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PSYCHOMIMETIC REACTIONS AFTER LOW-DOSE KETAMINE INFUSION
Comparison with neuroleptanaesthesia

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SUMMARY

Low-dose ketamine anaesthesia was compared with neuroleptanaesthesia, in respect of immediate and longer-term psychomimetic reactions, in 40 female patients undergoing elective gynaecological surgery. Qualitatively, but not quantitatively, different psychomimetic reactions occurred in both groups. In the neurolept group the predominant complaint was of a dissociative nature, reported after 24 h by 11 (55%) of the patients, while in the ketamine group the predominant experience was dreaming, reported by eight (40%) of the patients after 24 h. Interviews after 3 months revealed a low frequency of psychomimetic reactions in both groups. However, 30% of all the patients (12) complained of impairment of intellectual function, and in seven patients this was severe enough to interfere with their ability to work.

Modification of the psychomimetic effects of ketamine has been reported following the administration of benzodiazepines (Bovill et al., 1971; Kothary and Zsigmond, 1975; Dundee, 1979), a decrease in the dose of ketamine (Sadove et al., 1971; Slogoff et al., 1974), or the combination of ketamine and nitrous oxide with or without neuromuscular blockade (Wessels, Allen and Slogoff, 1973; Vaughan and Stephen, 1974). More recently it has been claimed that a continuous infusion of low-dose ketamine decreases the frequency of psychomimetic reactions (El-Naggar et al., 1977; Hatano, Mishiwada and Matsumura, 1978; Idvall et al., 1979).

We have compared the frequency of psychomimetic reactions following ketamine with that associated with neuroleptanaesthesia.

PATIENTS AND METHODS

Forty otherwise healthy female patients (age range 23–50 yr) were randomly divided into two equal groups. Informed consent was obtained from each patient before her inclusion in the study.

Patients with mental illness, epilepsy or chronic alchoholism were excluded. All were undergoing elective gynaecological procedures requiring laparotomy.

Each patient received diazepam 0.2 mg kg^{-1} by mouth 1 h before surgery and atropine 0.006 mg kg^{-1} i.v. immediately before the induction of anaesthesia. Anaesthesia was supplemented with nitrous oxide in oxygen (2:1). Pancuronium 0.1 mg kg^{-1} was administered and the trachea intubated. Neuromuscular blockade was reversed with neostigmine.

In the neurolept group (NLA group) anaesthesia was induced with incremental doses of droperidol to a total of 250 $\mu g\ kg^{-1}$ and fentanyl 5 $\mu g\ kg^{-1}$. During anaesthesia fentanyl 0.05 mg was given when necessary. The ketamine group received an additional dose of diazepam 0.2 mg kg^{-1} i.v. at induction of anaesthesia followed by an infusion of ketamine 100 $\mu g\ kg^{-1}\ min^{-1}$ for 10 min. Anaesthesia was maintained with ketamine 9–16 $\mu g\ kg^{-1}\ min^{-1}$. ECG and heart rate were monitored during anaesthesia and arterial pressure recorded every 5 min.

Following anaesthesia the patients were observed by the nurses in the recovery room and special attention was paid to the level of awareness and any evidence of excitation, fear or hallucinations. Arterial blood samples were drawn 30 and 90 min following surgery. To obtain information about the patients' subjective experiences of anaesthesia and recovery, they were interviewed on the 1st day after their operation and again 3 months later. A questionnaire, designed in collaboration with a hospital psychologist, was used, and on each occasion the doctor questioning the patient was unaware of which anaesthetic had been given.

Analysis of data

Quantitative data were analysed with the

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Mann–Whitney test. Qualitative data were analysed with Fisher's exact test. Values of probability <0.05 were considered significant.

RESULTS

Both groups were comparable with regard to age, body weight, previous anaesthesia and psychomimetic experiences related to previous anaesthesia. The course of anaesthesia was similar in the two groups, apart from evidence of significant cardiovascular stimulation in the ketamine group.

The median total dose of ketamine was 2.2 mg kg^{-1} (range 1.7–4.5 mg kg^{-1}).

