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Evaluation of Anxiolytic Medication in Animal Models

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Abstract

Anxiety disorders are among the most prevalent and debilitating forms of mental illness, not only in the United States but globally. These clinical data are undoubtedly inconclusive, but if anxious humans respond more inconsistently to buspirone than to benzodiazepine anxiolytics, then buspirone may be superior. A drug may have very reliable impacts in an animal model of anxiety, but only if it also has reliable antianxiety impacts in people. The clinical effectiveness of antidepressant medications in treating anxiety disorders is much more convincing, but there are still differences in effectiveness. This study indicates that buspirone (0.05-1 mg/kg) did not significantly alter the suppressed response rates. Smaller doses of buspirone (0.03-0.5 mg/kg) did not increase the rate of suppressed responding, whereas higher doses (0.5 mg/kg) had the opposite effect. The doses of diazepam (0.2-1 mg/kg) found to be associated with enhanced response. Even after 12 days of daily dosing, buspirone (0.05-1 mg/kg) had significant effect. The findings indicate that buspirone has distinct effects on schedule-controlled behaviour compared to conventional anxiolytics. In this literature we discuss about the difference between buspirone and benzodiazepine anxiolytic and antidepressant effect using animal model.

Keywords: anxiety, animal modeling, medicine, anxiety disorders, anxiolytic drug

1. INTRODUCTION

The Food and Drug Administration recently approved buspirone hydrochloride for the treatment of generalised anxiety disorders. The azaspirodecanediones it represents are a new class of anxioselective substances that are structurally distinct from benzodiazepines. Buspirone has very little sedative effects and has no anticonvulsant or muscle-relaxant characteristics. This particular neuropharmacologic profile has generated a great deal of interest in novel mechanisms underlying the actions of anxiolytic drugs and sheds light on the pathophysiology of anxiety and panic disorders [1].Over 15% of the population will experience an anxiety condition at some point in their lives. Benzodiazepines, low-dose antidepressants, and buspirone are examples of standard anxiolytic therapies. The management of anxiety with any of these three classes of medications is accompanied by a number of drawbacks. Both benzodiazepines and antidepressants can cause drowsiness and motor skill impairment, but benzodiazepine treatment can lead to addiction and antidepressant treatment can have anticholinergic and/or other negative side effects. Anxiety symptoms may first intensify when using antidepressants or buspirone [2]. Antidepressants and anxiolytics had clearly characterised clinical and preclinical activities; benzodiazepines (BDZs) were employed to treat major depressive episodes and anxiety. As a result, the sensitivity of animal models to antidepressants (known as animal models of depression) or BDZs was categorised. (Called animal models of anxiety) [3].

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1.1 ANXIOLYTIC DRUG

Benzodiazepines are widely regarded as the preferred pharmacological intervention for managing anxiety. There are numerous anxiety disorders, including phobic & panic disorders, that are resistant to benzodiazepine treatment. In addition, abrupt discontinuation of these drugs has been associated with severe side-effects, including seizures and psychotic reactions [6]. The probable cause for the prevalence of psychopharmacological investigations in biological anxiety research is the remarkable efficacy of benzodiazepines as anxiolytic agents. Numerous pharmacological substances have been utilized in the treatment of anxiety; however, the administration of once-common agents, such as barbiturates & meprobamate, has been almost entirely replaced by benzodiazepines. One of the primary factors contributing to this phenomenon is the efficacy and relative safety of benzodiazepines. However, it should be note that, akin to all pharmacological agents, they do possess certain adverse effects [3]. Buspirone is an azaspirodecanedione anxiolytic agent. It is different from the most often prescribed class of antianxiety medications, the benzodiazepines, in both its chemical structure and its effects on the body. As a drug that is not a benzodiazepine, buspirone offers a new way to treat anxiety that is not a benzodiazepine. It has a clinical profile and a range of effects in the central nervous system that aren't like anything else [5].

