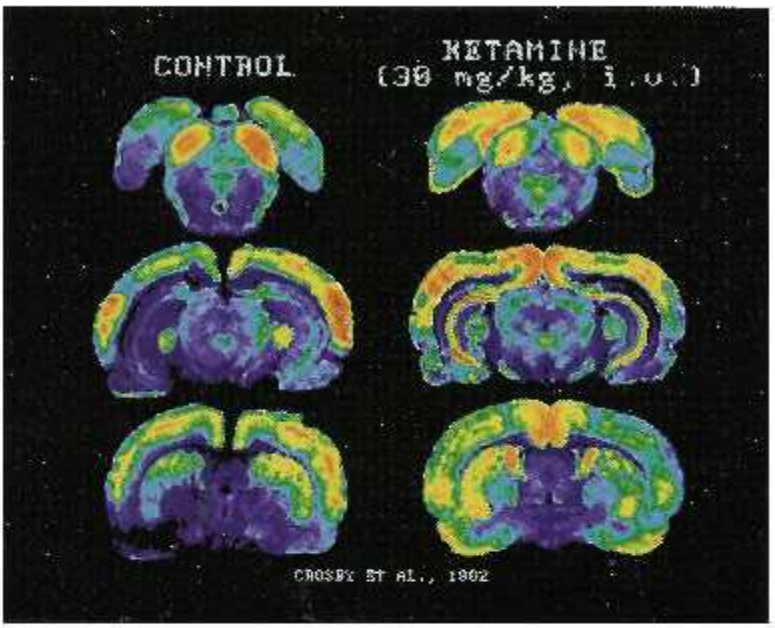
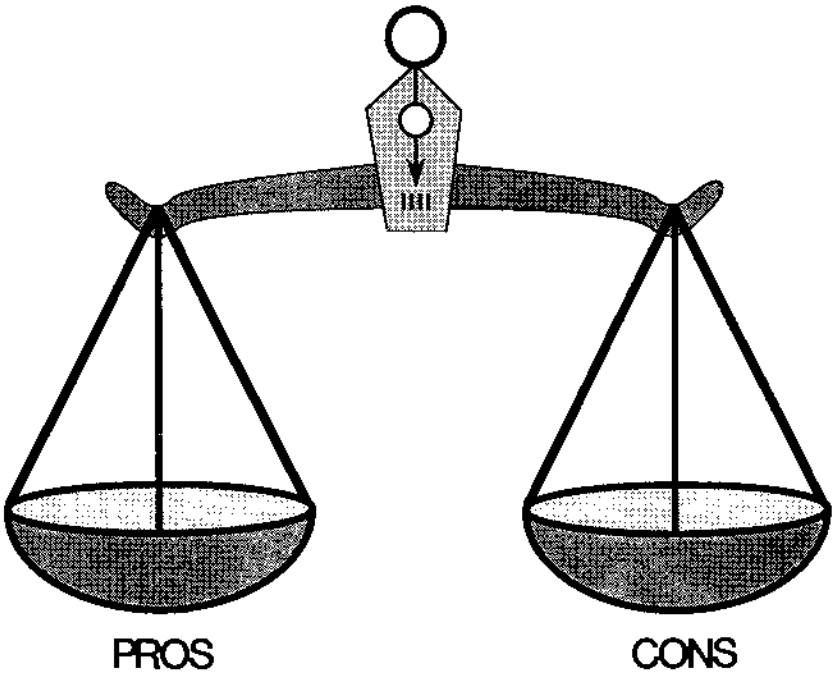
STATUS OF KETAMINE IN ANESTHESIOLOGY



