Pharmacology Biochemistry and Behavior, Vol. 42, pp. 465–471, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

β-Blocker Effects on 24-h Activity in Normotensive and Renovascular Hypertensive Baboons

JAYLAN S. TURKKAN,*[1] ROBERT D. HIENZ,*†
RICHARD P. ALLEN‡ AND H. JOSEPH BEZOLD*

**Department of Psychiatry and Behavioral Sciences, Division of Behavioral Biology*
†Center for Hearing Sciences
‡Sleep Disorders Center
The Johns Hopkins University School of Medicine, Baltimore, MD 21224

Received 5 December 1991

TURKKAN, J. S., R. D. HIENZ, R. P. ALLEN AND H. J. BEZOLD. *β-Blocker effects on 24-h activity in normotensive and renovascular hypertensive baboons.* PHARMACOL BIOCHEM BEHAV **42**(3) 465–471, 1992.—Spontaneous motor activity of normotensive and renovascular hypertensive baboons was measured during oral dosing with the β-adrenergic antagonists atenolol HCl (2.6 mg/kg/day) and *d,l*-propranolol HCl (6.8 mg/kg twice daily) in separate studies. Each study administered active drug for 21 consecutive days. Piezoelectric monitors sensitive to movement were worn continuously by the baboons. Propranolol decreased overall 24-h average activity during the third week of dosing in normotensive baboons but not in renovascular hypertensive baboons. The greatest reductions in activity averaged 20% at those times of day corresponding to the second daily drug dose both in normotensive baboons and, at this time of day only, in the majority of hypertensive baboons. Activity decreases reversed to baseline levels when propranolol was discontinued. For atenolol, most normotensive but no hypertensive baboons showed decreases in activity at the time of day corresponding to the daily drug dose.

β-Adrenergic blocking agents Propranolol Atenolol Motor behavior Renovascular hypertension
Blood pressure Antihypertensive agents Adverse side effects Nonhuman primates Baboons

THE use of β-adrenergic receptor blocking agents in clinical medicine has become particularly widespread in the last two decades, with their major use in cardiovascular diseases such as hypertension, angina, arrhythmias, and obstructive disorders. Propranolol, the prototypical β-blocker, is widely used as the first or second drug in stepped-care control of hypertension (7). Atenolol, a hydrophilic β_1 selective antagonist, has been used in place of propranolol when patients would not comply with a multiple-pill daily dose regimen; atenolol in a single daily dose has been shown to control blood pressure for 24 h (21).

Collaborative group studies such as the Boston Collaborative Drug Surveillance Program (8) cite common instances of disturbances in CNS function with β-blockers. During oral propranolol, for example, reported side effects have included fatigue, dizziness, impaired sleep, and alterations in mood and thought that appear to be independent of dose. Up to 14% of adverse reactions to oral propranolol have been found to be sensory and behavioral, although it has been suggested that such side effects may be the result of either reduced cardiac output or direct CNS action (8). The β-blockers have, however, heterogeneous pharmacological properties that make their behavioral study difficult. In the CNS, β-blockers interact with a variety of systems such as in altering the metabolism of norepinephrine, dopamine, serotonin, and acetylcholine. In addition to β-blockade, the β-blockers show properties such as membrane stabilization (i.e., local anesthetic effects) and β-receptor stimulation (intrinsic activity). In addition, compounds in this class vary with respect to their ability to cross the blood-brain barrier. For example, propranolol is highly lipid soluble (lipophilic) and readily crosses the blood-brain barrier, in comparison to atenolol (a hydrophilic agent).

Consistent with the heterogeneous pharmacology of the β-blockers, the laboratory literature has been contradictory on the adverse or ameliorative behavioral effects of the β-blockers in both humans and animals (15,25). Studies with

[1] Requests for reprints should be addressed to Jaylan S. Turkkan, Ph.D., Division of Behavioral Biology, Behavioral Biology Research Center, Hopkins Bayview Research Campus, 5510 Nathan Shock Drive, Suite 3000, Baltimore, MD 21224.

mildly hypertensive adults have found no changes in simple or complex reaction times after propranolol (11,14). In another study that found propranolol to worsen complex reaction time performance, scores progressively improved during the 3-week dosing period (2). Propranolol has worsened accuracy of visual discrimination tasks in rhesus monkeys (17).

Atenolol has been reported to produce fewer behavioral side effects than propranolol (4) and has had little effect on a variety of psychomotor tasks in human studies [e.g., (26,27)]. In addition, atenolol has not been detected in the cerebral brain stem of squirrel monkeys after 30 min despite the rapid onset of a hypotensive effect (1). Some studies performed with hypertensive human subjects have found atenolol to produce increased concentration [e.g., (24)], but others also performed with hypertensive subjects have found atenolol to slightly impair learning and recall of everyday objects (13).