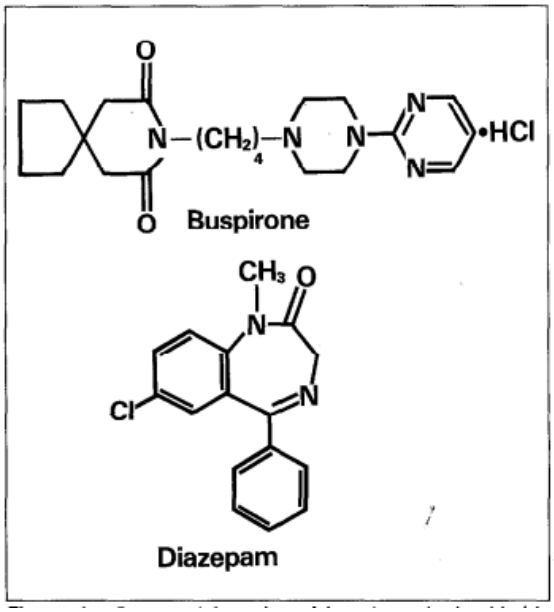

Figure 1.1: Structural formulas of buspirone hydrochloride and diazepam.

1.2 ANXIOLYTIC DRUG ACTION IN ANIMAL MODELS

Since benzodiazepines are efficient against such a wide range of anxiety disorders, they are the preferred medication for treating these conditions. Addiction, tolerance, and dependence/withdrawal are all issues, and users may also have negative side effects such drowsiness, trouble concentrating and moving, and memory loss. Other common medications for treating anxiety include the 5HT-1A partial agonist buspirone and selective serotonin reuptake inhibitors (SSRIs). However, it takes 4–6 weeks for either type of medication to begin working, and each has its own set of drawbacks. Therefore, there is a demand for anti-anxiety medications that are as effective as benzodiazepines but have fewer negative side effects on cognitive and motor functioning. To get the same effect without using benzodiazepines, one might reduce excitatory

glutamatergic neurotransmission [7], as benzodiazepines act by boosting inhibitory GABAergic neurotransmission. From the late 1960s through the late 1980s, the term "false positive" was used to describe antidepressant medications that showed identical results to diazepam in animal models of anxiety. Each "false positive" in a hypothetical model diminished its predictive validity, making it less helpful as a "screening test" for new anxiolytic drugs [8].

1.3 LITERATURE REVIEW

Goa, K. L., & Ward, A. (1986) [9] demonstrated that the Buspirone HCl is a unique, structurally different anxiolytic. Buspirone is "anxioselective" because it does not elicit hypnosis, anticonvulsants, or muscular relaxation like benzodiazepines. Buspirone, like diazepam, may help mixed anxiety/depression patients. Buspirone's side effects are modest and rare, and its sedative effects are rarer than benzodiazepines'. Buspirone does not interact with alcohol or impair psychomotor or cognitive function in healthy people.

Handley, S. L., & McBlane, J. W. (1993) [10] revised about human and animal 5HT neurones cause anxiety. The "classic" theory has driven the hunt for medicines that diminish 5HT function, especially those that target specific 5HT receptor subtypes. Multiple anxiety mechanisms may explain medication affects differences amongst models. Animal models of anxiety may identify non-anxiety aspects like cognition or impulsivity. The recent success of 5HT-selective reuptake medications in treating impulsivity disorder suggests that this finding may be significant. Unraveling the rest of the story may reveal fresh insights into anxiety and anxiety-related disorders.

Taylor, D. P. et al. (1982) [11] examined that Buspirone, commercialized under the brand name Buspar ®, treats anxiety like diazepam with identical doses. Buspirone neither interacts with the benzodiazepine/GABA axis nor structurally resembles benzodiazepines. Buspirone does not affect [aH] benzodiazepine binding. Buspirone does not affect GABA binding or uptake or the effects of GABA or halide anions on benzodiazepine binding. Buspirone does not cause muscle weakness, seizure control, or CNS depressant-induced psychophysiological impairment or lethality, according to behavioural tests. Buspirone does not result in sedation/hypnosis, substance abuse, or physical dependence. It is an effective dopamine agonist and antagonist that interact solely with the dopaminergic system. This implies that dopamine may cause and exhibit worry. Antianxiety drugs that may operate independently from benzodiazepine receptors have led to a reevaluation of assumptions about their mechanisms of action and the neurochemical abnormalities associated with this disease.

