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Psychiatric side effects of ketamine in hospitalized medical patients administered subanesthetic doses for pain control

Rasmussen KG. Psychiatric side effects of ketamine in hospitalized medical patients administered subanesthetic doses for pain control.

Objective: To assess the psychiatric side effects of ketamine when administered in subanesthetic doses to hospitalized patients. It is hypothesized that such effects occur frequently.
Methods: In this retrospective study, the medical records of 50 patients hospitalized on medical and surgical units at our facility who had continuous intravenous infusions of ketamine for pain or mild sedation were reviewed. Patient progress in the days following the start of ketamine infusion was reviewed and response to ketamine was noted.
Results: Twenty-two percent of the patients were noted to have some type of psychiatric reaction to ketamine, including agitation, confusion, and hallucinations. These reactions were relatively short lived, namely, occurring during or shortly after the infusions. No association was found between patient response to ketamine and gender, age, or infusion rate.
Conclusion: Awareness of the psychiatric side effects of ketamine is an important consideration for clinicians administering this medication either for pain control or for depressive illness.

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Keywords: agitation; confusion; hallucinations; ketamine; pain

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Significant outcomes

- Patients receiving ketamine infusions for pain commonly experience short-term psychiatric side effects including agitation and hallucinations.

Limitations

- Study has a retrospective design with non-standardized outcome assessments.

Introduction

Ketamine is a non-competitive antagonist of the *N*-methyl-D-aspartate receptor – one of several glutamate receptors involved in synaptic plasticity, learning, and memory. First introduced as an anesthetic in 1964, it has since evolved for use as a veterinary anesthetic, a recreational drug (Special K) sought out for its hallucinatory and dissociative effects, and an analgesic frequently used in the postoperative setting as well as in the management of pain syndromes (1–4). Ketamine has also become a popular choice for mild sedation when airway reflexes and hemodynamic stability must be maintained. Enthusiasm for the use of ketamine as an antidepressant was sparked by a preliminary study of seven subjects who received a single dose of the drug and showed rapid and prolonged improvement in depressive symptoms (5). Numerous subsequent reports, including several placebo-controlled trials, have confirmed strong antidepressant effects of ketamine (6).

The use of ketamine, however, has been hindered by its psychotomimetic side effects – studied in large part through the examination of recreational drug users (7). Ketamine use in clinical medicine can be broadly divided into anesthetic doses used for surgical procedures and sub-anesthetic doses used for procedural sedation, chronic pain, and major

depression. Several studies have investigated the psychiatric effects of ketamine administered as an infusion at sub-anesthetic doses (8–12). In general, these reports document that the types of doses typically used for pain control and depression do have detectable effects on feelings of dissociation, thought disorganization, negative psychotic symptoms (e.g. apathy and avolition), and positive psychotic symptoms (e.g. hallucinations and delusions). What is not so evident in these reports, however, is the degree to which the experimental subjects found the ketamine experience to be uncomfortable or frightening, if at all.

Although there is continued interest in the use of sub-anesthetic dose ketamine for depression and pain syndromes, literature on the psychiatric side effects of this drug when used in clinical populations for these purposes, as opposed to healthy experimental participants, is limited. Furthermore, it is important to assess any uncomfortable or dysphoric reactions on the part of the patients and not just subtle rating scale elevations that might be detectable upon in-depth neuropsychiatric assessment but which may not translate into patient discomfort. Along these lines, we felt it would be informative to review the experience of a large number of medically hospitalized patients who are given ketamine for pain control in sub-anesthetic doses to see if reports emerge of psychologically uncomfortable reactions. On the medical services of our large, tertiary referral medical center, ketamine is used frequently for patients with various pain states. By reviewing the charts of a large sample of such patients, with particular attention to reports of dysphoric reactions, we sought to add to the extant literature on the psychiatric side effects of ketamine when used at sub-anesthetic doses in the general hospital setting.

Aims of the study

By reviewing the medical records of a large number of patients given sub-anesthetic doses of ketamine, it was intended to assess the incidence of spontaneously reported psychiatric side effects as enumerated by the treating clinicians. Results are analyzed to determine if age, gender, or ketamine infusion rate influences likelihood of psychiatric side effects.