This report documents the effects of atenolol hydrochloride (Study 1) and propranolol hydrochloride (Study 2), two widely used β-adrenergic blocking agents that differ with respect to lipophilicity and β_1 selective properties, on spontaneous motor activity. Although there is a large literature on the psychomotor and sleep side effects of β-blockers (15), and β-blockade has been found not to affect spontaneous activity of rodents (5,9), no studies have obtained objective laboratory information about the effect of β-blockers on continuous activity of humans or nonhuman primates. Objective information is particularly lacking about the effects of β-blockers on activity in hypertensive subjects and during chronic dosing as found in clinical settings. In this series of studies, both hypertensive and normotensive baboons were studied to determine the degree to which each drug's effects on spontaneous activity may be modulated by the hypertensive condition.

METHOD

Subjects

Six adult, male baboons (*Papio cynocephalus & Papio anubis*) served as subjects. Animals ranged in weight between 17–28 kg. Three baboons surgically prepared with unilateral renal artery stenosis (2-kidney, 1-clamp) were obtained from the Southwest Foundation for Biomedical Research [San Antonio, TX; see (16) for details of the surgical procedures] approximately 4 years prior to the current study. These hypertensive baboons are referred to as the "renovascular hypertensive" baboons (SBP/DBP ± SEM 152 ± 10/96 ± 4 mmHg). The remaining three baboons were surgically intact and were normotensive (113 ± 1/79 ± 2 mmHg).

Apparatus and Environment

Animals were individually housed in home cages [(LWH) 1.2 × 0.9 × 1.4 m] except during daily 75-min behavioral testing periods. Cages contained a seating bench and a spout for ad lib ingestion of tapwater. Two housing rooms each contained between seven to nine other individually caged baboons. Each baboon's field of view included at least one other baboon at all times. The light : dark cycle of the housing rooms was 12 L : 12 D; lights were on at 0600 h.

Animals wore a noninvasive, 1-oz. activity-monitoring device with no external wires (LWH = 5.5 × 3.3 × 1.5 cm; Individual Monitoring Systems, Inc., Baltimore, MD) that was slightly modified from one developed at NIH (3). The modification adjusted the response frequency to be maximum for 0.5–10 Hz, the range noted to be most significant for body movements in humans (19). The monitor was inserted into a padded metal container mounted on the outer surface of a soft leather collar. The collar did not interfere with eating or movement, was well tolerated, and allowed animals' access to all body parts.

A microprocessor within the monitor records activity over 1,024 time intervals, each of 0.88-s duration. Each interval is further divided in 4,096 equal time bins, with each bin set to either 0 or 1, depending upon whether or not any activity within that time bin exceeds the threshold level (0.1 g force) of the piezoelectric sensor. These activity counts are then summed over the 4,096 bins. Dividing these counts by 4,096 thus provides a measure of the proportion of active periods (referred to as "activity density") within each of the 1,024 time intervals. We report here the proportion of these intervals during a 60-min period. For intense movement such as running or rapidly jumping up and down the movement density approaches 100% (proportion × 100) and for inactive periods such as during sleep the activity density approaches 0%. Movement of the animal in any direction was recorded.

The activity density for each successive 60-min period was recorded by the unit for up to 42 days; at the end of the recording period, data were transferred from the monitor to a computer for analysis. Within-subject reliability of activity measurements across days was previously determined by use of odd–even day (i.e., test–retest) correlations [e.g., (20)] during a 260-day prestudy evaluation period of the monitoring system in two baboon subjects. Correlations of odd–even day activity density were significant at $p < 0.01$ (Pearson's $r = 0.513$ and 0.525 for each of two baboons), showing that the system was reliable.

Procedures

Drugs studied were the β_1 selective β-adrenergic antagonist atenolol hydrochloride (2.6 mg/kg/day, PO; Study 1) and the nonselective β-adrenergic antagonist *d,l*-propranolol hydrochloride (6.8 mg/kg twice daily, PO; Study 2). Drugs were administered orally to mimic human clinical dosing methods. For precise dosing, both atenolol and propranolol (Sigma Chemical Co., St. Louis, MO) were weighed in powdered form and inserted into a small piece of fruit as vehicle. On no occasion was an animal seen to reject the drug; ingestion occurred in less than 5 min. Doses were chosen to be at the high end of doses clinically used for hypertension, matched with humans for mg/kg body weight.