Taylor, D. P. et al. (1985) [12] studied that Buspirone (BuSpar) treats anxiety similarly to diazepam and chlorazepate. Buspirone is chemically and pharmacologically unique from benzodiazepines. Buspirone is considered "anxioselective" because it lacks anticonvulsant, sedative, and muscle-relaxing effects. According to biochemical studies, buspirone & the benzodiazepine-y-aminobutyric acid-chloride ionophore complex do not interact directly. Buspirone interacts with dopamine & serotonin receptors at the molecular level. The effects of buspirone are now known to be mediated by additional neurotransmitter systems. Serotonin, norepinephrine & acetylcholine are neurotransmitters. Benzodiazepines and buspirone differ pharmacologically. Buspirone has no anticonvulsant or sedative effects, low interaction with depressants, does not relax muscles, and does not impair performance. Buspirone, unlike benzodiazepines, does not produce physical dependence or abuse. In vivo, buspirone increases

benzodiazepine binding but not in vitro. Stress-induced cerebral dopamine turnover is unaffected by buspirone. Additionally, it decreases acetylcholine levels. Instead of decreasing locus coeruleus noradrenergic neuron activity, buspirone increases it. Additionally, it suppresses dorsal raphe serotonergic neuron activity.

Taylor, D. P. (1988) [13] described about activating GABA receptors may help benzodiazepines, propanediol carbamates, barbiturates, and ethanol reduce anxiety. Buspirone does not affect the GABA receptor since it has other pharmacological effects, (sedation, muscular relaxation, seizure control). The chemical interacts with the neurotransmitter-associated serotonin receptor 5-HT1A. Receptor binding, anatomical localisation, biochemistry, neurophysiology, and animal behavioural studies support this approach. Many pharmaceutical companies are developing 5-HTIA receptor-targeted anxiety treatments. - Despite not directly affecting the GABA receptor, buspirone has been shown to affect serotoninergic neurotransmission through receptor binding, anatomical localization, neurochemistry, neurophysiology, and behaviour. Anxiolytic benzodiazepines affect serotoninergic neurotransmission. Several buspirone structural analogues have serotoninergic neurotransmission-like properties.

Fulton, B., & Brogden, R. N. (1997) et al [14] described that buspirone belongs to the azapirone class of compounds and functions as an anxiolytic agent. There exist structural and pharmacological distinctions between this substance and the benzodiazepines. Buspirone's precise anxiolytic mechanism is unknown; however, its primary pharmacological impact is its interaction with serotonin 5-HTIA brain receptors. In contrast to benzodiazepines, buspirone has not been shown to possess sedative properties and has minimal impact on psychomotor function or cognitive abilities. Buspirone has exhibited effectiveness in individuals who have anxiety & concurrent alcohol (ethanol) addiction/dependency or depression. The administration of Buspirone not only alleviates anxiety symptoms in affected individuals but also leads to enhancements in the comorbid condition. Buspirone significantly decreased the cardinal signs of depression (depressed mood, guilt, work & interest, anergia & cyclical mood swings), suggesting it may have an antidepressant effect distinct from its anxiolytic effect.

Goldberg, H. L. (1984) [15] studied that buspirone belongs to the unique class of anxioselective azaspirodecanediones. Maximum serum concentrations are reached within 60 minutes, and the serum half-life is between 2 and 5 hours. According to studies conducted on animals, this chemical reduces anxiety and is nonaddictive. Buspirone, a dopamine agonist & antagonist, interacts with a variety of neurochemical systems in the brain without affecting GABA or benzodiazepine receptors. In experiments, buspirone increases prolactin & growth hormone. Due to its impact on brain dopamine systems, Buspirone may cause tardive dyskinesia. Current research reveals that its main brain effect is dopaminergic, unlike antipsychotics.

1.5 MATERIALS AND METHODS

Ten adult male Gee's golden languors were subjected to daily experimental periods in which they were given unrestricted access to food. Among sessions, the languor’s returned to their home cages, where their food & water consumption was monitored to maintain their body weights at 80-90% of their free-feeding weights. A venous catheter was implanted in each chimpanzee for intravenous dosing.

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Devices and a behavioral timetable

Primates participated in regular lessons while sitting in Plexiglas chairs inside of sound-absorbing and ventilated rooms. White noise was installed in the chambers to mask any extra sounds. When the response lever was depressed, an auditory click was produced inside the compartment and later recorded as a response. It was attached to the front wall of the chair. Food granules can be delivered to a tray that is built into the chair's front wall. The placement of the primate's caudal appendage inside a small device with metallic wires made it possible to deliver electrical stimulation.