EDWARD F. DOMINO, EDITOR

STATUS OF KETAMINE IN ANESTHESIOLOGY



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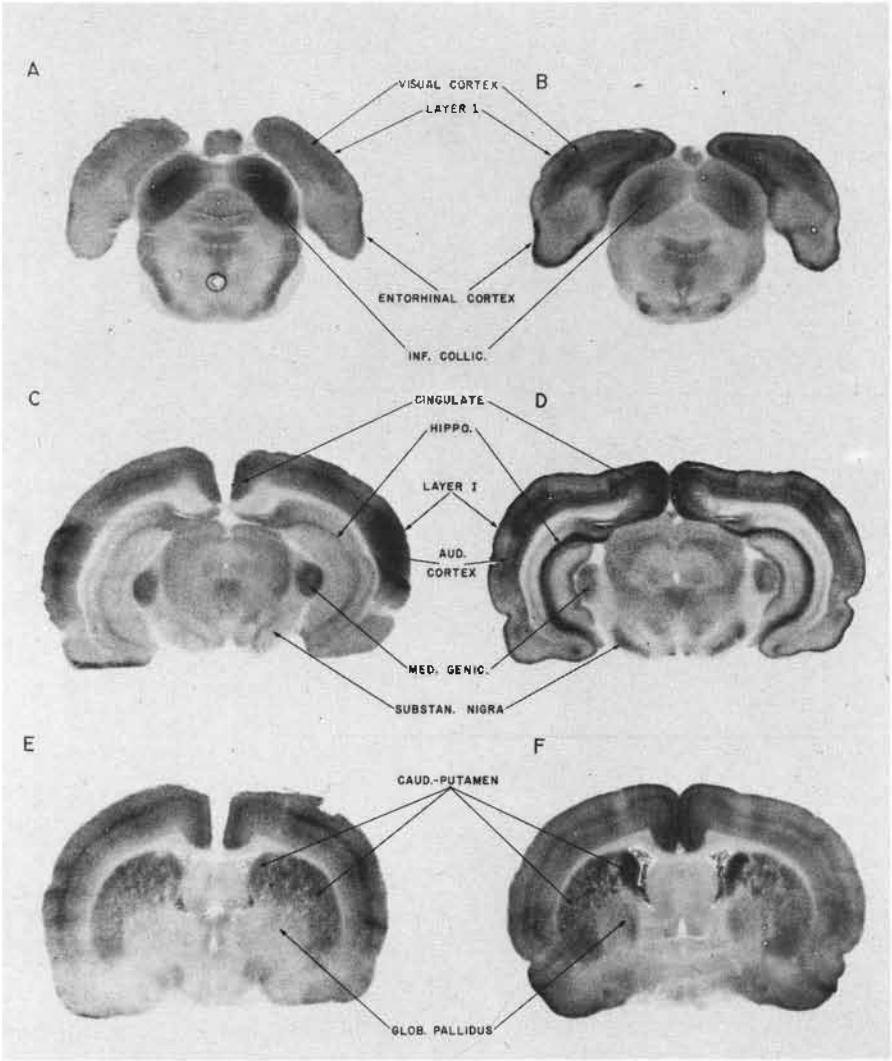

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Status of Ketamine in Anesthesiology
The University of Michigan, Ann Arbor, MI
June 19-21, 1989

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Status of Ketamine in Anesthesiology

Proceedings of the 25th Anniversary of Ketamine Symposium held at the University of Michigan in Ann Arbor, MI June 19-21, 1989

Sponsors

The Symposium was sponsored by the Departments of Anesthesiology and Pharmacology of the University of Michigan Medical School and the University of Michigan School of Dentistry. The Symposium supporters included: Merck, Sharp & Dohme Research Laboratories, NPP Books, Parke Davis, Division of Warner Lambert, Morris Plains, NJ, Parke-Davis and Co., Berlin, Federal Republic of Germany, Pfizer Central Research, Groton, CT, Roche Laboratories, Hoffmann-LaRoche, Inc., Nutley, NJ, University of Michigan Department of Anesthesiology, University of Michigan Department of Pharmacology, University of Michigan Office of Vice President for Research, The Upjohn Company, Warner Lambert/Parke Davis Pharmaceutical Research Division, Ann Arbor, MI, Warner-Lambert International Operations, Morris Plains, NJ.

Facilities

The facilities of the University of Michigan School of Dentistry provided an ideal setting for presentations, discussion and exchange of ideas among all of the participants. The entire scientific program was video taped and is available on standard ½ inch VHS cassettes. Arrangements can be made for their purchase from the University of Michigan by contacting the editor.