Each study consisted of the following consecutive phases: a 14-day baseline (daily vehicle alone), followed by a 21-day active dosing period with drug, and concluding with a 14-day vehicle-alone condition ("postdrug recovery"). Changes in dosing conditions (e.g., onset of active dosing, termination of active drug) occurred on Tuesdays.

Propranolol was administered twice daily and atenolol was administered once daily. During baseline and postdrug recovery conditions, vehicle alone was administered once daily for the atenolol study, and twice daily for the propranolol study. Propranolol was administered at a 2-h dosing interval for practical reasons 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 weekdays, drug administration was staggered to coincide with each animal's behavioral testing session. Drug administration occurred between 0800–1700 h across animals, with the order of drug administration strictly alternated between normotensive and hypertensive baboons. On weekends, all animals were administered drug at 9 a.m.; the second daily dose of propranolol was administered at 3 p.m.

TABLE 1

MEAN (±SEM) ACTIVITY DENSITY/24 h BEFORE, DURING, AND FOLLOWING PROPRANOLOL DOSING

	Baseline WK2	PROP WK1	PROP WK2	PROP WK3	POST WK1	POST WK2
Renovascular hypertensive*	40.65 ± 13.47	39.33 ± 12.68	41.80 ± 12.8	40.86 ± 12.45	40.78 ± 12.85	47.26 ± 13.98
Normotensive†	23.31 ± 8.00	23.93 ± 8.15	23.05 ± 6.97	19.52 ± 6.16	26.65 ± 8.42	24.62 ± 7.61

PROP, propranolol; WK, week.
*n = 3.
†n = 2.

During these studies, baboons were tested daily (Mon–Fri) on an operant repeated-acquisition task during 75-min experimental sessions conducted in a separate testing chamber. Behavioral performances and response reaction time data measured during the sessions are reported elsewhere (Turkkan and Hienz, submitted).

Data analysis. A "day" was defined as a 24-h period beginning at 0300 h. For comparison of the treatment conditions, weekly (5-day means excluding weekends and holidays) data were analyzed as percent change from the baseline week immediately preceding drug administration. Several measures of activity were summarized for data analysis: a) average activity density/day (activity density/60 min as an average for 24 h); b) total inactive periods/day (total number of 60-min periods/24 h containing zero activity); c) consecutive inactive periods/day (total number of consecutive 60-min periods of zero activity/24 h); and d) average activity during each of six daily time periods, each 4 h in duration. Finally, sleep fragmentation was indexed by the number of inactivity interruptions per 24-h period.

Omnibus hypothesis testing employed repeated-measures analysis of variance (ANOVA) for group (hypertensive vs. normotensive) and treatment week (percent change from baseline across dosing and postdrug weeks). Probability levels less than or equal to 0.05 were considered significant. The more conservative Huynh–Feldt probability levels were used to control for violations of sphericity due to repeated measures, which may result in inflated ANOVA F ratios. All posthoc comparisons of means were conducted with use of 95% confidence intervals. Because each animal received drug at an individual time of day, ANOVAs to determine time of day effects were conducted on activity levels of individual subjects across experimental weeks; the most conservative Greenhouse–Geisser probability levels are reported for individual-subject ANOVAs. Also, individual-subject ANOVAs were conducted only if an overall significant treatment effect was observed. Due to monitor malfunction, data were excluded from one normotensive baboon (PW) during the propranolol study.

RESULTS

Propranolol Effects

Group differences. Average activity density/24 h decreased below baseline in the third week of propranolol dosing and increased to or above baseline after active drug was discontinued [treatment: $F(4, 12) = 8.82, p = 0.0015$]. For the normotensive baboons, activity was decreased by approximately 4% in the third week of dosing (Table 1 and Fig. 1); decreases in activity during the third week were significantly greater