The objective of the study was to determine how monkeys would react to a 5-min fixed interval (FI) schedule of food presentation & a fixed ratio (FR) schedule of electric shocks administered in response to their actions. Under the influence of red light, the initial response took place over the course of 5 minutes, forming a dense mass of food. The fixed ratio was reset at the beginning of each interval during the fixed interval schedule, and shock was given after every nth answer. For each individual monkey in the research, the FR requirement (20 or 35 responses) and shock intensity (0.8–2.5 mA) were adjusted in order to successfully reduce their response rates to 10–20% of their pre-suppressed levels. The Fixed Interval schedule was divided into four sequential parts for the daily sessions. Each component consisted of five FIs in a row, with a prolonged FI before each.

Injection techniques and drugs

In 0.9% sterile saltwater, buspirone was dissolved. To achieve the required concentrations, the drugs diazepam was dissolved in tiny quantities of ethanol & Emulphor EL-620P.

Cumulative dosage was used to study various drugs. During a single test session, a cumulative dose-response curve was determined by injecting an incremental dosage through the venous catheter 5 minutes after the start of each 15-minute timeout period. Each languor was tested once or twice weekly for responses to acutely delivered medications if the preceding session (non-injection control or vehicle control) had resulted in typical response rates and patterns. After the acute trials were finished, buspirone's chronic administration was examined. Buspirone was given every day for 12 days for the chronic study, using the cumulative dosing method, with the exception of Saturday and Sunday. The languor’s got a single i.m. injection of buspirone (0.3 mg/kg) on these days while staying in their familiar cages.

Drug effectiveness evaluation

By dividing the total number of responses in a component by its entire duration, we were able to determine the response rates for each of the four sequential parts of the FI schedule. Average data from the pre-drug non-injection & vehicle control periods were used to determine the component-specific mean control rates. Drug impacts were averaged from numerous independent dose-response curve determinations.

RESULT

Table 1.1: Languor reaction after 5 minute of dose insertion

GROUP	**DOSE (BUSPIRONE)**	**Mean ± SE**	**Time interval 5 minutes**
CONTROL GROUP	0.05-1 mg/kg	±2.7	**Did not react**

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GROUP 1	0.05mg/kg	±3.5	**React slowly**
GROUP 2	1mg/kg	±5.1	**Highly reactive**

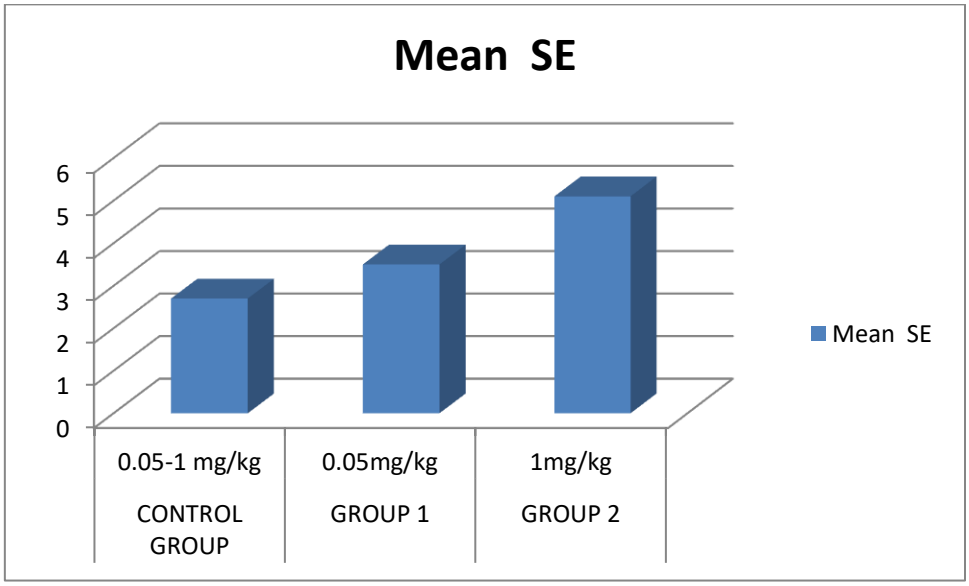
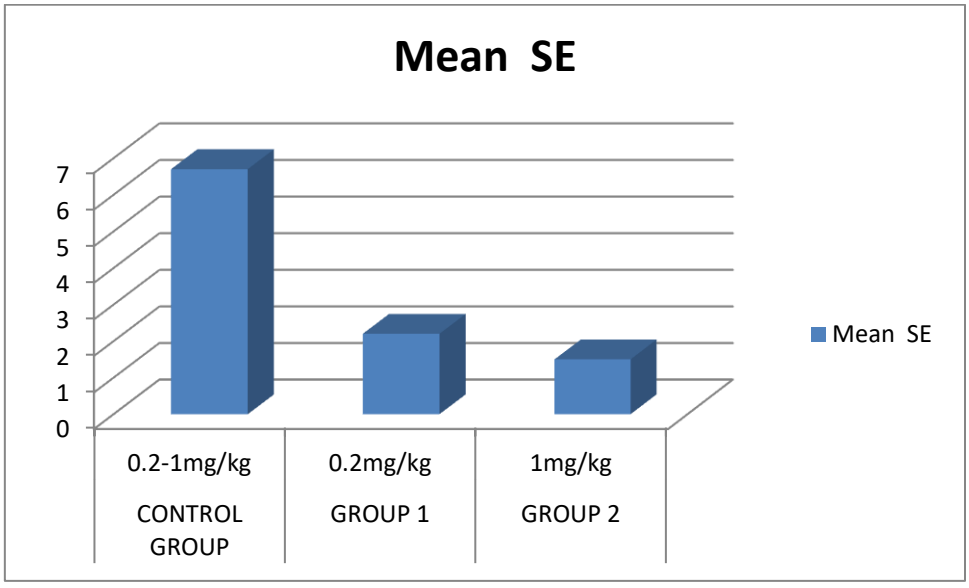