The facilities of the University of Michigan League were utilized for the reception, poster session and banquet. The color collages on the two following pages represent selected photographs of some of these events.

Sixteen years ago a patient was given ketamine anesthesia as part of a study conducted by Dr. Elemer Zsigmond. When the patient recovered she was asked what kind of "dreams" she experienced. At the time she was not able to fully express in words her experience under ketamine anesthesia. But it did inspire her to do a painting of her "dream." It was a "heavy experience, but a beautiful one" to her. (Courtesy of Dr. Zsigmond.)

Preface

The chapters in this book represent almost all of the presentations at the Twenty-Fifth Anniversary of Ketamine Symposium held in Ann Arbor, June 19-21, 1989 at the University of Michigan. About 82 U.S. and international scientists gave oral and poster presentations covering various aspects of this Symposium. All participants were asked to present their findings in a critical manner regarding the pros and cons of ketamine use in anesthesiology today. Clearly, ketamine is not the ideal anesthetic anesthesiologists dream will become a reality, nor is it the nightmare that many believe, at least in the United States. There is a place for ketamine in anesthesiology. The purpose of the twenty fifth anniversary ketamine symposium was to define what that place is today.

Seven sessions were held including: I. Historical and Present Perspectives; II. Biotransformation and Pharmacology; III. Analgesic Actions; IV. Pharmacokinetics; V. Clinical Applications; VI. Problems and Modern Uses; VII. New Basic Science Developments: NMDA Antagonist Actions and Neuroprotective Effects. These form the basis for the organization of this book.

The editor would like to thank Mrs. Ellen Howard and numerous students for their efforts in helping to ready this book for publication.

January 2, 1990

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Notice

The authors and publisher have taken great care in an attempt to provide all information regarding dosage, side effects, indications, etc. of ketamine and other drugs described in this book to the best of their abilities. Errors may occur that have been overlooked. As a result, it is extremely important that any person planning to administer ketamine should obtain detailed instructions from persons experienced with its use as well as consulting appropriate package insert information, etc. The information contained in this book should be used merely as a guideline to supplement first hand knowledge and experience with the use of ketamine and other drugs. Although ketamine has a large therapeutic index compared to other anesthetic agents, when given alone it has significant and serious side effects that require the attention of one experienced with anesthetic and airway management.

Table of Contents

Status of Ketamine in Anesthesiology,
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Historical Aspects of Ketamine—First Clinical Experience

G. Corssen

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The synthesis of phencyclidine (CI-395, PCP, Sernyl, Sernylan) by Maddox (1981), laboratory testing by Chen *et al.* (1959), and clinical testing by Greifenstein *et al.* (1958) and Johnstone *et al.* (1959) provided the basis for human pharmacologic studies and clinical exploration of the chloroketone analogue of PCP, CI-581, later known as ketamine (Ketalar, Ketaject). Ketamine was synthesized by Stephens (1963) and initial laboratory testing with CI-581 was conducted by McCarthy *et al.* (1965). This was followed by human pharmacologic studies carried out by Domino and Corssen and their associates (Domino *et al.*, 1965). Clinical trials were begun in 1964 and the first clinical experience in 130 patients was reported by Corssen and Domino (1966). At that time, the authors introduced the term "dissociative anesthesia" to describe the peculiar state of unconsciousness produced by ketamine in which the subject is profoundly analgesic and in a trance-like state, not appearing to be asleep or anesthetized, but rather disconnected from the surroundings. Corssen and Domino attributed the special features of this state to a dissociation between the thalamoneocortical and the limbic systems. Since visual and somatosensory impulses travel unimpaired from the periphery to the primary sensory cortex, it appeared that the sensory isolation occurred within the brain, presumably in the association areas. The authors postulated that under the effect of ketamine the patient is unable to interpret impulses and make the appropriate response; therefore, there is no reaction to light impulses introduced into the eye nor to pain impulses that ordinarily would be evoked by surgical stimulation (Fig. 1).