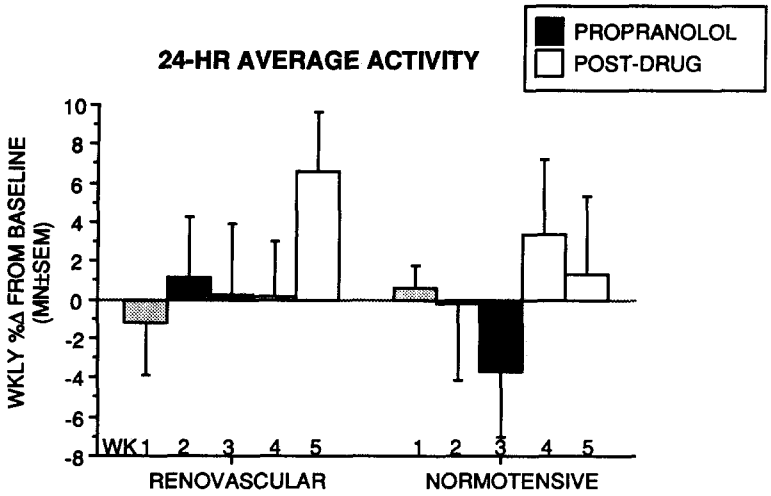

FIG. 1. Average (±SEM) percent change in activity density across propranolol (filled bars) and postdrug weeks (unfilled bars) as a function of baboon group (renovascular n = 3; normotensive n = 2). Each datum is a 24-h average, averaged across 5 days. Significant differences between means were found for normotensive baboons: between the first and third propranolol dose weeks and between the third propranolol dose week and the first postdrug week.

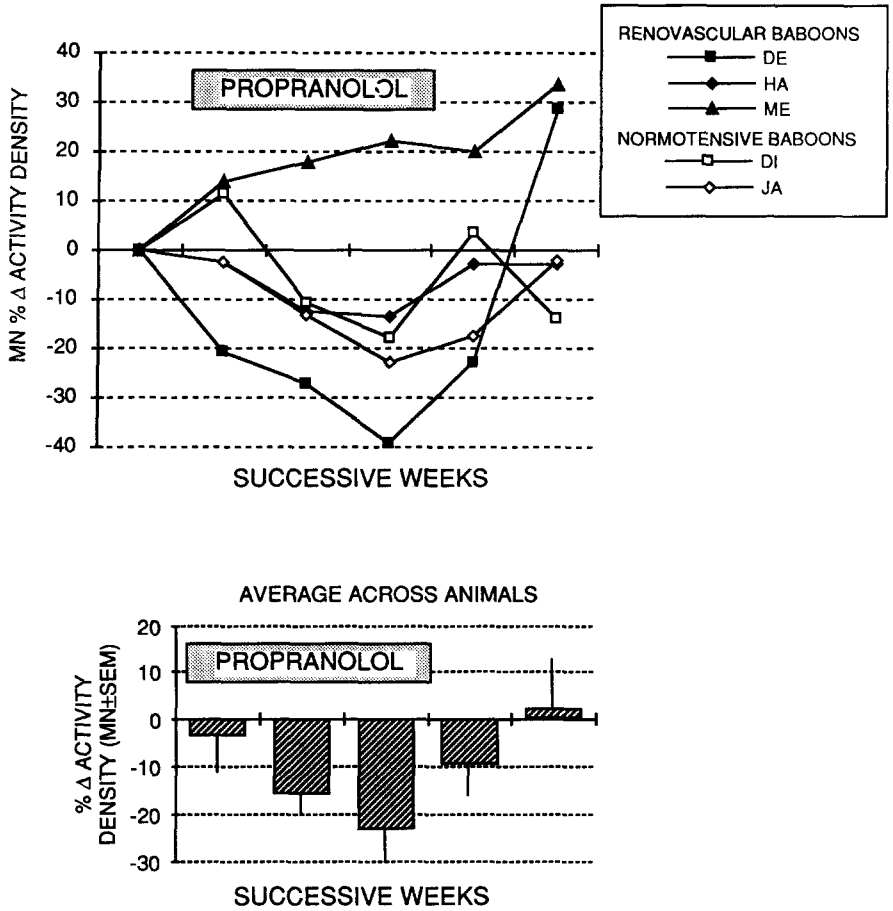

FIG. 2. Upper: Percent change in average activity density at the time of day of the second daily propranolol dose as a function of successive weeks. Functions for individual baboons are shown for renovascular hypertensive (filled data points) and normotensive baboons (unfilled). Each datum is an average over 4 h encompassing the time of day that an animal's second daily dose of propranolol was administered, averaged over 5 successive weekdays. Lower: mean (±SEM) percent change averaged over animals across successive experimental weeks. Baboon ME, who showed an increase in activity, is omitted from the average.

than in the first week. Overall activity for the renovascular baboons was unchanged across experimental weeks [treatment week × group: $F(4, 12) = 6.25, p = 0.006$; Table 1 and Fig. 1]. Activity in both groups increased after propranolol was discontinued, although increases reached significance only in the normotensive baboons.

