COMPARISON OF THE INFLUENCE OF DIAZEPAM AND NEW BENZODIAZEPINE DERIVATIVE (BD-1158) ON THE BEHAVIOUR OF RABBITS UNDER SPONTANEOUS CONDITIONS

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Abstract

The purpose of the present study was to compare the activity and side effects of diazepam and new benzodiazepine derivative (BD-1158). The experiments were performed in 2 groups of rabbits. In the first group BD-1158 was administered intraperitoneally at a dose of 10 mg/kg of body weight, diluted in 1% starch solution up to 1 ml. In the second group diazepam was injected intravenously at a dose of 1 mg/kg. The substances were administered 35-40 min before the behaviour recording. It was found that both substances produced similar effects on animal behaviour under physiological conditions. They had a strong anxiolytic and sedative influence and decreased orientation-searching reactions, grooming, and water and feed uptake.

Key words: rabbits, diazepam, benzodiazepines, behaviour.

The benzodiazepines (BDA) are used to modify behaviour in a wide variety of clinical situations ranging from the treatment of anxiety and insomnia to the management of alcohol withdrawal. They are used in veterinary practice as premedication before invasive procedures, to ease aggressive or anxious animals for transportation, adaptation and gathering animals in herds. They show anticonvulsant, muscle relaxant, anxiolytic and sedative-hypnotic effects (2, 8, 12). In addition to their therapeutic use, BDA are also associated with drug abuse (1). It has been reported that physical and psychological dependence develops upon chronic exposure to BDA and physical withdrawal symptoms have been observed after abrupt cessation of moderate to high doses. Interactions with other central nervous system depressants including alcohol are established (12). Additionally, humans develop tolerance to the anxiolytic effects of BDA although this problem is controversial (12).

One of the commonly used BDA is diazepam. BD-1158 is a new benzodiazepine derivative. The purpose of the present experiments was to compare the spontaneous behaviour of rabbits treated with diazepam and BD-1158, and thus to define and compare the activity and side effects of both substances under physiological conditions.

Material and Methods

The experiments were performed on 20 male Chinchilla rabbits of mean body weight of 3250 g, divided into 2 equal experimental groups. The animals were kept under the standard laboratory conditions at the temperature of 20 ± 2°C, with free access to water and feed.

In both groups, after one-hour adaptation to the surrounding conditions, spontaneous behaviour was tested during two hours (the first day of the experiment). Six forms of behaviour were distinguished and estimated: tension, orientation-searching behaviour, comfort, grooming (nursing activity), water and feed uptake. The tension phase was manifested by the immobility of the rabbit, increase in tension of dorsum and skeletal muscles and the acceleration of breathing. The orientation-searching phase manifested by the immobility of the rabbit, increase in tension of dorsum and skeletal muscles and the acceleration of breathing. The orientation-searching phase was the increased motor activity with the cognitive aim, searching movements and environment examining movements. The comfort phase was the relaxation of the animal, very often somnolence, and decrease in the muscle tension. To make the recording easier, the time of observation was divided into 10-minute intervals. Duration of each phase was measured in seconds with a stopwatch.

On the second day of the experiment, the first group received intraperitoneal injection of 1ml of 1% starch solution and the day after - intraperitoneal injection of BD-1158 at a dose of 10 mg/kg of body weight, diluted in 1% starch solution up to 1 ml, and the second group was injected intravenously (vena
marginalis) with diazepam (Relanium solution, Polfa Poznań, N211197) at a dose of 1 mg/kg of body weight. The substances were administered 35−40 min before the testing of the behaviour. The behaviour was recorded for 2 h during each day and expressed in percentages as the share of given phase in the observation period.