In subsequent studies conducted in primates at the University of Alabama in Birmingham (Sparkes *et al.*, 1973, 1975), the effects of ketamine on visually evoked potentials recorded from the visual cortex were compared with those recorded from non-specific midbrain and

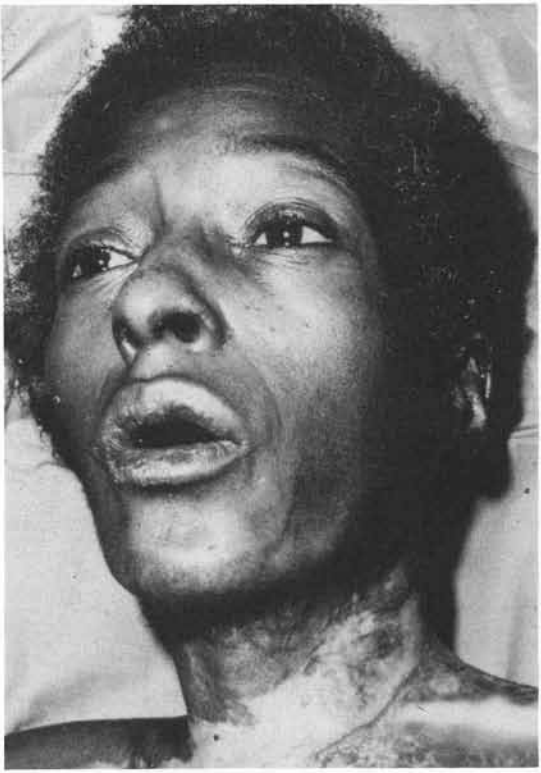

Fig. 1. Patient anesthetized with ketamine.

thalamic areas. The results indicated that the diffuse neocortical projection system is the primary site of action of ketamine. Furthermore, the results showed that the profound analgesic action of the drug probably results from the functional disorganization of nonspecific pathways in midbrain and thalamic areas.

Initial experiences with the clinical use of ketamine at the University of Michigan, and later at the University of Alabama, corroborated the observations made earlier in human volunteers; namely, that ketamine differs markedly from conventional intravenous and inhalational anesthetic agents. This difference results from its selective, dissociative action on the central nervous system which produces a unique anesthetic state characterized by profound analgesia, cardiovascular stimulation, lack of respiratory depression, maintenance of protective reflexes and amnesia.

Early during the exploratory use of ketamine in surgical patients, it became apparent that the drug was particularly suitable when the pro-

cedure involved skin, bone, and joints (Corssen *et al.*, 1968). Therefore, ketamine was successfully employed in body surface procedures such as wound debridement and skin grafting in burn therapy. Also, repetitive orotracheal intubation could be avoided in the surgical treatment of thermal injury since preservation of the laryngo-pharyngeal reflexes under ketamine anesthesia facilitated the maintenance of an unobstructed airway. For the same reason, positional problems often encountered during radiodiagnostic and radiotherapeutic procedures in infants and in children were largely overcome by ketamine's ability to preserve airway patency.

The sympathomimetic effects of ketamine (increases in cardiac output, pulse rate, and systolic and diastolic pressures) may be of benefit in the anesthetic management of poor risk patients. In particular, these effects may benefit patients suffering from hypovolemic shock following massive hemorrhage where transfusion cannot promptly restore the blood volume and where temporary improvement of cardiovascular function is of vital importance (Corssen *et al.*, 1974). We also found ketamine suitable as the sole anesthetic or in combination with nitrous oxide-oxygen for pain control during cardiac surgery, especially in infants and children (Corssen *et al.*, 1970).

Ketamine is an excellent bronchodilator and may be the anesthetic of choice for induction of anesthesia in the asthmatic. We have successfully administered ketamine by i.v. infusion to terminate an asthma attack after conventional methods of treatment failed (Corssen *et al.*, 1972).

