CLINICAL TRIALS OF TWO NEW DRUGS IN THE FIELD OF ANAESTHESIA†

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May I say first of all, that I sincerely appreciate the privilege of being asked to speak to the International Medical Journal Club, Kathmandu. It was thought that you would be interested in a progress report of some clinical trials of two fairly new drugs which we have been using in the United Mission Medical Center in Kathmandu since September of 1969. These drugs may or may not come into general use in the field of Anaesthesiology, but it is possible that at least they will be given the status of "stepping stones" toward our elusive goal of "the perfect anaesthetic". Unfortunately the small number of cases presented here cannot be considered conclusive, but may stimulate further interest.

1. KETAMINE (CI-581, "Ketalar", Park, Davis, & Co.)

The search for an ideal anaesthetic has gone on for probably two or three thousand years. Primitive pain-relieving drugs included alcoholic drinks, hemp, hashish, and marihuana. Hypnotism was tried in the 18th Century. Inhalation agents in the 19th Century brought to the world the first really humane surgery. It was soon recognized that good anaesthesia included not only rendering the patient insensitive to pain, but reducing stress before, during, and after the surgery.

All general anaesthetics up to the present decade have provided pain control by totally depressing the central nervous system, from the cortex and sub-cortex to the various pathways of perception.

It is startling to learn that physical chemists now say that we have considered all possible combination of molecular structures capable of inducing anaesthesia by inhalation. Unless some new and unsuspected molecular configuration is found, no new inhalation agent will appear. However, there is ample room for the discovery of injectable agents.

A modern trend of those doing research in this field is to search for methods of selectively blocking pain conduction and perception, thus leaving the remainder of the central nervous system free of depression by the drugs.

Laborit probably made the first attempt to selectively block pain perception with concept of "neuroplegia", and what he called the "lytic cocktail". This a combination of meperidine (Pethidine), promethazine (Phenergan), and chlorpromazine (Largactil). However, this often

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produced a shock-like state, and did not gain wide acceptance. More specific and potent tranquilizers have been developed, including phenoperidine and fentanyl. The goal is to provide pain control during surgery, without the inherent dangers of deep anaesthesia. This selectivity would be especially beneficial for poor-risk and geriatric patients.

The phencyclidine group of compounds is being explored. Ketamine (CI-581) is one of these. It is a non-barbiturate, non-narcotic, which is administered by vein or into the muscle. The anaesthetic effects are of short duration, producing a profound analgesia with a somnolent state in which the patient appears to be "disconnected" from his surroundings. This "dissociative" state suggests a predominance of activity of the drug in the frontal parts of the cerebral cortex, probably the association area. Laboratory and clinical work confirms this.

Clinical studies with Ketamine, reporting a series of 1,508 cases, have been reported by Dr. G. Corssen and others of Ann Arbor, Michigan. The ages of patients ranged from five (5) days to 86 years, over two-thirds being children. Forty percent of the cases were eye examinations or surgery, 20% were burn treatments. The rest were ear surgery, neurosurgery, orthopedic, urology, and some general surgery.

Preanaesthetic medication recommended was scopolamine only, because of its effectiveness as a drying agent and amnesic. The majority were given Ketamine by the intravenous route in single or repeated doses. Supplementary anaesthetics were used in only 12% of cases, mostly to prolong the anaesthesia. Ketamine may also become useful as an induction agent, possibly for general anaesthesia for intra-abdominal surgery.

Recovery from Ketamine as a single intravenous injection usually occurs in 30 minutes, whereas with repeated injections, up to two hours may elapse before the subject is oriented. No out-patients were kept longer than three hours. In some situations, prolonged recovery may be a real disadvantage.

Complications were surprisingly few. Of their series, 8% showed a rise in blood pressure of more than 25%, and 4% showed a rise in pulse rate of 50% over the resting. Three percent had obstruction of breathing due to excess salivation. In the recovery period, about 6% had pleasant or unpleasant vivid dreams or emergence delirium.

My personal experience with Ketamine has not been great. My colleagues and I first received the drug for clinical trials in August of 1969. Our first cases were satisfactory and included pneumoencephalograms, removal of intervertebral discs, and caesarean section.

After arriving in Nepal at the United Mission Hospital, due to limited supplies of Ketamine, we have been able to administer it on only eleven occasions. However, these cases will serve to illustrate its use.

The first case was that of a child of ten months, weight 8.3 kg, hemoglobin 10 grams, with severe burns of the face and head three months previously. He had three eruptions under

Ketamine; the first for removal of the right parietal bone, which was necrotic, the second for removal of the right frontal bone; and the third for extensive skin grafting requiring 75 minutes. The second patient was a man of 19 suffering from a fracture-dislocation of the spine. He had a three hour procedure under Ketamine anaesthesia, in the prone position for laminectomy, exploration of spinal cord, spinal fusion, and body cast. There were two cases of closed reduction of fractured arms. A woman of 24 years was admitted in a toxic state six days after receiving a 30% body burn. The burns were debrided and dressed under Ketamine satisfactorily, but she showed a shock-like state for a short time upon return to her bed, probably from dehydration, anemia, and toxemia. Another woman of 24 years had a caesarean section and tubectomy. The baby was delivered in excellent condition, with an Apgar score of 10, under Ketamine. Following delivery, the mother was given ether and oxygen for the remainder of the procedure, since visceral pain is not well obtunded by Ketamine. A child of seven years had cystoscopy and urethral dilatation. A very anemic and debilitated girl of fifteen underwent incision and drainage of multiple abscesses. The most dramatic case we had was that of a small girl of 17, who had suffered from a tightly closed jaw for over three years, resulting from infection and dense scar tissue. An unsuccessful attempt was made to pass a nasotracheal tube blindly after trans-cricoid injection of lidocaine, with the patient awake. Ketamine was then injected intravenously in two doses, and the surgical procedure was completed in 45 minutes. During this time the patient managed her own airway with no respiratory or circulatory problems.