Time of day effects. Each animal received drug at an individual time of day to coincide with his daily operant testing session, necessitating individualized analysis of propranolol's effects on activity as a function of time of day. These analyses revealed that not all times of day were sensitive to the effects of propranolol on activity (all individual-subject ANOVAs were significant for treatment × time of day interactions). Maximal changes in activity for all animals were evident at about the time of day corresponding to their second daily propranolol dose. Four animals showed decreases in activity at this time of day, while activity of one renovascular animal increased (ME) as illustrated for individual animals across experimental weeks in Fig. 2 (top). Average maximal decreases in activity at this time of day were approximately 20% during the third week of propranolol dosing (Fig. 2, bottom).

Propranolol's effect on activity as a function of time of day is shown in 24-h functions for normotensive baboon JA (Fig. 3). Little change in activity occurred during the first week of propranolol dosing in comparison to baseline weeks, with progressive decreases evident during the second and third weeks of drug dosing. This animal's activity decreased maximally at 1100 h, the time of day when his second daily propranolol dose was ingested. Activity also was decreased at 0800 h, when the first daily dose was ingested.

No significant effects of propranolol were obtained for the sleep fragmentation index, the number of 1-h periods with inactivity, or for consecutive periods with inactivity.

Atenolol Effects

Although statistically significant changes in activity were not obtained across the atenolol study weeks (treatment $p > 0.10$), atenolol decreased activity in two normotensive baboons at the time of day corresponding to the daily drug dose. Maximal activity decreases for the normotensive baboon group (Table 2) averaged approximately 15-25% (depending upon time of day; Fig. 4) below baseline during the second and third atenolol dosing weeks. Activity increased toward

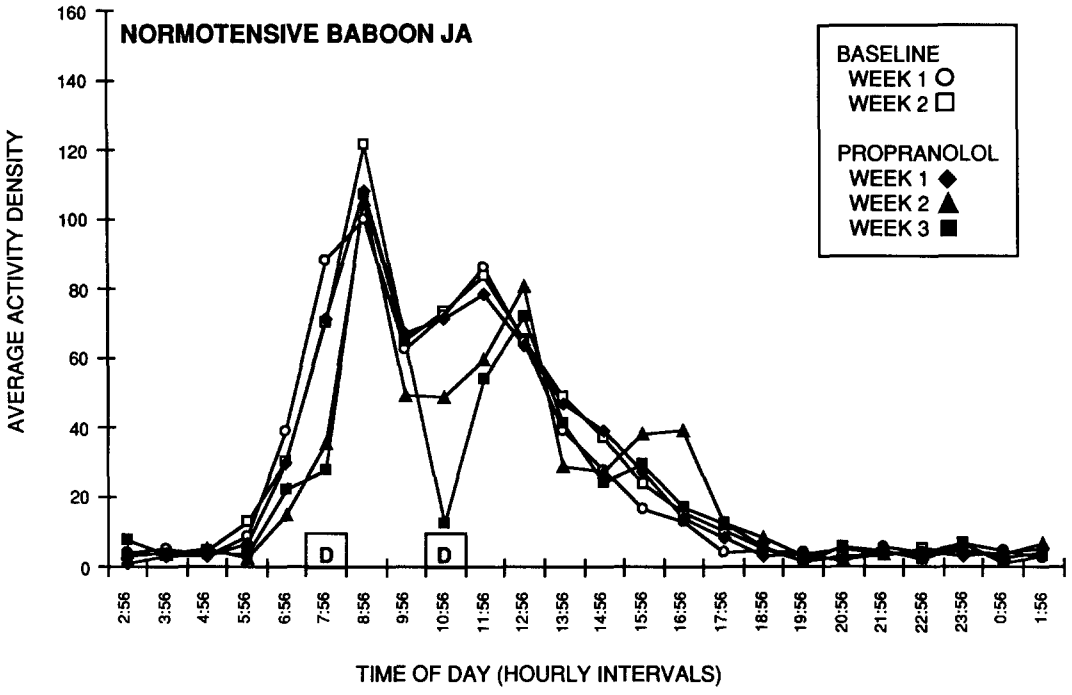

FIG. 3. Weekly average 24-h plots of hourly activity density for normotensive baboon JA. Baseline weeks (unfilled data points) are contrasted with propranolol dosing weeks (filled data points). Each data point is activity density recorded over a 1-h period, averaged over 5 successive weekdays. D denotes times of day when drug was administered. Seventy-five-minute operant sessions occurred at 0900 h, and the animal received his daily food ration at approximately 1200 h.

baseline in the postdrug weeks. There was sufficient variability across baboon groups that treatment × group interactions were not, however, significant.