When administered in subanesthetic amounts, a painless state is produced without loss of consciousness in which shortlasting ambulatory surgery and dental procedures may be performed. Being water soluble, ketamine does not irritate veins and does not cause pain on injection. When administered i.m., the drug is rapidly absorbed without local irritation or induration. During our initial human pharmacologic and clinical trials, ketamine's psychedelic properties presented a drawback, particularly in the human volunteers in whom any type of preanesthetic medication was omitted. In fact, emergence reactions of agitation, delusions, illusions, hallucinations, and delirium occurred with such frequency in the volunteers and, to a lesser degree, in surgical patients who received commonly used preanesthetic medication, that we began to have serious doubts of successfully introducing ketamine as a clinically useful anesthetic.

Other disadvantageous properties of ketamine which were of concern to us during the first months of clinical usage included its tendency to raise intracranial pressure and to produce hypertonicity, causing involuntary muscle movements and profuse salivation. Therefore, we became

increasingly more aware of the need to find methods and drugs to eliminate or attenuate the ketamine-induced undesirable and potentially dangerous effects.

Efforts to reduce the adverse effects of ketamine became partially successful by including various combinations of opiates, tranquilizers and belladonna drugs in the preanesthetic medication. Droperidol appeared to be especially effective in providing preanesthetic tranquility, reducing the incidence of unpleasant dreams under ketamine anesthetic, and terminating acute psychomotor emergence reactions. A real breakthrough in effectively "taming" ketamine by minimizing the incidence and degree of emergence psychic phenomena and reducing its adverse cardiovascular and musculo-skeletal effects came with the use of diazepam and its derivatives administered before, during, or after ketamine anesthesia (Coppel *et al.*, 1973).

It appears that most of our initial skepticism and doubts regarding ketamine's role as a general anesthetic have gradually been overcome and the drug has found its place as an unusually safe, rapidly acting parenteral anesthetic. Naturally, we fully agree with M. Johnstone, as quoted by T. Boulton (1987) of Reading, United Kingdom, that ketamine is probably the most important advance in the symptomatic treatment of pain since the discovery of aspirin.

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Early British Experience with Ketamine

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Ketamine had a long "gestation period" by standards of the 1960's. Almost 5 yr elapsed since the description of its pharmacology by Chen (1965) and McCarthy and associates (1965) and the clinical pharmacologic studies of Domino *et al.* (1965) and its clinical launch in North America. There was a prolific spate of American publications in early 1970, reflecting studies carried out in 1968-69, some of which drew attention to side effects both during (hypertension, tachycardia and hypertonus) and after anesthesia (emergence delirium and dreams).

The present requirements for organized clinical trials in the country of use, and consideration of reports by the national drug regulatory organization—Committee on Safety of Medicines (CSM) in the UK—equivalent to Federal Drug Administration (FDA) in the USA—did not exist in Britain 30 yr ago. A pharmaceutical firm could provide data in an "investigator's manual", based on studies carried out elsewhere. This happened when ketamine was introduced in Britain late in 1969 and early 1970.

A chemically similar drug, phencyclidine (CI-395, Sernyl) also introduced by Chen and colleagues (1959), was studied by Johnstone *et al.* from the Manchester Royal Infirmary in England. Their report, published in 1959, described its effects in 67 patients. Greifenstein and De Vault (1958) described maniacal excitement following surgery under phencyclidine lasting up to 3 hr. The significance of these findings, in relation to ketamine, was not appreciated at the time.

One can say without much doubt the introduction of ketamine into Britain was a "disaster" from which the drug never recovered. Yet it was one from which many lessons have been learned. The reasons for this fiasco are reviewed. Table 1 summarizes the information available to initial British investigators. Table 2 gives the manufacturer's main indications for the use of ketamine.

The wording of Table 1 caused much concern with the early British

TABLE 1. Guidelines available for the first British use of ketamine

1. Rapidly acting nonbarbiturate general anesthesia (manufacturer's brochure).
2. Producing "dissociative anesthesia" characterized by complete analgesia with only superficial sleep (Corssen and Domino, 1966).
3. A compound with a cataleptic analgesic and anesthetic action, but without hypnotic properties.
4. Catalepsy = a characteristic akinetic state, with a loss of orthostatic reflexes, but without impairment of consciousness (Chen, 1965).

