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The Effect of Ondansetron on Cognitive Performance in the Marmoset

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DOMENEY, A. M., B. COSTALL, P. A. GERRARD, D. N. C. JONES, R. J. NAYLOR AND M. B. TYERS. *The effect of ondansetron on cognitive performance in the marmoset.* PHARMACOL BIOCHEM BEHAV **38**(1) 169–175, 1991.—The 5-HT_3 receptor antagonist, ondansetron, was administered to marmosets to determine its effect on their performance in a Wisconsin General Test Apparatus using an object discrimination reversal learning task. Briefly, this comprised a test situation in which marmosets were required to select a food rewarded object to reach criterion in performance (this was termed the initial discrimination task); the rewarded object was then changed (in the same test session) and the marmoset was required to abandon its recently learned strategy to gain reward by selection of the second object (this was termed the reversal task). At doses of 1–10 ng/kg SC b.i.d. ondansetron improved performance in both the initial discrimination and reversal tasks. This was indicated as a reduction in the number of trials required to reach criterion, a reduction in choice latency time and a reduction in the number of errors made in each test session. Higher doses of ondansetron impaired performance as measured by several criteria. The major conclusion of this study is, therefore, that ondansetron at low doses is able to improve the performance of marmosets in a cognitive task. This would support the concept that a 5-HT_3 receptor antagonist can act as a cognitive enhancer.

5-HT_3 receptor antagonist Ondansetron Marmoset Cognition Object discrimination reversal

DISTURBANCES in cognition are a feature of the dementia of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and conditions related to cerebral vascular disorders such as multi infarct dementia (14, 19, 22). Because of the long established link between the processes of memory and cerebral cholinergic function, the majority of pharmacological strategies for memory impairments have focused on the use of agents which act at the synapse. However, although some clinical benefits have been reported for treatment with cholinomimetics such as arecoline (9), physostigmine (9), and more recently nicotine (23) and tetrahydroaminoacridine (THA) (32), no useful therapeutic treatment is available for cognitive impairments. Bartus et al. (2) have suggested that the major reasons why cholinomimetic agents have failed to become clinically useful are their short half-life, lack of specificity to CNS, a narrow therapeutic window and the incidence of adverse side effects.

Whilst the cholinergic hypothesis of memory dysfunction remains widely accepted, it is apparent that this may be oversimplistic, particularly since other neurotransmitter systems have been implicated in cognitive disorders (30). For example, Altman and Normile (1) reference a significant amount of evidence implicating a role for serotonin (5-HT) in the processes underlying learning and memory. Additionally, deficits in the 5-HT system have been reported in Alzheimer's disease (7, 15, 24, 26).

The availability of highly selective 5-HT_3 receptor antagonists, together with the knowledge of their ability to influence cholinergic transmission in the gastrointestinal tract, led to the evaluation of the effects of ondansetron (GR38032F) (8) on cognitive performance. Initial studies in rodents and marmosets (12,13) suggested that 5-HT_3 antagonism can enhance cognitive performance.

The present study reports a full investigation of the effects of ondansetron in the common marmoset using the Wisconsin General Test apparatus. The paradigm selected was that of object discrimination learning previously described by Ridley et al. (27).

METHOD

Experimental Animals

Male and female marmosets (there were no significant differences in performance between either sex) weighing 315–335 g were housed in single sex pairs. Animals were given free access to water and food (Mazuri primate diet, S.D.S. Ltd., Essex) which they received in the morning, a minimum of 2–3 h prior to the commencement of testing. The remainder of the diet (fruit, brown bread and malt loaf) was given after testing had finished between 4–5 p.m. Food deprivation was not required to maintain the performance of marmosets.

Holding rooms were maintained at 25 ± 1°C at a humidity of 55%. Rooms were illuminated for 12 h followed by 12-h dark cycle, lights being on between 7 a.m. and 7 p.m. Simulated dawn and twilight periods were programmed to occur 0.5 h before and after the main lights came on or went off. During the 12-h dark period a single 60-W red bulb was illuminated to avoid complete darkness.