In the recovery room all patients in the NLA group were awake on arrival. One patient in the ketamine group, lightly asleep on admission, was fully awake by 90 min. All patients in the NLA group were described as being mentally neutral, while two of the ketamine patients were described as being slightly restless, and one had expressed fear. None of the patients in either group required additional sedatives in the recovery room, and none appeared to suffer from hallucinations. There were no differences between the groups with regard to duration of stay in the recovery room, analgesic requirements or frequency of nausea and vomiting. Respiration, as mirrored in arterial blood-gas tensions, was similar in both groups apart from a significantly lower Pa_{CO_2} in the ketamine group after 30 min (table I).

Awareness during anaesthesia (table II) was reported by four patients in the NLA group who all remembered the mask, and one of these found the experience unpleasant. One patient in the ketamine group reported dreaming, possibly during surgery, but she could not account for any relevant sounds or events. Her dream was pleasant, but stopped when she awoke.

During recovery (table II), defined as the first 24 h after operation, dreams were reported by two patients in the NLA group, but the dreams were not unpleasant. In the ketamine group, dreams were reported by eight patients, including the patient mentioned earlier. Four of these found their dreams unpleasant and three had dreamt in vivid colours. Colour vision was not reported after NLA, while one patient in the ketamine group reported that although she saw colours when dozing with her eyes closed, everything was normal when her eyes were open.

Eleven patients in the NLA group reported to have suffered from various degrees of locked-in feelings associated with inner restlessness, dysphoria and unnatural tiredness (dissociation) during recovery. Six found this very unpleasant. Complaints of this kind were not encountered in the ketamine group and the difference was significant.

The patients' judgement of anaesthesia and recovery (table III) was not significantly different between the groups.

After 3 months no significant differences could be found between the groups with regard to the frequency and character of dreams and nightmares (table IV). One patient (NLA) had persistent nightmares about surgery and hospitals, while another patient (ketamine) had nightmares in which she was

TABLE I. *Arterial blood-gases 30 and 90 min. after operation. Medians and (ranges).* *$P<0.05$

	Time (min)	NLA ($n=19$)	Ketamine ($n=19$)
Pa_{O_2} (kPa)	30	12.0 (9.3–19.5)	12.4 (8.7–27.0)
	90	11.5 (9.0–25.0)	12.4 (10.3–17.0)
Pa_{CO_2} (kPa)	30	5.1 (3.9–6.0)	4.8 (3.8–5.7)*
	90	5.1 (4.2–5.8)	5.1 (3.8–5.7)

TABLE II. *The patients' subjective experiences during anaesthesia and in the first 24 h following operation. Numbers and (per cent) of patients.* **$P<0.002$

	NLA	Ketamine
Dreaming		
Pleasant	2 (10)	4 (20)
Unpleasant	0	4 (20)
Dissociated	11 (55)	0**
Awareness	4 (20)	1 (5)
Painful recovery	9 (45)	6 (30)
Amnesia for recovery	2 (10)	2 (10)
Nauseated	4 (20)	5 (25)
Felt dizzy	2 (10)	1 (5)

TABLE III. *The patients' judgement of anaesthesia and recovery. Numbers and (per cent) of patients*

	NLA	Ketamine
Anaesthesia		
Good	14 (70)	17 (85)
Indifferent	2 (10)	2 (10)
Bad	4 (20)	1 (5)
Recovery		
Pleasant	2 (10)	4 (20)
Indifferent	12 (60)	11 (55)
Unpleasant	6 (30)	5 (25)

TABLE IV. *Numbers and (per cent) of patients with psychomimetic reactions reported after 3 months*

	NLA	Ketamine
Dreaming	1 (5)	1 (5)
Nightmares	1 (5)	1 (5)
Hallucinations	0	2 (10)
Illusions	0	0

haunted by dogs, for a fortnight after discharge from hospital. Two patients (ketamine) reported symptoms of a possible hallucinatory nature. One of these reported that, when tired, she heard a whistling sound; this was annoying, but not accompanied by fear. The other patient had hypnagogic flashbacks of being transported on a sheet through a long corridor; this was only occasional and was always preceded by alchohol ingestion. It was unpleasant, but not frightening, and ceased after 9 months.

Difficulties with memory and concentration were reported after 3 months in a number of patients in both groups (table V).