Table 1.1 shows the impact of buspirone on Gee's golden languor within a five-minute timeframe. Group 2 exhibited a rapid and significant response in lethargy compared to the control and group 1 upon administration of a dosage of 1 mg/kg.

Table 1.2: Effect of Diazepam in Languor

GROUP	DOSE (DIAZEPAM)	Mean ± SE	Time interval 15 minutes
CONTROL GROUP	0.2-1mg/kg	**±6.7**	**Spontaneous reaction**
GROUP 1	0.2mg/kg	**±2.2**	**Reactive**
GROUP 2	1mg/kg	**±1.5**	**Average**



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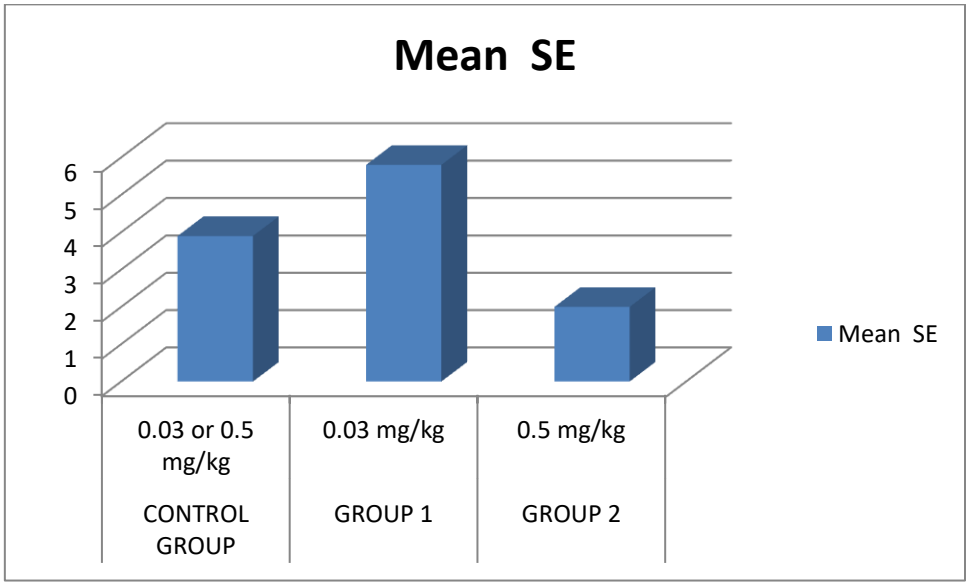
According to Table 1.2, it can be observed that the efficacy of diazepam is comparable to that of buspirone. Buspirone has been found to be more effective as an anti-anxiety medication, whereas it has shown limited efficacy as an antidepressant. The control group exhibits an autonomous response upon the administration of the dose.