Assessment of Performance of Marmosets Using the Wisconsin General Test Apparatus (WGTA)

Apparatus. The studies assessed the performance of marmosets in a miniature WGTA. This consisted of a solid opaque box (45 cm high × 42 cm × 45 cm deep) with an opaque shutter at one end to separate the marmoset from the operator. The shutter could be raised and lowered by the operator to reveal a tray containing two food wells located 14 cm apart. The marmoset was able to place its arms between bars to reach the food wells and displace an object to obtain a reward. During testing, the marmoset was placed behind the shutter in a transport cage suitably large to allow the marmoset complete freedom to move during the test session.

Opposite to the marmoset cage and food wells the WGTA had a one-way screen (12 cm depth) which allowed the marmoset to be viewed by the operator. The one-way screen was located above a hinged flap through which the operator could bait the test tray containing the food wells. The interior of the WGTA was illuminated by a 15-W strip light and all testing took place in a darkened room.

Training. Throughout initial training, animals were presented with a series of trials in the WGTA in which the screen was raised to reveal two plastic junk objects (e.g., a rubber bung and a hypodermic needle case) covering 2 food wells. Only one object (a rubber bung) which could be selected by the marmoset provided a food reward. Food rewards consisted of syrup-coated cubes (0.5 cm) of brown bread. The left/right position of the rewarded object altered throughout each test session according to a pseudorandom schedule [Gellerman, (16)]. The intertrial interval was maintained constant at 15 s and each trial lasted until the marmoset made a response (i.e., selected one of the objects).

Animals were considered to be trained when they were able to perform the above task to an accuracy of 90% correct. In an average daily test session animals generally completed in the order of 40 trials. Initial object discrimination training to 90% correct (i.e., 90 correct responses out of 100) took between 1–3 weeks. Once animals were achieving 90% accuracy on the above task they were tested over a smaller number of trials, 40, 20 and then 10, to ensure that this level of performance was maintained (e.g., an animal giving 90 correct responses out of 100 should then give correct responses in the order of 36 out of 40, 18 out of 20 and 9 out of 10). When consistency of performance was verified, the animals were considered to be trained in object discrimination and could then be utilised in object discrimination reversal tasks.

Object Discrimination Reversal Learning

In this task the basic test system was identical to that of simple object discrimination training, with the exception that the animals were introduced to two novel junk objects which were subject to a changing reward contingency in the same test session. The task consisted of two components, an initial object discrimination task followed by reversal of this task.

On the first day of testing the marmoset was required to displace one of two plastic junk objects covering a food well to collect the reward (initial discrimination task). Once the animal had selected the rewarded object to a criterion of 6 consecutive correct responses the reward contingency was changed such that the previously unrewarded object became the rewarded object. The animal was then required to select this object to the same criterion (reversal task). Both the initial and reversal tasks took place within the same daily test session. On the second test day, the last rewarded object on day 1 now became the initially rewarded object on day 2. Animals were tested over a 5-day period. Following a break of 2 days to coincide with weekends, when the feeding routine differed slightly from the weekday routine, testing recommenced for a further 5 days.

Assessment of Choice Latency

Recording the duration of each completed initial discrimination and reversal task allowed the calculation of choice latency using the following formula.

$$\text{Choice latency} = \frac{\text{Total test time} - ((n-1) \times 15)}{n}$$

where n = number of trials and the intertrial period = 15 s.

Learning Curves

These reflect the total number of errors made by the marmosets in blocks of 5 trials for either the initial or the reversal learning tasks (see the Results section).

Mean daily errors. Regression analysis of the learning curve data indicated that there was no significant ($p>0.05$) change in response between days either before drug treatment or during drug treatment and hence the number of daily errors made by individual marmosets on either the initial or the reversal task was calculated for each treatment week and is presented as mean daily errors.

Drugs

Drug treatments were administered twice daily (8 a.m. and 6 p.m.) for 5 days according to a random, blind crossover design, using a minimum of 4 animals at each dose level. Treatment protocols were designed such that each 5-day drug treatment was preceded and followed by 5 days of vehicle.

Ondansetron (GR38032F, Glaxo) was dissolved in sterile saline and administered in a volume of 1 ml/kg body weight by the subcutaneous route. Testing commenced between 2.5–3 hours following the morning injection. Dose schedules are indicated in the Results section.

Statistical Analysis

Data was analysed using a paired *t*-test for number of trials to criterion, an unpaired *t*-test for choice latency and paired *t*-test for learning curve data (calculated on mean errors in each task).

