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Prolonged Adverse Reactions to Ketamine in Children

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Ketamine, a phencyclidine derivative, has been employed as an anesthetic agent since 1965.[1] A troublesome problem has been psychic disturbances on emergence. The incidence of emergence phenomena in adults ranges from 5 to 50 per cent; the greatest incidence has been associated with large doses of ketamine or excessive stimulation of the patient during the recovery period. Usually dreams and visual hallucinations disappear within a few hours.[2–4] However, recurrent hallucinations one to three weeks after ketamine administration have been reported to occur in adults.[5]

The frequency of emergence reactions in children is only 0–5 per cent, considerably less than that in adults. No recurrent hallucinations have been reported.[6–10] We have encountered two children who had marked prolonged adverse reactions, probably due to ketamine.

REPORT OF TWO CASES

Patient 1. A 3-year-old 16.4-kg white girl was given an eye examination under anesthesia. Past history included congenital colobomas, congenital cataracts, and an asymptomatic heart murmur, probably caused by a ventricular septal defect. Anesthesia with halothane–N_2O–O_2 had been administered nine times without problem for cateract extractions, needling of pupillary membranes, lens implant, strabismus correction, and eye examinations.

Although the child's vision was impaired, she was able to see to walk about and to read. Mental development seemed precocious, for she could read numbers to one hundred. She was toilet trained and enjoyed a warm, close relationship with her parents. She was physically well developed. She was taking no medication. Laboratory findings disclosed no abnormality.

The patient was unpremedicated and calm on arrival in the operating room. A single im dose of ketamine, 50 mg, and atropine, 0.3 mg, was given, and the eye examination accomplished uneventfully. Thirty minutes later she awakened without problem in a quiet room; an hour following ketamine administration she was returned to her hospital room, where peculiar behavior was noticed. She refused to allow anyone near, including her mother, shrank to the corner of the crib, which she ordinarily disliked, and refused to get out. She reported bugs in her bed and picked at imaginary objects. She reported seeing red and green lights and cried out, "It's going to get you—red, green—there it goes—they're going to get me!" Later, she staggered about the room and appeared wild-eyed. Four hours later she would allow only her father near her, but looked at him strangely. Five hours later, she was seen by the author (EM) and appeared normal. But she awakened several times during the night, having nightmares about lights that were going to "get" her.

The following morning the patient appeared her usual self, and was discharged from the hospital. After returning home, she hid behind her bed or in the closet for hours and stared. When approached, she stated, "The lights were going to get me, so I hid." She awakened two or three times nightly for months, crying hysterically that the lights "are going to get me." She became unable to go to the bathroom for fear of the lights; lapses in toilet training developed. She became fearful of traffic lights. Occasionally she would see an ordinary white light bulb and point to its red and green colors.

Nine months following administration of ketamine the patient was admitted to the hospital for removal of the dislocated lens implant. She was still awakening once or twice nightly, screaming hysterically that the lights were going to "get" her. Twelve months after ketamine administration, the nightmares finally stopped. Sixteen months after ketamine administration the child was readmitted to the hospital for a corneal transplant. Her behavior had been normal except for occasional bedwetting.

Patient 2. A 3-year-old 15-g white boy had an eye examination under anesthesia. Past history included congenital rubella syndrome, many surgical procedures and eye examinations under anesthesia for congenital glaucoma, and myringotomies and tube placement for serous otitis. Anesthesia with halothane–N_2O–O_2 had been administered 28 times without problem. During the first one and a half years of life, the patient had suffered discomfort from elevated eye pressures and cried a great deal. His hearing had been poor; he had spent hours on his hands and knees rocking back and forth. Eye pressures were finally controlled, but vision was very poor. The corneas became cloudy, necessitating penetrating keratoplasty four days before the present admission.

The patient had been cared for from birth by his maternal grandparents, who had adopted him after his mother deserted him. He was closely attached to his grandmother, who, in the immediate postoperative periods, always held him or lay beside him. He was toilet trained, slept all night, and was friendly and sociable with family members. Hearing was poor and he spoke little. Laboratory findings were normal. He was taking no medication.

Premedication with pentobarbital, 45 mg and atropine, 0.2 mg, im, was given 90 minutes before the patient arrived in the operating room, awake and uncooperative. Ketamine, 50 mg, was given im, N_2O–O_2 4:2 l/min administered via face mask, and the examination under anesthesia completed without problem. Thirty minutes later the patient was taken to a quiet corner of the recovery room, where he awakened without untoward reaction in one and a half hours. On his return to his room, his grandmother reported that he was restless and difficult to manage; he refused to allow her to hold him or to lie beside him as usual. He insisted on staying on the floor, where he staggered about and picked at his hands. The rocking behavior, absent for one and a half years, reappeared.

The following day the patient seemed all right and was discharged from the hospital. On his return home, he crawled under a table, where he stayed during waking hours for two weeks. When his grandmother tried to get him out, he cried and

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hit her. He hit and bit all members of the family, broke dishes and toys, and could no longer be trusted near a baby in the household. He awakened screaming two to four times nightly for a month, and was given sedation for sleep. He rocked back and forth while sitting or standing. Lapses in bowel and bladder control occurred. These symptoms persisted for two months following ketamine administration. Ten months later the child had not quite returned to normal behavior, for he still bit family members, suffered lapses in bladder control, and occasionally rocked back and forth. However, he had no problem sleeping.

Discussion

It appears that ketamine may be a hallucinogen: a psychedelic or psychotomimetic drug. Hallucinogens may cause flashbacks, *i.e.*, the recurrence after a drug-free period of an effect, usually of an anxiety-provoking nature, that occurred during the drug experience. Psychedelic drugs usually elicit distortions of perception, primarily visual.[11-12] The word psychedelic is derived from the Greek meaning "mind manifesting" to emphasize the extraordinary changes in states of consciousness brought about by these agents.

The persistent flashbacks so vividly described by the first child seem similar to those reported by Rosenthal[13] to result from repeated injections of lysergic acid diethylamide (LSD), after which adverse reactions, while usually short-lived, may last a few months to two years.

In the past, most investigators have been impressed by the paucity of adverse reactions following ketamine in children. Poletto[14] has even advocated its use to avoid the psychic trauma of transportation to the operating room. The problem of ketamine reactions is difficult to assess in children because they are often unable or unwilling to describe dreams and hallucinations.

To our knowledge, these are the first reported cases of prolonged problems following ketamine administration in children. Other possible causes of adverse sequelae were considered. Large doses of atropine or hyoscine may cause delerium; however, neither child received anticholinergic eye drops. Inadequate anesthesia with painful stimuli could result in psychological trauma; however, in both cases mere brief unilateral eye examination was done, with little or no painful stimulation.

Both mothers connected the immediate emergence problems, but not the long-term sequelae, with the anesthetic drug. Neither noticed similar problems or sequelae from previous or subsequent anesthesia with halothane–N_2O–O_2.

Both children were possibly more vulnerable to the psychotropic action of ketamine than average children, due to the psychic trauma of their visual problems and hospital experiences. In the study of Khorramzadek and Lofty,[15] a correlation between personality problems and unpleasant side effects from ketamine was found.

We, like Johnstone,[16] believe that ketamine is contraindicated for a person who has suffered a bad ketamine "trip," for fear of prolonged, even permanent psychologic damage. The incidence of psychotropic problems resulting from ketamine may be greater than is known, particularly in children.

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