TABLE 2. Early recommended indications for the use of ketamine

1. As the sole anesthetic agent for diagnostic and surgical procedures. Although best suited for short procedures, it can be used with additional doses, in procedures requiring anesthesia for periods of 6 hr or longer.
2. For the induction of anesthesia prior to the administration of other general anesthetic agents.
3. To supplement low potency agents such as nitrous oxide.

(From the literature supplied to clinical investigators in Britain)

anesthetists. First, a recognized classification (Dundee and Wyant, 1974) divides intravenous anesthetics into rapidly acting and slower acting. Rapidly acting drugs will, in adequate doses, induce loss of consciousness in one arm-brain circulation time. When injected as a bolus at the height of forearm reactive hyperemia, this can be as short as 10-12 sec, and in normal clinical conditions is in the 30-40 sec range. Attempts to achieve this expected rapid onset by increasing dosage also increased sequelae (Knox *et al.*, 1970).

The new terms "dissociative anesthesia" and catalepsy were never fully understood by those who had little previous experience with neurolept anesthesia. While popular in continental Europe, this had not been widely used in Britain. In retrospect, one can appreciate the greater American familiarity with this technique when Pender (1971) described the effects of ketamine as resembling that of neurolept drugs, but produced by one agent. Clearly those advising the initial investigators were unaware of these transatlantic differences in practice. The difficulty of rapidly placing a woman's legs in lithotomy stirrups caused frustration and problems with which we had no previous experience.

It was (and still is) common British practice to concentrate initially on "pure" studies—no or little premedication, no supplementary drugs and a standard large patient population providing facilities for using the drug as

the main agent. Clearly, the first indication listed in Table 2 pointed to its initial use as the sole (or main) agent for women having minor gynecologic operations, which was one of the specific fields of use recommended by the company. This typical short operation seldom lasted more than 5 to 6 min, which was very different from North American practice. It was not unusual to have a turnover of one such operation every 10 min in a single operating room, often with one anesthetist. With hindsight, we know we had most of the factors which contribute to an unacceptably high incidence of emergence delirium, *i.e.*, unpremedicated young women, very short operations, and no other sedation or hypnotic drugs.

The situation was made worse by the then common practice of returning patients directly to their ward (often an open "Florence Nightingale" type with 10-20 beds) without a stay in the recovery ward. While it is often stated that patients themselves are unaware of and not upset by emergence delirium, this does not apply to other patients, some of whom may be waiting for an operation. Patients having the minor operation discussed above do not normally receive (or require) postoperative sedation and one can imagine how the emergence deliriums of the other patients contributed to the chaos in the ward during these early studies.

Without being critical of the individuals involved, one realizes that medical advisors to the pharmaceutical industry have to deal with a wide spectrum of drugs. The British advisors to Parke Davis & Company, headed by Dr. John Gorringe, while being most helpful, had no previous experience with anesthetics and certainly were unaware of the differences between British and American practice. The author had worked in Philadelphia and was aware of American practice, as were two of our fellow investigators. Even this experience did not alert us to the problems which we were to experience. The Lancet of June 27, 1970, contained the report of our experience in over 450 anesthetic inductions with ketamine (Dundee *et al.*, 1970). This was a very intensive clinical trial, carried out in about three months in four hospitals. It involved adult gynecology and general surgery patients and 40 children undergoing minor surgical procedures. Our findings are best described by a direct quote from our final paragraph ". . .narcosis with ketamine is quite different from that produced by other available drugs, and the term dissociated anesthesia is very descriptive. Anesthesia is accompanied and followed by a high incidence of undesirable side effects in adults. Although these are decreased by certain forms of premedication, more work is needed to find the most suitable adjuvants and to clarify the specific indications for its use."

Looking back on the British experience with this drug, this was a

temperate understatement of our problems. Some of my coworkers felt that there was no place for this drug in British anesthetic practice. Others of us appreciated its analgesic action and its possible potential in certain limited fields. It certainly was not the universal, non-hypotensive substitute for thiopental which we had expected. If only our pharmaceutical advisors had been more knowledgeable, the situation would have been quite different. Yet it was a privilege to learn so much about clinical trials in such a short time.