RESULTS

Performance of Normal Marmosets in an Object Discrimination Reversal Task

Marmosets found performance of the reversal task (22.7 ± 1.25, mean trials to criterion) to be more difficult than the initial discrimination task (14.1 ± 0.9, mean trials to criterion), and consistently required more trials before reaching criterion for reversal.

Effects of Ondansetron on the Performance of Individual Marmosets in an Object Discrimination Reversal Task

The effects of ondansetron were assessed in four marmosets at each dose level. Examples of individual animal performance are shown in Figs. 1 and 2. Marmosets showed an improvement in performance on both the initial and reversal learning tasks when tested over a 5-day period in comparison with vehicle-treated animals. The improvements in performance of individual animals (treated with ondansetron 10 ng/kg SC b.i.d.) is most clearly shown in Figs. 1 and 2. Improved performance was characterised

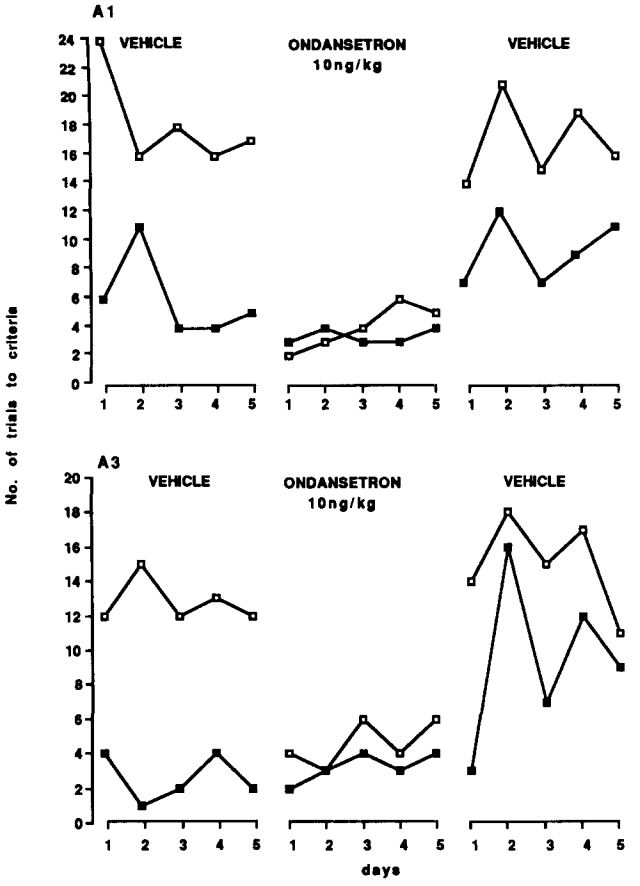

FIG. 1. Effect of ondansetron, 10 ng/kg SC b.i.d., on an object discrimination task (■) and a reversal learning task (□) in the marmoset. Data are given for two individual animals, A_1 and A_3. Animals were tested daily for 5 days during which they received twice daily injections of vehicle. Following a two-day break in testing, animals received twice daily injections of ondansetron (10 ng/kg SC b.i.d.) and were subsequently retested daily for 5 days. Following another two-day break animals received 5 days of twice daily vehicle treatment and daily testing. There was no statistical difference in group means for pre- and posttreatment data.