DISCUSSION

Propranolol decreased spontaneous motor activity of normotensive baboons and had little overall effect on activity in hypertensive baboons. Maximal decreases in activity of normotensive baboons occurred in the third week of twice-daily oral dosing. Propranolol's effects on activity corresponded to times of day when ingestion of the second daily dose occurred. Atenolol produced a similar, although nonsignificant, trend for normotensive baboons. As reported elsewhere (Turkkan and Hienz, submitted for publication), the two drugs produced differential changes in blood pressure with BP decreased during propranolol but not during atenolol.

The differential effects of atenolol and propranolol on spontaneous activity conform to some suggestions in the literature that propranolol produces greater CNS side effects than atenolol due to its nonselective β-antagonist and high lipophilic properties (15). Comparisons of the psychomotor effects of atenolol vs. propranolol have, however, produced a variety of outcomes. In a pair of studies using identical single-dosing protocols in normal humans, for example, both atenolol and propranolol impaired psychomotor function to an equivalent degree (22,23). On the other hand, normal human subjects show enhanced CNS effects of propranolol on sleep variables but not on psychomotor measures, whereas atenolol has no effect on either of these measures (10). In other studies, neither atenolol nor propranolol affected psychomotor performances after up to 7 days of chronic dosing [e.g., (12)].

With regard to sleep and 24-h ambulation measures, Kostis and Rosen (10) examined a variety of measures including sleep variables, psychomotor performance, and self-reported mood after administration of several β-blockers differing in dimensions of lipophilicity, selectivity for β_1 receptors, and intrinsic sympathomimetic activity. Their data suggest that lipophilic agents such as propranolol impair sleep, perhaps due to their relative ease in crossing the blood-brain barriers. No changes

TABLE 2

MEAN (±SEM) ACTIVITY DENSITY/24 h BEFORE, DURING, AND FOLLOWING ATENOLOL DOSING

	Baseline WK2	ATEN WK1	ATEN WK2	ATEN WK3	POST WK1	POST WK2
Renovascular hypertensive*	41.03 ± 12.8	37.25 ± 12.35	41.17 ± 12.77	40.59 ± 12.8	40.63 ± 12.96	40.59 ± 12.73
Normotensive†	24.78 ± 6.89	19.43 ± 5.55	19.08 ± 5.42	19.05 ± 5.21	21.00 ± 5.75	21.47 ± 6.07

ATEN, atenolol; WK, week.
*n = 3.
†n = 3.

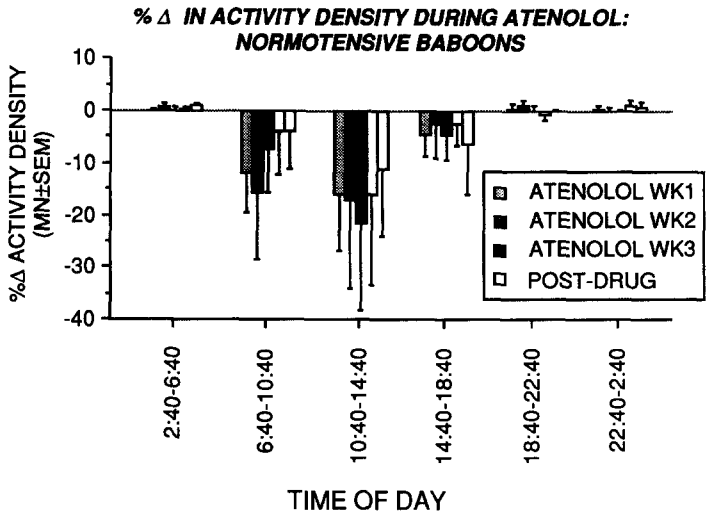

FIG. 4. Average percent change (±SEM) in activity density across atenolol (filled columns) and postdrug weeks (unfilled columns) as a function of time of day. Each datum is a 4-h average, averaged across 5 days and averaged over 3 normotensive baboons.

in the indirect sleep indexes were found in the present study, such as increases in 1-h periods with inactivity or the sleep fragmentation index. It may be that the 1-h recording intervals used were not sufficiently sensitive to changes in these indices. And, since electroencephalogram activity was not recorded occasions of sleep had to be inferred indirectly from the present activity measures.