Acknowledgements

The author is appreciative of the help of the many stalwart colleagues in these early studies.

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The Taming of Ketamine

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The early British experience with ketamine has been described as disasterous (Dundee, 1990), with an unexpectedly high incidence of emergence delirium and hypertension. The first large British study, involving more than 450 administrations, although highlighting the problems encountered, concluded "Ketamine has certain actions not possessed by other agents, and these should guarantee it a place in anesthesia . . . Although these (undesirable side effects) are decreased by certain forms of premedication, more work is needed to find the most suitable adjuvants and to clarify the specific indications for its use." (Dundee *et al.*, 1970)

This paper describes these early studies, which were aimed at minimizing the side effects of the drug, while retaining its desirable properties. Some of these attempts involved the use of adjuvant drugs while others looked at the types of procedures and patients for which the drug would be more suitable. The title "The Taming of Ketamine" is taken from a paper by Coppel *et al.* (1973) which describes studies carried out to retain the best and minimize the worst effects of this unique drug.

Unpleasant Sequelae

Table 1 lists the most common sequelae encountered with ketamine anesthesia (Bovill and Dundee, 1972). The severity of these have been shown to depend on a number of factors such as individual predisposition, the nature and duration of the operation and the (supposed) circumstances of awakening. The emergence delirium does not upset the patients, but does upset their attendants and other patients. By contrast unpleasant dreams do upset the patients but not their attendants, who are unaware of them. Early fears of "flashback" incidents, whereby patients can relive the dreams after several days, have been exaggerated.

Early in the use of ketamine, we demonstrated (Knox *et al.*, 1970) that dosage is a factor influencing the occurrence of unpleasant dreams

TABLE 1. Main problems associated with the use of ketamine

Intraoperative	*Postoperative*
Hypertonus	Emergence delirium
Hypertension	Unpleasant dreams
	Emetic sequelae

and emergence delirium. With a constant patient population and operations (women having short gynecologic operations) the incidence increased with dosage (Table 2). Contrary to a widely expressed view, the condition of patients on leaving the operating room was not found to be a factor (Table 3).

The early British studies were carried out in adult women. It was difficult to get a comparable group of men and women having a similar short operation to compare the incidence (there being no male equivalent to minor gynecologic operations). The data in Table 4 were obtained from patients having longer but otherwise comparable operations. This shows that the tendency of women to have both emergence delirium and unpleasant dreams (Coppel *et al.*, 1973; Lilburn *et al.*, 1978) is greater than with men.

Studies described to date show that the two factors predisposing to a high incidence of emergence sequelae were short operations in young women and the administration of large doses of ketamine. Table 4 shows that in this susceptible group of patients orthodox premedication clearly

TABLE 2. The percentage of sequelae are related to the dose of ketamine

	<2 mg kg^{-1}	*2-3 mg kg^{-1}*	*3+ mg kg^{-1}*
Dreams	23	33	38
Delirium	19	12	27

(Knox *et al.*, 1970)

TABLE 3. Percentage incidence of emergence delirium following 2 mg/kg ketamine in patients who were awake or asleep on leaving the operating room

Condition arrival in recovery ward	*N*	*Emergence upset*		
		Mild	*Severe*	*Total*
Awake	70	18	16	34
Asleep	55	14	22	36

modifies the incidence and severity of complications. However, this may be achieved at the cost of delayed recovery.

Even with major operations lasting 1 1/2 hr, the importance of premedication cannot be underestimated. The patients listed in Table 5 had ketamine as the main anesthetic, yet in the absence of an opioid, one quarter were unhappy about the anesthesia. The data in Tables 4 and 5 are drawn from different patient populations, yet they show similar results.