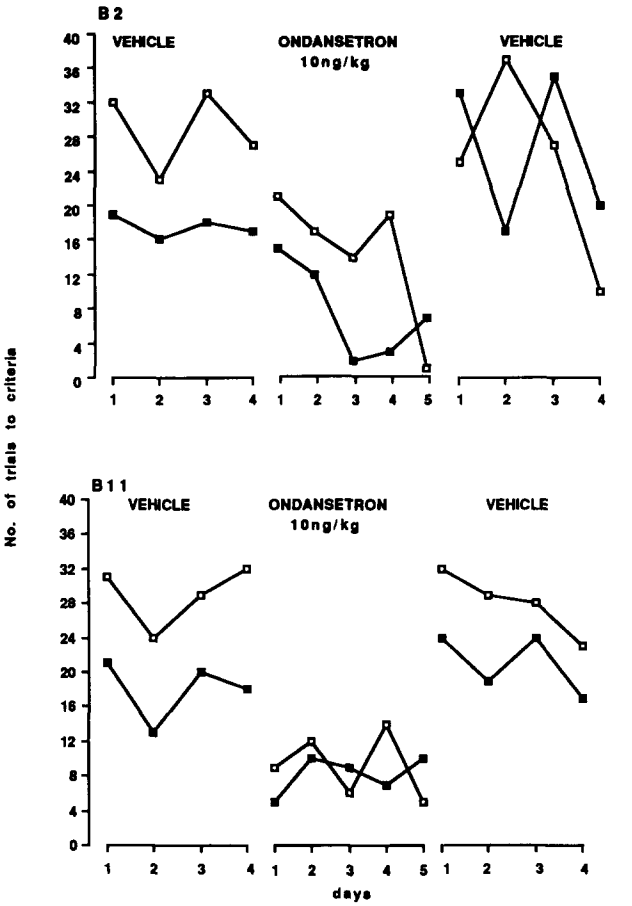

FIG. 2. Effect of ondansetron, 10 ng/kg SC b.i.d., on an object discrimination task (■) and a reversal learning task (□) in the marmoset. Data are given for two individual animals, B_2 and B_1. Animals were tested daily for 5 days during which they received twice daily injections of vehicle. Following a two-day break in testing, animals received twice daily injections of ondansetron (10 ng/kg SC b.i.d.) and were subsequently retested daily for 5 days. Following another two-day break animals received 5 days of twice daily vehicle treatment and daily testing. There was no statistical difference in group means for pre- and posttreatment data.

by a reduction in the number of trials required to reach criterion for both the initial and the reversal learning tasks. These effects, particularly for the reversal learning task, were apparent on day 1. The improvements in performance were maintained throughout the 5-day testing period. Following withdrawal of drug treatment, the performance of 3 out of 4 animals showed a slight worsening of accuracy which was unstable for several days although not significantly different to predrug levels. Choice latency was not significantly affected by withdrawal of drug treatment.

Ondansetron (1 ng–10 ng/kg SC b.i.d.) could be shown to cause significant ($p<0.05$) dose-related reductions in the mean number of trials required to reach criterion for both the initial and reversal learning tasks (Fig. 3). At 1 ng/kg SC b.i.d., ondansetron reduced the number of trials to criterion for the initial discrimination task by 62.2%, and by 59.6% for the reversal task, all comparisons being to vehicle treatment. Similarly, at 10 ng/kg SC b.i.d., ondansetron reduced the number of trials to criterion for both initial and reversal learning tasks by 47.0% and by 54.4% respectively. At a higher dose of 10 μg/kg SC b.i.d., significant ($p<0.05$) reductions in the number of trials to reach criterion were only obtained for performance of the reversal task. Increasing the dose further, to 100 μg/kg SC b.i.d., caused performance of the reversal task to be significantly impaired ($p<0.05$). This impairment was measured as a 57% increase in the number of trials required to reach criterion to complete the reversal task.

Effects on Choice Latency

Marmosets treated with ondansetron at a dose of 1 ng–10 ng/kg SC b.i.d. showed a significant reduction ($p<0.05$) in choice latency (Fig. 4). This reduction reflected an increase in efficiency of responding and corresponds with improved performance. At 10 μg/kg SC b.i.d., ondansetron failed to significantly modify choice latency compared to vehicle control values ($p>0.05$), and increasing the dose further to 100 μg/kg SC b.i.d. resulted in a significant ($p<0.05$) increase in choice latency when comparisons were made to the responses of vehicle-treated animals.