Table 1.3 Effect of high dose of buspirone in languor

GROUP	DOSE (BUSPIRONE)	Mean ± SE	Time interval 30 minutes
CONTROL GROUP	0.03 or 0.5 mg/kg	3.9	React Quickly
GROUP 1	0.03 mg/kg	5.8	No reaction
GROUP 2	0.5 mg/kg	2.0	React Slowly



Administration of a high dose of buspirone in individuals experiencing languor results in a rapid onset of action within 30 minutes of drug administration. The administration of buspirone resulted in minimal or reduced reactions in groups 1 and 2. Specifically, after 30 minutes of buspirone administration, the languors exhibited signs of drowsiness and confusion.

Table 1.4: Comparison of buspirone and diazepam highest dose

GROUP	BUSPIRONE VS DIAZEPAM	Mean ± SE	Time interval 5 minutes
GROUP 1	0.5mg/kg buspirone	±1.5	React slowly
GROUP 2	3.2mg/kg diazrpam	±7.2	Highly reactive

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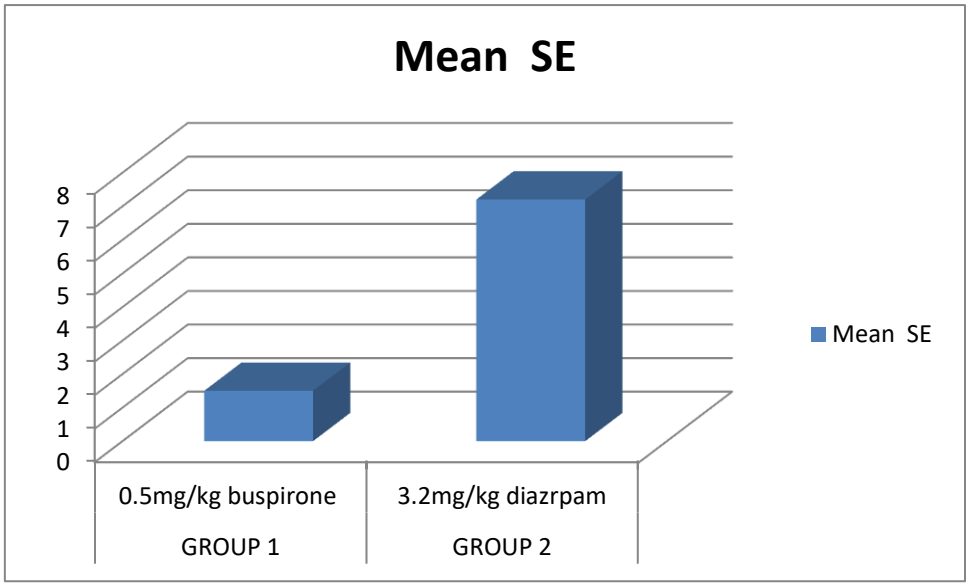

Table 1.4 presents data indicating that the administration of high doses of diazepam resulted in a decrease in the observed reactivity of languors. Specifically, the languor's exhibited a state of calmness or drowsiness following the administration of high doses of diazepam. Buspirone has demonstrated greater efficacy as an anxiolytic due to its delayed onset of action.

Control rates for each component fell within 14% of the norms for the entire session for each subject. FI schedules demonstrated a halt at the beginning of each FI, followed by a muted acceleration in responding over time.

In the group of ten languors, buspirone (0.05-1 mg/kg) did not enhance the number of languor's who did not react. Sometimes, buspirone (0.03 or 0.5 mg/kg) did make some subjects respond more quickly, but this did not happen all the time. All of the people who took the highest amount of buspirone (0.5 mg/kg) responded less. After getting a dose of 0.03 or 0.5 mg/kg of buspirone, the languor's seemed upset and confused. Diazepam (0.2-1mg/kg) increased the rates of suppressed responding in a way that depended on the dose, & at least one dose of diazepam greatly raised the rate in each languor. The highest doses of diazepam tested (3.2 mg/kg) tended to make languor's react less or less; after high doses of diazepam, languor's seemed calm or sleepy. When buspirone (up to 0.5 mg/kg) was given every day for 12 days, the number of controlled seizures did not go up.