Protection by benzodiazepines

The early use of ketamine coincided with the increasing use of oral benzodiazepines as premedication and the availability of parenteral preparations of flunitrazepam and lorazepam, in addition to diazepam. There are many studies on this topic. Table 6 summarizes some of these, while Table 7 shows the benefit of giving a small dose near the end of the

TABLE 4. Effect of sex, nature and duration of the operation, and premedication on the percent incidence of unpleasant sequelae from ketamine

	Emergence Delirium	*Unpleasant Dreams*
Men	6	6
Women	24	14
Atropine premedication		
Minor operations	34	40
Major operations	20	10
Opioid premedication		
Minor operations	11	26
Major operations	5	0
Droperidol premedication		
Minor operations	5	36
Major operations	6	15

TABLE 5. Percent incidence of unpleasant sequelae and acceptability of anesthesia in patients undergoing body surface operations, related to premedication

	Atropine 0.6 mg	*P 20 mg H 0.4 mg*	*D 5 mg F 0.1 mg*
Mean duration of operation (min)	64 (23-90)	85 (31-180)	80 (38-150)
Severe emergence delirium	75	0	0
Unpleasant dreams	50	0	75
Acceptable to patient	75	90	95

(P = papaveretum; H = hyoscine; D = droperidol; F = fentanyl)

TABLE 6. Percent of sequelae associated with i.m. benzodiazepine premedication

	Prolonged emergence sequelae	*Unpleasant dreams*
0.9% NaCl	40	30
Diazepam 15 mg	25	32
Flunitrazepam 1.5 mg	22	2
Lorazepam 4 mg	4	4

TABLE 7. Percent incidence of troublesome sequelae, and patients dissatisfied with anesthesia. The patients were unpremedicated women having short minor gynecological operations under ketamine-nitrous oxide anesthesia. Supplements were given at the end of the operation.

Additional drug given i.v.	*Nil*	*Droperidol 5 mg*	*Diazepam 5 mg*
Emergence upset	34	5	65
Unpleasant dreams	40	40	15
Patients dissatisfied with anesthesia	52	40	15

operation. Both of these sets of data were obtained from "high risk" patients, *i.e.*, women having short (5-10 min) minor gynecologic operations. The data show clearly the benefit of a longer acting benzodiazepine such as lorazepam and for many this has become the method of choice for preventing unpleasant sequelae after ketamine.

Droperidol. This drug provided benefits similar to diazepam but some patients were unhappy about their condition on awakening. They felt disorientated or "dissociated" and, since lorazepam is more effective, it is probably preferred to droperidol. When given i.v., the relatively long duration of action of droperidol should be remembered.

In summary, the following factors affect the severity of ketamine emergence sequelae:

Doses of ketamine ($2+$ mg kg^{-1})
Nature and duration of operation
Preanesthetic medication (more frequent with "light premedication")
Sex of patient (women more susceptible than men)
Use of concurrent drugs

The circumstances of awakening, whether in a busy operating room, the quieter surroundings of the recovery room, or the ward, do not appear

to be as important a factor as once thought. Preoperative briefing may reduce the incidence, but this has not been adequately researched. Sequelae become less frequent and severe on repeated use, as during the treatment of burns.

Reduction of Hypertension

Early in the clinical use of ketamine, Bovill *et al.* (1971) demonstrated that, with a constant dose of 2 mg kg^{-1}, the rate of administration did not influence the cardiovascular response to ketamine. Neither was there less hypertension when the equivalent dose (10 mg kg^{-1}) was given i.m.

A wide variety of drugs have been studied to reduce this ketamine induced hypertension. These include hexamethonium, adrenoreceptor blockers, droperidol, labetalol, promethazine, procaine amide, and phentolamine. Since most of these drugs were without effect in reducing hypertension and tachycardia, this work is not described in detail. Furthermore, with proper selection of cases, we no longer consider tachycardia and/or hypertension a major clinical problem except when the drug is given by continuous infusion (Coppel and Dundee, 1989). It is sufficient to say that best results were obtained from pretreatment with the adrenoreceptor blocker, labetalol. The best overall effect was produced by following ketamine with a low concentration of halothane and avoiding pancuronium with its known chronotropic effects.

Summary

Careful selection of patients, operations, and correct premedication can be used successfully to mitigate the unpleasant sequelae from ketamine, while retaining its desirable properties.

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KEY WORD INDEX

This index is based upon key words and therefore is incomplete. The reader should refer to the Table of Contents for individual chapters that summarize in detail various topics related to ketamine.