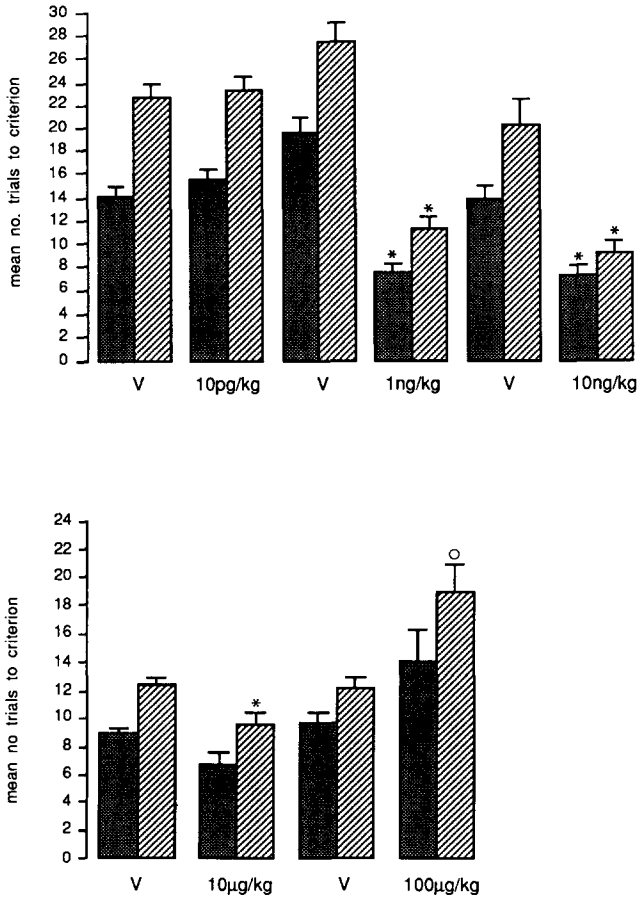

FIG. 3. Ability of ondansetron to modify the performance of marmosets in an object discrimination reversal task. Data are presented as number of trials to criterion (six consecutive correct responses) on an initial learning task, (dotted bars) with subsequent reversal learning of this task (hatched bars). The mean number of trials to criterion for both the initial and reversal tasks of animals receiving ondansetron (doses indicated) were compared to the appropriate vehicle (V) treatment. Significant improvements in performance are shown as $*p<0.05$, whilst significant impairments are shown as $°p<0.05$ (paired t-test) n = 4.

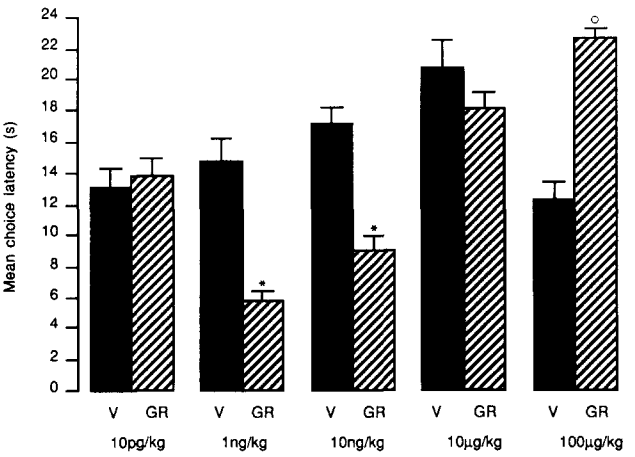

FIG. 4. The effects of ondansetron on mean choice latency. Mean choice latency was calculated for the total number of trials completed in each daily test session (initial and reversal tasks) and compared to vehicle treatment. Significant reductions in choice latency are shown as $*p<0.05$, whilst significant increases in choice latency are shown as $°p<0.05$ (calculated on day 2 responding of animals receiving 100 µg/kg SC b.i.d.) (Student's t-test) n = 4.

Effects on the Number of Errors Made by Marmosets in Performance of Tasks

Learning curves. The learning curves for each task at each dose of ondansetron (10 pg/kg–100 µg/kg SC b.i.d.) are shown in Figs. 5 and 6. These were obtained by calculating the numbers of errors in blocks of 5 trials by all the animals and the mean data presented representing errors in the 1st, 2nd and 3rd, etc., block of 5 trials on days 1, 2 and 3, etc., of testing. The start of each curve represents the errors performed by all the animals tested, whilst the last point of each curve represents the errors performed by the number of animals which were deemed the slowest performers. The learning curves shown in Fig. 5A for both ondansetron, 10 pg/kg, and vehicle treatment are indistinguishable. However, learning curves for ondansetron, 1 ng/kg SC b.i.d. (Fig. 5B) and 10 ng/kg SC b.i.d. (Fig. 5C) clearly demonstrate the ability of ondansetron to improve the performance of the animals tested. Not only did animals reach criterion more quickly, but they made fewer errors in doing so. Increasing the dose of ondansetron further to 10 µg/kg SC b.i.d. (Fig. 6A) failed to modify the learning curves in such a marked manner, although there was a trend for a reduction in the number of errors made. At the highest dose assessed (100 µg/kg SC b.i.d.), animals required a greater number of trials to reach criterion, and also showed a trend to make more errors whilst performing each task.