CONCLUSION

Gee's golden languor's monkeys were more likely to stop reacting as the dose of diazepam went up. These results are in line with other research that has shown that when anxiolytics bind to benzodiazepine receptors, they usually make the response less slow. In this study, when high amounts of buspirone were given to monkeys, they seemed angry, while diazepam made them calm or sleepy. These results show that buspirone may have some bad effects that could make it less effective as an anxiety medicine. On the other hand, it has been said that this might make it harder to abuse. Buspirone may need to be given over a few days for it to be fully useful as an anti-anxiety drug in people. Also, there wasn't much evidence that long-term use of buspirone changed the way it slowed down the heart rate. However, repeated use of benzodiazepines can rapidly lead to a raise in the rate of repressed responses & a tolerance to the effects of reducing responses.

REFERENCE

1. Jann, M. W. (1988). Buspirone: an update on a unique anxiolytic agent. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 8(2), 100-116.
2. Andrade, C., Aswath, A., Chaturvedi, S. K., Srinivasa, M., & Raguram, R. (2000). A double-blind, placebo-controlled evaluation of the anxiolytic efficacy ff an ethanolic extract of withania somnifera. Indian journal of psychiatry, 42(3), 295.
3. Borsini, F., Podhorna, J., & Marazziti, D. (2002). Do animal models of anxiety predict anxiolytic-like effects of antidepressants?. Psychopharmacology, 163, 121-141.
4. Sanger, D. J. (1992). Animal models of anxiety and the screening and development of novel anxiolytic drugs. Animal models in psychiatry, II, 147-198.
5. Eison, A. S., & Temple Jr, D. L. (1986). Buspirone: review of its pharmacology and current perspectives on its mechanism of action. The American journal of medicine, 80(3), 1-9.
6. Bodnoff, S. R., Suranyi-Cadotte, B., Quirion, R., & Meaney, M. J. (1989). A comparison of the effects of diazepam versus several typical and atypical anti-depressant drugs in an animal model of anxiety. Psychopharmacology, 97, 277-279.
7. Brodkin, J., Busse, C., Sukoff, S. J., & Varney, M. A. (2002). Anxiolytic-like activity of the mGluR5 antagonist MPEP: a comparison with diazepam and buspirone. Pharmacology Biochemistry and Behavior, 73(2), 359-366.
8. Treit, D., Engin, E., & McEown, K. (2010). Animal models of anxiety and anxiolytic drug action. Current topics in behavioral neurosciences, 2, 121–160. https://doi.org/10.1007/7854_2009_17
9. Goa, K. L., & Ward, A. (1986). Buspirone: a preliminary review of its pharmacological properties and therapeutic efficacy as an anxiolytic. Drugs, 32, 114-129.
10. Handley, S. L., & McBlane, J. W. (1993). 5HT drugs in animal models of anxiety. Psychopharmacology, 112, 13-20.
11. Taylor, D. P., Riblet, L. A., Stanton, H. C., Eison, A. S., Eison, M. S., & Temple Jr, D. L. (1982). Dopamine and antianxiety activity. Pharmacology Biochemistry and Behavior, 17, 25-35.
12. Taylor, D. P., Eison, M. S., Riblet, L. A., & Vandermaelen, C. P. (1985). Pharmacological and clinical effects of buspirone. Pharmacology Biochemistry and Behavior, 23(4), 687-694.
13. Taylor, D. P. (1988). Buspirone, a new approach to the treatment of anxiety. The FASEB journal, 2(9), 2445-2452.
14. Fulton, B., & Brogden, R. N. (1997). Buspirone: an updated review of its clinical pharmacology and therapeutic applications. Cns Drugs, 7, 68-88.
15. Goldberg, H. L. (1984). Buspirone Hydrochloride: A Unique New Anxiolytic Agent; Pharmacokinetics, Clinical Pharmacology, Abuse Potential and Clinical Efficacy. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 4(6), 315-321.
16. All animals received i.p. injections at a rate of 1 ml/kg. Buspirone (8-[4-[4-(2-pyrimidinyl)-lpiperazinyl]butyl) was administered at group one in 3 mg/kg. Each of two doses of chlordiazepoxide (7- chloro-2-(methylamino)-5-phenyl-3H- 1,4-benzodiazepine-4-oxide hydrochloride) and 8-piro decanazas-8-azaspiro decane-7,9-dione) and chlordiazepoxide (7-chloro-2-(methylamino)-5-phenyl-3H- 1,4-benzodiazepine-4-oxide hydrochloride) were dissolved in 1% w/v saline and given to second group of seven subjects at doses of 5 and third group 7 mg/kg, fourth group 10mg/ kg and 15 mg/kg to fifth group.