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Anxiolytic-like action in mice treated with nitrous oxide and oral triazolam or diazepam

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Abstract

Few animal studies have explored the interaction of nitrous oxide (N_2O) with a benzodiazepine (BNZ) administered by the oral route, as used in clinical procedures involving "conscious sedation". The purpose of this study was to evaluate the relative "anxiolytic-like" and sedative effectiveness of N_2O, oral triazolam (TRIAZ; Halcion®) or oral diazepam (DIAZ; Valium®), either alone or in various combinations of drugs and doses. One hundred and twelve Swiss Webster male mice, 35–45 days old, were assigned to 28 groups, each of which contained four mice. The mouse staircase test was used for the assessment of anxiety (number of rearings) and sedation (number of steps ascended). Three doses of oral TRIAZ (0.1, 0.3, 1.0 mg/kg) or DIAZ (2.0, 3.5, 5.0 mg/kg) were given in combination with room air, or N_2O/O_2 at a N_2O concentration of 25, 50 or 75%. Each mouse was tested once. N_2O alone did not reduce NR in any concentration, but caused a significant increase in locomotion. DIAZ without N_2O reduced NR only with the middle and high doses, but the addition of N_2O significantly enhanced the anxiolytic-like effect of all DIAZ doses. TRIAZ, alone, reduced NR only in the highest dose, but added N_2O resulted in anxiolytic-like behavior with all three TRIAZ doses. The sedative effects of the BNZs were extremely variable. Only the middle dose of DIAZ plus 25% N_2O unequivocally reduced the number of steps ascended, i.e., caused sedation. TRIAZ lacked the inverted U-shaped dose-response relationship with NR usually seen with DIAZ. TRIAZ, therefore, provides better dose

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control. This behavioral animal model indicates that the optimal combinations for reduction of anxiety-like behavior with minimal effects on sedation are 0.1 mg/kg oral TRIAZ with 25% N_2O or 2.0 mg/kg oral DIAZ with 25% N_2O.

Keywords: Nitrous oxide; Diazepam; Triazolam; Benzodiazepines; Conscious sedation; Sedation; Behavioral; Anxiolytic; Anxiolytic-like; Mice

Introduction

Conscious sedation with combinations of nitrous oxide (N_2O) and a benzodiazepine (BNZ) is a common clinical procedure, especially in pediatric medicine and dentistry. Many pediatric dentists use some form of conscious sedation for young children in their office practice (Houpt, 2002). The main clinical objective of conscious sedation is to reduce anxiety while maintaining vital reflexes in order accomplish a medical or dental treatment (Amer. Acad. Ped., 1992). An animal behavioral model referred to as the "staircase" paradigm has been validated for screening potential BNZs for conscious sedation (Simiand et al., 1984; Steru et al., 1987; Quock et al., 1992). Triazolam (TRIAZ) has not been evaluated for its anxiolytic-like effect in laboratory experiments, either alone, or in combination with N_2O. The present study was performed in mice using the staircase test to establish whether N_2O plus oral TRIAZ, would be an effective combination for reducing anxiety-related behavior.

Methods and materials

Animals

Swiss Webster male mice (Charles River Laboratory) approximately 4–5 weeks old and weighing 16–18 g were housed at the UMDNJ Animal Laboratory Facility in groups of 6 under standard conditions of temperature, lighting, and ventilation, with food and water freely available. The day before testing, groups of mice were put into separate cages in the testing laboratory for acclimatization. Three hours before testing they were denied food and water.

The mice were 35–45 days old when tested, approximately at puberty, a time associated with increased anxiety in novel situations. One hundred and twelve animals were randomly assigned to one of 28 experimental groups, each of which contained four mice. Each mouse was tested only once. The 24 groups were used for 3 doses of TRIAZ and 3 doses of DIAZ each of which was administered together with room air or 1 of 3 doses of nitrous oxide. Four groups that received only room air or nitrous oxide were used as controls.

Equipment

A clear plexiglass chamber (100L vol.) was fitted with inflow (top) and outflow (bottom) tubes to accept N_2O and O_2 from a McKesson analgesia machine. The outflow tube was exhausted into a gas