Mean daily errors. Representation of the number of errors as mean daily errors (Fig. 7) corresponds with that shown on learning curves. Ondansetron at doses of 110 ng/kg SC b.i.d. significantly ($p<0.05$) reduced the number of errors made by the marmosets on both the initial and reversal tasks. At higher doses, ondansetron failed to significantly modify the number of errors made by the marmosets in the performance of each task.

DISCUSSION

In the present study the 5-HT_3 receptor antagonist, ondansetron, improved the performance of normal marmosets in an object discrimination reversal paradigm. The ability of ondansetron to improve cognitive performance in its own right extends preliminary data reported from studies in the marmoset (13) as well as those found in the rodent, where ondansetron attenuates scopolamine-induced or age-related deficits in a T-maze reinforced alternation task (12) and in a mouse habituation test (5). Because of the nature of the rodent studies, improvements in basal performance were difficult to detect. The marmoset studies were specifically designed to look for these, and the improvements in basal performance were marked.

The 'same day' object discrimination protocol in the marmoset produces deficits in performance which allow for the detection of agents which can improve cognition. Such information cannot be obtained from protocols where animals are performing to a high level of accuracy, over which any improvement would be difficult to test. Such tests include the T-maze reinforced alternation task in the rodent and a 24-h object discrimination reversal paradigm in the marmoset as described by Ridley et al. (29). Whilst the high levels of accuracy in performance in these tests can be reduced by either scopolamine treatment or disruption of the cholinergic projections to the neocortex by lesioning of the

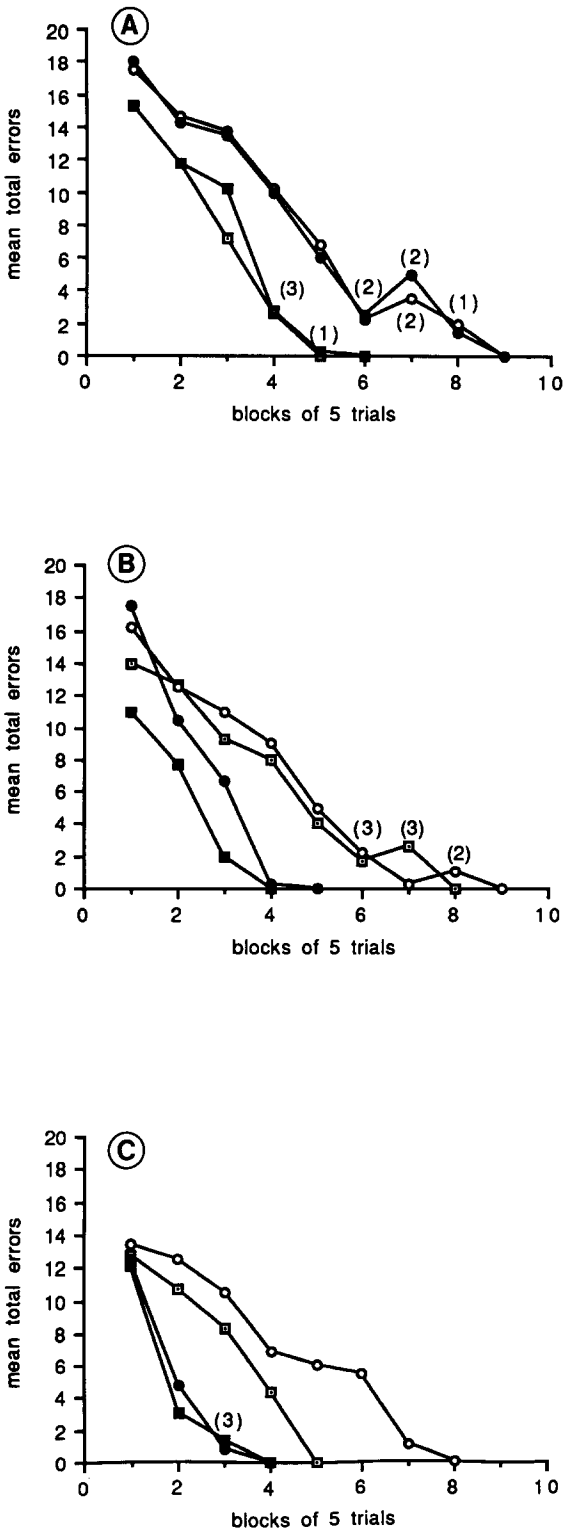

FIG. 5. Learning curves for the initial discrimination task following treatment with vehicle (□) or ondansetron (■) and for the reversal task following treatment with vehicle (●) or ondansetron (○) at the following doses of ondansetron, (A) 10 pg/kg SC b.i.d., (B) 1 ng/kg SC b.i.d. and (C) 10 ng/kg SC b.i.d. The beginning of each curve represents the total number of errors in blocks of 5 trials made by all 4 animals tested. The numbers in parentheses indicate when fewer animals are involved since some animals may have reached criterion.