The overall frequency did not differ between the groups, but a majority of the patients with severe problems, defined as problems which interfered with their ability to work, were found in the neurolept group.

Patient acceptance after 24 h and after 3 months (table VI) did not differ significantly between the groups, although a larger number of patients preferred not to have neuroleptanaesthesia again. In the NLA-group rejection was associated with the presence of dissociation in all such patients, of whom five rejected neuroleptanaesthesia consistently at both interviews. The two patients who rejected ketamine at the first interview had changed their minds after 3 months; one claimed to have been misunderstood, while the other now felt that the problems had been insignificant. One of the two patients who rejected ketamine after 3 months did so because she found that she had been sluggish for the first few days after surgery, the other because of a possible psychomimetic reaction (hearing a whistling sound).

TABLE V. *Numbers and (per cent) of patients with subjective feelings of intellectual impairment 3 months after surgery.* *$P < 0.05$

	NLA	Ketamine
Memory affected		
Severely	1 (5)	1 (5)
Slightly	1 (5)	2 (10)
Memory and concentration affected		
Severely	5 (25)	0*
Slightly	0	1 (5)
Concentration affected		
Severely	0	0
Slightly	0	1 (5)

TABLE VI. *Numbers and (per cent) of patients in favour of NLA, and ketamine, anaesthesia at first and second interviews after operation*

	NLA	Ketamine
After 24 h	15 (75)	18 (90)
After 3 months	14 (70)	18 (90)

DISCUSSION

In the present study we have found evidence of reactions to anaesthesia plus major surgery occurring shortly after surgery, and at some time following operation. The first interview after operation demonstrated the presence of psychomimetic reactions in both groups of patients. As reported by El-Naggar and colleagues (1977) we were unable to demonstrate any difference in the frequency of psychomimetic reactions between ketamine and neuroleptanaesthesia. However, a marked difference was observed in the type of psychomimetic reactions after the two anaesthetic techniques, and the results suggest that these differences played a major role in the acceptance by the patient of the anaesthetic.

Not unexpectedly, we found that dreaming was the most frequently encountered psychomimetic reaction associated with ketamine, and the frequency was similar to that found with ketamine anaesthesia alone (Garfield et al., 1972; Krestow, 1974; Biersner, Harris and Ryman, 1977). However, the dreams were not described as "terrifying" or "morbid" and, as such, differed from those described by Fine and Finestone (1973) and King and Stephen (1967). We found, as did Garfield and colleagues (1972), that dreaming did not adversely influence acceptance by the patient of ketamine anaesthesia.

In contrast, the psychomimetic reactions associated with NLA contributed significantly to the rejection of this form of anaesthesia by some of the patients. We think that these side-effects of NLA were similar to those reported after premedication with droperidol (Morrison, Clarke and Dundee, 1970; Clarke and Cooper, 1970; Ellis and Wilson,

1972). However, Tornetta (1977) found that these reactions to droperidol could be attenuated significantly by the administration of opiate analgesics—the combination used in NLA. Like Tornetta (1977), we found our patients outwardly calm and relaxed during recovery from anaesthesia, but on more detailed questioning this was found to conceal a high frequency of severe emotional distress.

The 3-month follow-up interview did not produce any alarming evidence of prolonged psychomimetic reactions after either of the two anaesthetic techniques studied.

Of more concern was the fact that a number of patients in both groups complained of impairment of memory and with their ability to concentrate. In seven patients this was severe enough to interfere with working capacity. It is impossible to say whether this was a drug-induced, or stress-induced, effect. Short-term mental effects have been described by Simpson and co-workers (1976) after both i.v. and inhalation anaesthesia. Corssen, Oget and Reed (1971) found, however, no effect on mental performance in prisoners 3 months after a single dose of ketamine. Neither could Storms and colleagues (1980) and Davison and associates (1975) demonstrate any detrimental effects of inhalation agents on mental performance after 14 and 30 days, respectively, and Rühanen and co-workers (1978) were unable to demonstrate any decrease in mental ability 7 days after anaesthesia. However, i.v. anaesthesia with psychotropic agents was only studied to a limited extent, and most of the surgery was minor.

