether BP decreases necessarily modulated the behavioral side-effects observed. It should be noted, however, that some dissociation of BP and behavioral performance was obtained during the postcombination verapamil alone period: color discrimination improved while BP remained lowered, suggesting that the BP: behavioral performance relationship is not inevitable.

The data in the present study show that combined antihypertensive medications may produce side-effects not observed during monotherapy with either drug, but that these effects are not as marked as behavioral impairments typically induced by the sedative and opiate classes of drugs. Many other compounds such as beta-blockers, angiotensin-converting enzyme inhibitors and vasodilators are combined with diuretic therapy but their combined behavioral side-effects have not been studied in the laboratory. The source of therapeutic drop-outs due to reported side-effects may be profitably examined in these baboon models.

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