Activity decreases obtained during chronic propranolol could have resulted from orthostatic (postural) hypotension. During chronic dosing, systolic blood pressures decreased by 12–17 mmHg across animals, with no differences observed for the normotensive vs. renovascular groups (Turkkan and Hienz, submitted). Because blood pressure decreases of this magnitude were obtained in normotensive baboons, blood pressures may have fallen below levels needed for adequate perfusion, resulting in orthostatic hypotension with attendent dizziness. Blood pressure decreases of similar magnitude in the renovascular hypertensive baboons merely returned their blood pressures to normal levels. This hypothesis is consistent with the finding that although blood pressures decreased in both groups during propranolol only normotensive baboons demonstrated decreases in average 24-h activity (Table 1). Orthostatic hypotension as assessed by acute BP decrease to vertical tilt has not, however, been found in cynomolgous monkeys after acute infusions of propranolol (18). The doses studied, however, were lower than the present dose. Also, in the present study maximal decreases in activity occurred in the third week of propranolol dosing, suggesting that if orthostatic hypotension developed it may not be problematic until propranolol is administered for some duration. It should be noted that anecdotal observations of animals did not reveal decreases in activity to the degree of immobility (e.g., lying on the cage bench), which is supported by a failure to find increases in the number of hourly intervals with zero activity.

It is unclear why one of the renovascular hypertensive baboons displayed increases in activity during propranolol. An examination of the circadian patterns of this animal revealed a shift in the activity pattern so that peak activity occurred earlier in the day in addition to overall increased activity; the source of these shifts is, however, unknown. It is unlikely that the increased activity was due to the drug since activity did not return to baseline levels after drug was terminated. All animals showed increased activity after propranolol was discontinued, either back to or slightly above baseline levels. The abrupt withdrawal of propranolol, as done here, has not been recommended therapeutically (28).

Psychomotor performances of animals were assessed in daily sessions with use of a repeated acquisition paradigm (Turkkan and Hienz, submitted). Atenolol but not propranolol increased response latencies and decreased accuracy. The time of day activity outcomes of the present study suggest the possibility that stronger evidence of psychomotor impairment under propranolol may have been obtained if the behavioral sessions had been conducted after the second daily dose rather than after the first daily dose. While renovascular hypertensive baboons showed little overall decreases in activity, two of three hypertensive animals did display decreased activity following ingestion of the second daily dose, with one hypertensive baboon's activity dropping by 40%. Although acute blood pressure decreases are maximal within 30 min after oral dosing at the dose used here, previous studies have shown that peak plasma concentrations of propranolol occur at 1½–2 h after oral dosing in humans (6). This is the interval following the first daily drug administration after which maximal effects on activity were obtained, coinciding and perhaps summating with the effects of the second daily dose.

We have objectively demonstrated decreased activity during chronic oral dosing with the prototypical β-blocker propranolol. The decreases occurred in the initial weeks of dosing, corresponding to frequent patient reports of fatigue, weakness, and lethargy at the onset of medication with β-blockers (15). Since the behavioral side effects of propranolol and to some extent also for atenolol appear to be modulated by times of day coinciding with drug ingestion, the measurement of spontaneous motor activity can be an important adjunct to the study of the behavioral pharmacology of antihypertensive drugs by providing data about behavioral side effects outside of explicit testing sessions. These data also

prompt similar investigations of long-acting or patch methods of pharmacotherapy, as these methods may stabilize blood levels of drug and therefore minimize fluctuations in ambulation and activity.

ACKNOWLEDGEMENTS

This research was supported by U.S.P.H.S. NHLBI Grant HL34034. The authors thank S. Holmes, L. Daley, and G. Brinkley for technical support.