Material and methods

Utilizing pharmacy records, we were able to locate the medical charts of 50 adult patients admitted to medical and surgical units at the Mayo Clinic Rochester between January 1, 2009 and December 31, 2010 who were administered ketamine infusions for non-anesthetic purposes. Thus, we did not include use of ketamine for induction or maintenance of general anesthesia nor did we include the use of ketamine in patients <18 years of age. All of the patients in our series had been administered continuous infusions of intravenous ketamine at some point in their hospitalization, at the recommendation of either the primary service caring for them or a specialist pain consult service. Data extraction was performed for all cases by one person collecting the following data points: patient gender, age, and infusion rate. The last data point was extracted from the ordering physician's note and confirmed against the nursing medication administration record (MAR). Where there was a discrepancy between the two values, the dose charted in the MAR was used. Physician and nursing progress notes from the initiation of treatment with ketamine to its discontinuation were examined for explicit reporting of patient responses. Outcomes were categorized into five groups: no response, adequate sedation/analgesia, agitation, confusion, and hallucinations. The first two categories were considered to be non-adverse responses, whereas the latter three categories were grouped as psychiatric adverse effects; this simplified grouping was used for statistical purposes given the small sample size of this study.

Comparisons of gender, age, and infusion rate between positive responders and patients who had adverse effects were evaluated using χ^2 and Wilcoxon rank sum tests. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC, USA). All tests were two-sided and p-values <0.05 were considered statistically significant. This study was conducted in full compliance with all policies and procedures of the Institutional Review Board at Mayo Clinic Rochester. Study data were abstracted from medical records of patients who gave informed consent for their charts to be reviewed for research purposes.

Results

The table summarizes pertinent data extracted from the medical records. Of the 50 patients studied, 39 (78%) responded favorably by having no reaction or adequate sedation/analgesia. The remaining 11 (22%) patients developed agitation, confusion, or hallucinations after initiation of treatment with ketamine. Of note, five of the patients experienced hallucinations (Table 1).

A univariate comparison of reaction types between genders (34 men and 16 women) showed no statistically significant difference in the occurrence of psychiatric adverse effects, with seven men (21%) and four women (25%) having adverse reactions (χ^2 value = 0.1234, $p = 0.7278$).

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Table 1. Patients administered ketamine infusions for pain management or mild sedation in the general hospital setting

	Age	Primary diagnosis	Indication for ketamine	Infusion rate (mg/kg h)	Response to infusion
Females ($n = 16$)	21	Thumb reimplantation	Pain	0.12	Adequate analgesia
Non-adverse responses ($n = 12$)	24	Pancreatectomy	Pain	0.07	No response
	30	Cancer	Pain	0.26	adequate analgesia
	33	Cancer	Pain	0.10	Adequate analgesia
	37	Gastric bypass repair	Pain	0.11	Adequate analgesia
	43	Laminectomy	Pain	0.07	No response
	49	Hip revision	Pain	0.11	Adequate analgesia
	52	Hip revision	Pain	0.06	Adequate analgesia
	57	Hip revision	Pain	0.16	Adequate analgesia
	58	Cardiac bypass surgery	Pain	0.10	Adequate analgesia
	68	Post-herpetic neuralgia	Pain	0.05	Adequate analgesia
	73	Cancer	Pain	0.10	No response
Adverse responses ($n = 4$)	23	Gunshot wound	Pain	0.10	Agitation
	31	Cancer	Pain	0.10	Agitation
	33	Clavicle reconstruction	Pain	0.51	Confusion
	44	Cancer	Pain	0.01	Hallucinations
Males ($n = 34$)	18	Bone cyst	Pain	0.08	Adequate analgesia
Non-adverse responses ($n = 27$)	21	Tibia–fibula reduction and fixation	Pain	0.09	Adequate analgesia
	22	Myelopathy	Pain	0.05	Adequate analgesia
	22	Lymphoproliferative disorder	Pain	0.38	No response
	25	Respiratory failure	Mild sedation	0.10	Adequate sedation
	36	Peritonitis	Pain	0.02	No response
	37	Bowel resection	Mild sedation	0.50	Adequate sedation
	39	Foot hardware removal	Pain	0.06	Adequate analgesia
	40	Cancer	Pain	0.10	No response
	41	Bowel resection	Pain	0.05	Adequate analgesia
	45	Cancer	Pain	0.10	Adequate analgesia
	45	Spinal surgery	Pain	0.39	Adequate analgesia
	46	Temporomandibular joint arthrotomy	Pain	0.10	Adequate analgesia
	46	Bowel resection	Pain	0.10	No response
	46	Sepsis	Mild sedation	0.36	Adequate sedation
	47	Below-knee amputation	Pain	0.74	Adequate analgesia
	47	Complex regional pain syndrome	Pain	1.64	Adequate analgesia
	48	Rhinoplasty	Pain	0.11	Adequate analgesia
	49	Cancer	Pain	0.11	Adequate analgesia
	51	Hip revision	Pain	0.09	Adequate analgesia
	55	Total knee arthroplasty	Pain	0.10	Adequate analgesia
	58	Cardiorespiratory collapse	Mild sedation	0.20	Adequate sedation
	60	Lysis of bowel adhesions	Pain	0.10	Adequate analgesia
	60	Cancer	Mild sedation	0.30	Adequate sedation
	62	Cardiac bypass surgery	Pain	0.30	Adequate analgesia
	67	Cancer	Mild sedation	0.09	Adequate sedation
	67	Cancer	Pain	0.10	Adequate analgesia
Adverse responses ($n = 7$)	23	Cancer	Pain	0.20	Hallucinations
	33	Epidural abscess	Pain	0.10	Agitation
	34	Cancer	Pain	0.10	Confusion
	36	Leg amputation	Pain	0.20	Hallucinations
	42	Hip decompression	Mild sedation	0.25	Hallucinations
	52	Spinal surgery	Pain	0.10	Confusion
	65	Lung segmentectomy	Pain	0.15	Hallucinations
	Mean = 43			Mean = 0.19	
	$\sigma = 14$			$\sigma = 0.25$	