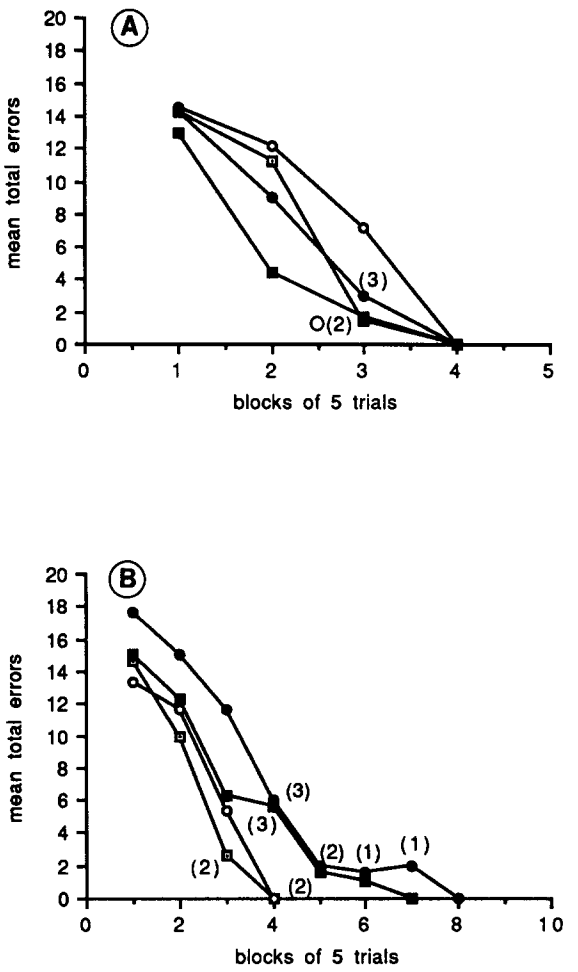

FIG. 6. Learning curves for the initial discrimination task following treatment with vehicle (□) or ondansetron (■) and for the reversal task following treatment with vehicle (○) or ondansetron (●) at the following doses of ondansetron, (A) 10 μg/kg SC b.i.d. and (B) 100 μg/kg SC b.i.d. The beginning of each curve represents the total number of errors in blocks of 5 trials made by all 4 animals tested. The numbers in parentheses indicate when fewer animals are involved since some animals may have reached criterion.

nucleus basalis (13, 28, 29, 31), such strategies were not considered appropriate for initial studies in normal marmosets.

During treatment with ondansetron (1–10 ng/kg) marmosets required, on average, approximately half the number of trials to reach criterion than when treated with vehicle. These improvements were observed for both the initial discrimination and reversal tasks. At the same doses, ondansetron also reduced the time taken for animals to choose an object (choice latency). Thus, at lower doses, marmosets not only completed the tasks in fewer trials, but also made accurate choices more quickly. As the dose of ondansetron increased above 1 μg/kg, these effects were less profound. In contrast to the effects observed at low doses of ondansetron, the highest doses failed to modify the number of trials to criterion on the initial discrimination task, and actually caused significant increases in the number of trials required by the animals to reach criterion on the reversal task. This high dose of ondansetron also increased the choice latency as calculated on the second day of testing. The ability of low doses of ondansetron to enhance performance, whilst a very high dose impaired perfor-