The duration of each phase after diazepam and BD-1158 injection was compared with the duration of the same phase under control conditions (the first day of BD-1158 injection was compared with the duration of the first day of the experiment). The significance of solvent and the same phase under control conditions (the first day of BD-1158 injection was compared with the duration of the first day of the experiment). The significance of solvent and the same phase under control conditions (the first day of BD-1158 injection was compared with the duration of the first day of the experiment). The significance of solvent and the same phase under control conditions (the first day of BD-1158 injection was compared with the duration of the first day of the experiment). The significance of solvent and the same phase under control conditions (the first day of BD-1158 injection was compared with the duration of the first day of the experiment). The significance of solvent and the same phase under control conditions (the first day of BD-1158 injection was compared with the duration of the first day of the experiment).

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The duration of the comfort phase was prolonged after BD-1158 administration from 64.4% to 88.9% and after diazepam injection from 62.67% to 87.13%. These changes were statistically significant (P<0.05).

Both substances did not influence significantly the duration of grooming. It was decreased by diazepam from 4.38% to 2.96% and by BD-1158 from 3.13% to 1.78%.

BD-1158 significantly decreased feed and water uptake (changes from 16.59% to 3.81% and from 2.99% to 0.63%, respectively) (P<0.05). Diazepam inhibited also eating and drinking (the decrease from 5% to 0.66% and from 1.11% to 0.66%, respectively), but only the shortening of the feed uptake phase was statistically significant change (P<0.05).

Discussion

The present study demonstrated that both substances produced similar effects on animals’ behaviour under physiological conditions. They reduced the tension phase to a zero value and significantly prolonged the comfort phase, which resulted from their anxiolytic and sedative effects, characteristic of the benzodiazepine group drugs (2, 7, 12). It has been established that BDA bind to at least two classes of binding sites called central and peripheral type BDA binding sites (4). Anxiolytic and sedative effects are presumed to be mediated by receptors located within the central nervous system (CNS) and coupled to the GABA receptor-chloride channel complex (2, 4). BDA potentiate GABA-ergic transmission by an alteration in the postsynaptic response to GABA (3, 12). It has also been suggested that the effects of BDA on other transmitter systems in the CNS may be secondary to their actions on the GABAergic system. Because of the extensive GABA-ergic innervation of the monoamine and ACh systems, any modification of GABA-ergic system could result in extensive repercussions throughout the CNS (3). Probably there is an endogenic ligand of the benzodiazepine receptor, acting as a neurotransmitter. An exogenously applied BDA can act as an agonist, activating the receptor, or as an antagonist, blocking a tonic action of the natural ligand (9). The peripheral binding sites are distributed in the brain and in several peripheral tissues. They differ from the central ones in their lack of coupling to GABA receptors (4).

Both substances reduced the duration of orientation-searching reactions significantly and minimally the grooming phase. Perhaps it is associated with their sedative properties. Sherif et al. (10) note the intensification of exploratory activity in rats in a new environment after diazepam administration, which in their opinion may account for anxiolytic influence of the drug. Simultaneously, there is a decrease of motor activity of animals (10). Lopez et al. (6) report that clonazepam and triazolam decrease open-field activity in mice, expressed by a decrease in distance travelled and vertical movements. Resting time is increased (6).

In the present experiments BD-1158 as well as diazepam reduced water and feed uptake. These changes are not typical of drugs from the benzodiazepine group and they are not in accord with results of other authors’ research. Stout and Weiss (11) report that the diazepam-injected rats drink for significantly more time than animals injected with physiological saline, although diazepam minimally alters the amount of water consumed. The authors suggest that the dose of diazepam used (1 mg/kg) may have been mildly sedating, because of a decrease in the number of approaches to the water tube and the number of approaches in which drinking occurred. BDA exert eating. This effect is independent of their anxiolytic influence (11). The stimulatory effect of BDA on feed consumption does not interact with appetite and motivational factors associated with feed palatability. In other words, there is hyperphagia regardless of whether the feed is of the high or low palatability. On the contrary, the hunger group of rats exhibit a reduced preference for a low-palatability feed (5).

References

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