Wilcoxon rank sum tests were applied to look for response patterns based on age. Patient ages in the sample ranged from 18 to 73 years old, with an average age of 43 ± 14 years. No statistically significant difference was found in patient ages between those who did and those who did not have adverse reactions to ketamine ($p = 0.1229$). Similar analyses were conducted to evaluate patient responses based on ketamine infusion rate. The infusion rates used in the 50 cases studied ranged

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from 0.01 to 1.64 mg/kg h, with an average rate of 0.19 mg/kg h ($\sigma = 0.25$ mg/kg h). In comparing infusion rates between patients who responded poorly to ketamine and those who did not, no statistically significant difference was found ($p = 0.5307$).

Discussion

In a relatively large sample of naturalistically treated pain patients in a tertiary hospital setting given sub-anesthetic doses of ketamine, 22% reacted negatively with agitation, confusion, or hallucinations. There were no associations found between gender, age, or infusion rate and whether or not a patient had an adverse reaction to ketamine. The patient response types were categorized as either adverse or not for the purposes of statistical analyses with the small sample size. The broad range of negative reactions to sub-anesthetic infusions of ketamine – independent of gender, age, and infusion rate – suggests that clinicians in the general hospital setting must be prepared to manage the possible psychiatric sequelae of ketamine administration in non-surgical situations.

These results are limited by the retrospective nature of the study. The complicated medical status of most of the patients reviewed was at times confounding and also a limitation. That is, while psychiatric adverse effects observed after ketamine administration was attributed (by the treating physician) to the ketamine itself, there were many cases where patients were concurrently receiving opiates and/or anticholinergic medications that could have also exacerbated psychiatric symptoms. Delirium in these medically complicated patients may have also contributed to the observed mental status changes. However, the reactions occurred to ketamine at around the time of infusion or shortly thereafter, making the possibility of some other medication or medical condition causing the reactions quite small. An additional limitation of the study was the lack of consistently reliable and available data in the medical records on the total amount of ketamine administered to each patient. A comparison of response types based on total ketamine intake, in addition to infusion rate, would have been preferable to the current analysis based on infusion rate alone.

This study presents evidence that psychiatric side effects from ketamine can occur at sub-anesthetic doses (e.g. when used in pain management and mild sedation as in this study population). The potential for such adverse effects at small doses may pose a barrier to the use of ketamine in the treatment of depression. This study adds to the extant literature and calls for further investigation of the psychiatric sequelae of ketamine in consideration of its use as an antidepressant.

Author Contributions

The author designed the study, completed the manuscript for this study, and approved the final draft.

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