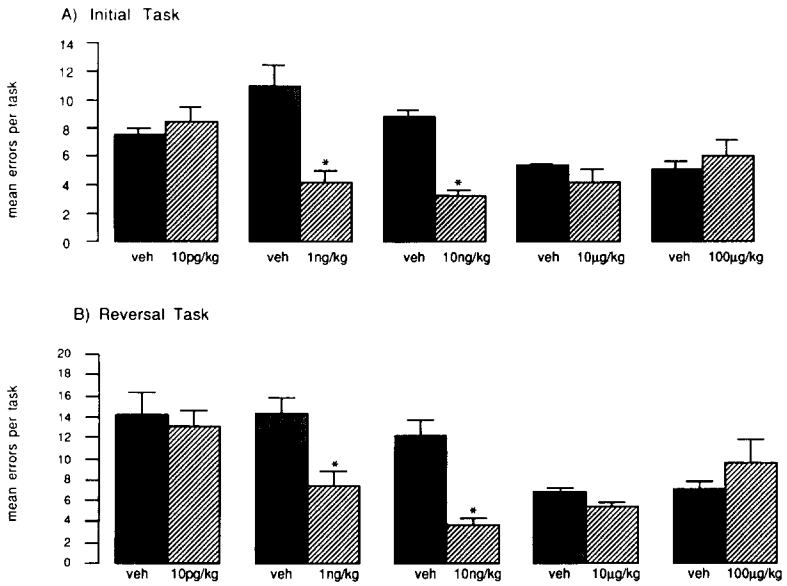

FIG. 7. The effects of ondansetron (µg/kg SC b.i.d.) on the number of errors made by marmosets for: (A) the initial discrimination task; and (B) the reversal task. Data are presented as mean daily errors per task during the 5-day treatment period with either vehicle or ondansetron and shown for increasing doses of ondansetron. Significant differences compared to vehicle control are shown as $*p<0.05$ (paired t-test). n = 4 animals at each dose level.

mance is also revealed in the learning curves constructed for both the initial discrimination and reversal tasks. The learning curves represent the numbers of errors made by animals as they performed each task and therefore can be regarded as an index of performance accuracy. Animals receiving low doses of ondansetron made fewer errors than when they had received vehicle alone, with the converse being true for the highest dose tested.

That a 5-HT_3 receptor antagonist can be shown to have cognitive enhancing properties in these measures of performance is clearly of importance. The mechanism by which ondansetron is producing these effects on the performance of marmosets is unknown. However, it is doubtful that these effects are a consequence of the action of ondansetron at other neurotransmitter receptors. Functional receptor studies and radioligand binding have revealed that ondansetron is highly selective for the 5-HT_3 receptor (8,20). This receptor has been located and fully characterised in both rodent and human brain (3, 4, 20).

At present the nature and mechanism(s) underlying the cognitive improvement afforded by ondansetron are not known. At the behavioural level, it may be suggested that these effects are related to state-dependent learning, however, there is no evidence from the data to support this. Alternatively, ondansetron may influence attentional or associative cognitive processes. At the biochemical level the present findings may be viewed against those of Barnes et al. (5) who demonstrated that 5-HT_3 receptors mediate inhibition of potassium-stimulated [^{3}H]acetylcholine release from rat entorhinal cortex. Such an action may be relevant to the present findings in the marmoset. Thus, it may be that ondansetron acts to enhance cholinergic function, which results in improvements in cognitive performance.

There are no clear explanations as to why ondansetron impaired performance at the highest dose tested. The mechanism(s) of this effect may be the same as that which causes the bell-shaped dose response effects seen in other animal tests such as models for the assessment of anxiolytic activity in rodent and primate (11,18), and models of mesolimbic overactivity in the rat (10,17). However, in the studies in the marmoset, lessening of the effect, and even impairment, occurred over a lower dose range of ondansetron (about 10-fold) than has been found in other species and tests. It is also clear that the effective dose range is considerably lower than previously observed in behavioural tests. The reason(s) for these differences is not known but may support the concept of species 'variants' of the 5-HT_3 receptor (21,25).

The results from the present studies provide no information relating to the mechanism of the declining effects at higher doses. The disinhibitory effects of ondansetron known to occur in the marmoset at doses of 0.1 µg/kg and greater (18) are also unlikely to contribute since diazepam did not impair performance except at doses in excess of those which released suppressed behaviour (unpublished data). From these and other studies it is apparent that the dose-effect relationships between species are not consistent.

In summary, therefore, the selective 5-HT_3 receptor antagonist ondansetron improves performance of marmosets in an object discrimination reversal task. Agents such as ondansetron may represent the first of a novel class of potential cognitive enhancing agents. If these effects can be found in man, these findings may have important implications for the use of 5-HT_3 receptor antagonists in cognitive deficits associated with a number of neuropathological disorders.

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