REFERENCES

1. Berzin, B.; Asseman, P. L.; Desry, D.; Vilarem, D.; Thery, C. Atenolol in the central nervous system of monkeys. Drugs 2:278; 1983.
2. Broadhurst, A. D. The effect of propranolol on human psychomotor performance. Aviat. Space Environ. Med. 51:176–179; 1980.
3. Colburn, T. R.; Smith, B. M.; Guarini, J. J.; Simmons, N. N. An ambulatory activity monitor with solid state memory. Presented at the 13th Annual Rocky Mountain Bioengineering Symposium, May 1976.
4. Durel, L. A.; Krantz, D. S.; Barrett, J. E. The antianxiety effect of beta-blockers on punished responding. Pharmacol. Biochem. Behav. 25:371–374; 1986.
5. Engel, J.; Liljequist, S. Behavioural effects of β-receptor blocking agents in experimental animals. In: Carlsson, C.; Engel, J.; Hansson, L., eds. Neuro-psychiatric effects of adrenergic beta-receptor blocking agents. Berlin: Urban & Schwartzenberg; 1976: 45–50.
6. Fitzgerald, J. D. Propranolol. In: Scriabine, A., ed. Pharmacology of antihypertensive drugs. New York: Raven Press; 1980: 195–208.
7. Frishman, W. H. Beta-adrenoceptor antagonists: New drugs and new indications. N. Engl. J. Med. 305:500–506; 1981.
8. Greenblatt, D. J.; Koch-Weser, J. Adverse reactions to beta-adrenergic receptor blocking drugs: A report from the Boston Collaborative Drug Surveillance Program. Drugs 7:118–129; 1974.
9. Kalkman, H. O. β-Adrenoceptor blockade in rats enhances the ambulation induced by 5-HT_{1A} receptor agonists. Eur. J. Pharmacol. 173:121–125; 1989.
10. Kostis, J. B.; Rosen, R. C. Central nervous system effects of β-adrenergic-blocking drugs: The role of ancillary properties. Circulation 75:204–212; 1987.
11. Kostis, J. B.; Rosen, R. C.; Holzer, B. C.; Randolph, C.; Taska, L. S.; Miller, M. H. CNS side effects of centrally-active antihypertensive agents: A prospective, placebo-controlled study of sleep, mood state, and cognitive and sexual function in hypertensive males. Psychopharmacology (Berl.) 102:163–170; 1990.
12. Landauer, A. A.; Pocock, D. A.; Prott, F. W. Effects of atenolol and propranolol on human performance and subjective feelings. Psychopharmacology (Berl.) 60:211–215; 1979.
13. Lichter, I.; Richardson, P. J.; Wyke, M. A. Differential effects of atenolol and enalapril on memory during treatment for essential hypertension. Br. J. Clin. Pharmacol. 21:641–645; 1986.
14. Madden, D. J.; Blumenthal, J. A.; Ekelund, L. G.; Krantz, D. S.; Light, K. C.; McKee, D. C. Memory performance by mild hypertensives following beta-adrenergic blockade. Psychopharmacology (Berl.) 89:20–24; 1986.
15. McAinsh, J.; Cruickshank, J. M. Beta-blockers and central nervous system side effects. Pharmacol. Ther. 46:163–197; 1990.
16. McGill, H. C., Jr.; Carey, K. D.; McMahan, C. A.; Marinez, Y. M.; Cooper, T. E.; Mott, G. E.; Schwartz, C. J. Effects of two forms of hypertension on artherosclerosis in the hyperlipidemic baboon. Arteriosclerosis 5:481–493; 1985.
17. Nicholson, A. N.; Wright, C. M. Behavioral studies in the monkey (*Macaca mulatta*) with sotalol and with (+)−, (+) and (−)-propranolol. Br. J. Pharmacol. 61:474–475; 1977.
18. Pals, D. T.; Orley, J. A nonhuman primate model for evaluating the potential of antihypertensive drugs to cause orthostatic hypotension. J. Pharmacol. Meth. 9:183–192; 1983.
19. Redmond, D. P.; Hegge, F. W. Observations on the design and specification of a wrist-worn human activity monitoring system. Behav. Res. Method. Instrum. Comp. 17:659–669; 1985.
20. Robbins, T. W. A critique of the methods available for the measurement of spontaneous motor activity. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology. vol. 7. Principles of behavioral pharmacology. New York: Plenum Press; 1977:37–82.
21. Ryan, J. R.; LaCorte, W.; Jain, A.; McMahon, F. G.; Rosenberg, A. Atenolol in the treatment of hypertension: A single daily dose. Curr. Ther. Res. 33:1035–1040; 1983.
22. Salem, S. A.; McDevitt, D. G. Central effects of beta-adrenoceptor antagonists. Clin. Pharmacol. Ther. 33:52–57; 1983.
23. Salem, S. A. M.; McDevitt, D. G. Central effects of single oral doses of propranolol in man. Br. J. Clin. Pharmacol. 17:31–36; 1984.
24. Schenk, G. K.; Lang, E.; Anlauf, M. Beta-receptor blocking therapy in hypertensive patients—effects on vigilance and behavior. Aviat. Space Environ. Med. 52:S35–S39; 1981.
25. Turkkan, J. S. Behavioral performance effects of antihypertensive drugs: Human and animal studies. Neurosci. Biobehav. Rev. 12:111–122; 1988.
26. Van Gelder, P.; Alpert, M.; Tsui, W. H. A comparison of the effects of atenolol and metoprolol on attention. Eur. J. Clin. Pharmacol. 28:101–103; 1985.
27. van Rooy, P.; Myburgh, D. P.; Cilliers, A. J. Evaluation of the effect of atenolol on the reaction time of healthy volunteers. Eur. J. Clin. Pharmacol. 28:105–107; 1985.
28. Weiner, N. Drugs that inhibit adrenergic nerves and block adrenergic receptors. In: Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad, F., eds. The pharmacological basis of therapeutics. New York: MacMillan Publishing Co.; 1985:181–214.