In conclusion, we found that an infusion of low-dose ketamine as part of a balanced anaesthetic technique was similar to neuroleptanaesthesia in regard to recovery, the frequency of psychomimetic reactions in the short and longer term although, if anything, ketamine seemed more acceptable to the patients.

The distressing dissociative experiences reported by a number of patients in the NLA group during recovery is similar to those reported earlier on the psychomimetic reactions associated with droperidol, and this suggests further evaluation of the indications for its use in anaesthetic practice. In addition, we believe that further investigations on the frequency and aetiology of complaints relating to alterations in intellectual function after anaesthesia are worthy of further study.

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PSYCHOMIMETISCHE REAKTIONEN NACH INFUSION MIT NIEDRIGDOSIERTEM KETAMIN

Vergleich mit Neuroleptanalgesie

ZUSAMMENFASSUNG

Bei 40 weiblichen Patienten nach elektiven gynäkologischen Eingriffen wurden Narkosen mit niedrig-dosiertem Ketamin und Neuroleptanalgesien hinsichtlich psychomimetischer Sofort- und Langzeitreaktionen miteinander verglichen. In beiden Gruppen kamen qualitativ, jedoch nicht quantitativ verschiedene psychomimetische Reaktionen vor. Bei der Gruppe nach Neuroleptanalgesie waren die vorherrschenden Beschwerden dissoziativer Natur, nach 24 Stunden von elf (55%) der Patientinnen geäußert, während in der Ketamin-Gruppe Träume vorherrschten, von acht (40%) der Patientinnen nach 24 Stunden berichtet. Interviews nach 3 Monaten ergaben eine geringe Häufigkeit psychomimetischer Reaktionen in Beiden Gruppen. Dreissig prozent (12) aller Patientinnen klagten jedoch über eine Beeinträchtigung der intellektuellen Funktion, und bei sieben Patientinnen was dies stark genug, um ihre Arbeitsfähigkeit zu beeinträchtigen.

REACTIONS PSYCHOMIMETIQUES APRES UNE INFUSION DE LA KÉTAMINE A DOSE FAIBLE

Comparaison avec la neuroleptanesthésie

RESUME

Une anesthésie par la kétamine, à faible dose, a été comparée avec une neuroleptanesthésie, pour ce qui concerne les réactions psychomimétiques immédiates et à plus long terme chez 40 patientes devant subir des interventions de chirurgie gynécologique règlée. Des réactions psychomimétiques qualitativement, mais pas quantitativement différentes, sont apparues dans les deux groupes. Dans le groupe "neuroleptanalgésie" la principale plainte concernait une dissociation, observée au bout de 24 h par 11 patientes (55%) alors que dans le groupe "kétamine" la principale expérience était onirique, décrite par huit patientes (40%) après 24 h. Des entretiens, après 3 mois, révèlaient une fréquence faible de réactions psychomimétiques dans les deux groupes. Cependant, 30% de l'ensemble des patientes (12) se plaignaient d'altération des capacités intellectuelles et chez sept patientes cette altération était suffisamment sévère pour interférer avec leurs capacités de travail.

REACCIONES SICOMIMÉTICAS DESPUÉS DE UNA INFUSIÓN DE QUETAMINA EN BAJA DOSIS:

Comparación con la Neuroleptanestesia

SUMARIO

Se llevó a cabo una comparación de la anestesia por baja dosis de quetamina con la neuroleptanestesia, con respecto a las reacciones sicomiméticas inmediatas y a largo plazo en 40 pacientes femininas sometidas a cirujía ginecológica electiva. Ocurrieron en ambos grupos distintas reacciones sicomiméticas desde el punto de vista cualitativo pero no asi del cuantitativo. En el grupo con neuroleptanestesia, el problema predominante era de naturaleza disociativa, tal como informaron 11 pacientes después de 24 h (55%), mientras que en el grupo con quetamina, la experiencia predominante eran los sueños, tal como informaron 8 de los pacientes después de 24 h (40%). Las entrevistas llevadas a cabo después de 3 meses revelaron una baja frecuencia de reacciones sicomiméticas en ambos grupos. Sin embargo, un 30% de todas las pacientes (12) se quejaron de un deterioro de la función intelectual, y en siete de ellas, este deterioro era lo suficientemente severo para interferir con su capacidad de trabajar.