In summary, ten of our eleven cases using Ketamine hydrochloride as a general anaesthetic were considered to be satisfactory. The only case not satisfactory was that of a two year old child with a fracture in which a somnolent state was not obtained. Possibly the injection did not reach muscle and absorption was delayed.

Corssen has condensed the advantages of Ketamine over conventional anaesthetics this way: It provides profound analgesia without significant impairment of respiration, and avoids hypotension by stimulating cardiovascular activity. Protective reflexes are preserved and an unobstructed airway is maintained regardless of position. Multiple administrations have not produced organ toxicity; there is excellent tissue compatibility, nearly absent post-operative nausea and vomiting. There appears to be a wide margin of safety, and antiarrhythmic properties and amnesia have been observed.

The disadvantages of Ketamine include occasional vasopressor activity, salivation in absence of antisialogogues, and exaggerated protective reflex activity in response to stimulation of the pharynx and larynx. There is cumulative action after multiple doses, with prolonged recovery. There may be occasional extra-pyramidal activity and vivid dreams bordering on hallucinations if emergence is premature.

The contra-indications of Ketamine were listed as follows:

1. Hypertension (blood pressure above 160/100 mm Hg.)

2. History of cerebrovascular accident.
3. Surgery involving the pharynx, larynx, and bronchial tree unless an endotracheal tube is placed and muscle relaxants are employed.
4. Marked cardiac decompensation.
5. Upper respiratory infection.
6. Abdominal surgery and other procedures involving "visceral" pain.

2. DIAZEPAM

The second drug which interests me now is Diazepam (Valium: Hoffmann-LaRoche Co.). You are undoubtedly acquainted with this drug which has been available as a tranquilizer, and anti-convulsant, in tablet form for at least six to eight years.

One of the first reports of its use as pre-anesthesia medication was in "Anaesthesia and Analgesia", January, 1965.

The first report I have of its use as an intravenous induction agent for general anesthesia came in the Canad. Anesth. Soc. J., 1966.

A further report in the same Canad. Anesth. Soc. J., May, 1968 (co-authored by one of my partners) compared Diazepam and Thiopentone as induction agents to general anesthesia.

They concluded that the onset of sleep was approximately 30% longer with Diazepam than with patients induced with Thiopental for halothane (fluothane) anesthetic. However, the Diazepam group were extremely docile, co-operative, and induction very smooth. The cardiovascular effects were comparable. Respiratory system effects were less pronounced with Diazepam. Amnesia is longer with Diazepam.

Before coming to Nepal, I learned that I would have no halothane or nitrous oxide but only ether for an inhalation anesthetic agent. Following previous experience with ether in war time, I was aware that pentothal could be troublesome as an induction agent followed by ether and oxygen. I was curious to know whether I could avoid the use of both pentothal and ethyl chloride for this purpose, prior to ether. It occurred to me that intravenous Diazepam might be advantageous before ether, in the absence of nitrous oxide and halothane.

With this in mind, I wrote to the Hoffmann-LaRoche company to enquire about any reports or advice they might have in this regard. I was unable to evaluate my idea at home, since my own department had removed ether and all other flammable, explosive agents several years ago. We had also discontinued all precautions and physical deterrents to explosive hazards.

The Hoffmann-LaRoche Medical Director replied that he had no reports of the use of intravenous Valium prior to ether, but expressed considerable interest in the idea and kindly donated a supply for our use at the United Mission Hospital.

The eighteen cases in which I had the opportunity of using Diazepam and ether in sequence included minor surgery, orthopedic procedures, and laparotomies. The ages ranged from 4 to 60 years, the body weight from 14 to 82 kgm. The premedication used was pethidine and atropine, 45 minutes pre-operatively. The dose of Diazepam used intravenously ranged from 5 to 25 mgm, which was 0.3 to 0.5 mgm per kgm. The apparatus available and used was:

- i) adult O₂ absorbing circle with in-circuit vaporizer,
- ii) child to and fro absorber,
- iii) E. M. O. apparatus. Oxygen was available in limited quantities, and there was no nitrous oxide.

The results of this small series were as follows:

Fourteen cases were considered satisfactory, with smooth induction and maintenance and no untoward effects. The remaining four cases were smooth, but the induction time in preparation for surgery required at least fifteen minutes and we felt that this was undesirable. One of the eighteen coughed slightly when ether was introduced. There were no cases of breath holding or bronchospasm.

Again I regret that I have not a larger series to report to you, but I suggest that further trials and more careful evaluation are warranted.

SUMMARY

1. A new "dissociative" anaesthetic, Ketamine hydrochloride is described, with illustrative examples of its use.
2. Intravenous Diazepam ("Valium") is suggested, possibly for the first time, as a method of ether-air, or ether-oxygen anaesthesia.

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