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The Use of Ethamivan in the Treatment of Barbiturate Poisoning

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ABSTRACT

Ethamivan was used as a respiratory analeptic in the treatment of nine cases of severe barbiturate poisoning. Initial intravenous injections of 100 to 150 mg. of ethamivan increased the depth of respirations within a minute. Prolonged respiratory stimulation was achieved by a continuous intravenous infusion of 500 to 3000 mg. of ethamivan per litre of fluid. If hypotension occurred, an intravenous drip of noradrenaline was used; fluid overloading was avoided by adjusting the concentrations of drugs given, so that no more than a total of 125 c.c. of fluid per hour was administered. The chief side effect of overdosage of ethamivan was muscular twitching. This did not prove to be a problem and was of some value in determining the amount of drug given. The nine patients survived. It was concluded that ethamivan is a useful agent in the treatment of barbiturate poisoning.

VARIOUS analeptics have been advocated for the management of barbiturate poisoning; one of those more recently developed is ethamivan or vanillic diethylamine (Emivan). This drug was synthesized in 1952,[1] but only in the past few years has it come into clinical use in this country. When injected intravenously in single doses of 0.5 to 2 mg. per kg., effects have been noted within 30 seconds and lasted approximately 10 minutes. The chief effect was an increase in the depth of respirations with a less marked increase in the rate of respirations. No significant changes in pulse rate or blood pressure occurred.[2] Ethamivan reverses respiratory centre depression caused by a variety of agents, such as barbiturates, alcohol, morphine and ether. It has also been used in the treatment of carbon dioxide accumulation associated with respiratory insufficiency. In patients with pulmonary insufficiency, measurements of arterial pCO_2 before and after the administration of ethamivan have shown a decrease corresponding with an increase in the depth of respirations.[3] Silipo *et al.*[4] reported their experience with ethamivan in the management of barbiturate poisoning and in respiratory insufficiency—seven cases of barbiturate poisoning were included. In the more severe cases initial priming doses of 400 to 500 mg. of ethamivan were given intravenously, followed by continuous infusions containing 1 g. ethamivan in 250 c.c. of 5% glucose in water, at rates up to 40 drops per minute, the rate of drip being guided by the depth of respirations. Six of the seven patients responded and in the seventh patient a respirator was also found necessary. One patient had been apneic and kept alive with a respirator for 21½ hours and began breathing spontaneously with the administration of ethamivan. This most interesting case had been previously reported in detail.[5] Ethamivan has also been found to be an effective arousing agent following the use of general anesthetics.[6, 7] The present report deals with our experience with this agent in the treatment of a number of patients with severe barbiturate poisoning.

General Plan of Treatment

Establishing an airway and adequate respiratory exchange is the immediate problem. The oropharynx is suctioned and a rubber airway inserted. If the patient shows very shallow breathing, he is immediately given a direct intravenous injection of 100 mg. of ethamivan over a period of one to two minutes and oxygen and artificial respiration are administered. With the immediate situation under control one can proceed to set up an intravenous infusion of ethamivan to prevent relapse into respiratory depression. As soon as possible a cut-down is performed to ensure that the intravenous route is secure. If severe hypotension is present, an intravenous infusion of noradrenaline may also be necessary for a time, as ethamivan has only a minor effect on the vasomotor centre. The presence of hypotension usually indicates a near-terminal state of barbiturate poisoning, or that a tranquillizer or alcohol has also been ingested.

It has been advocated by some that ethamivan should be given in large, single intermittent doses. The object of this is to bring the patient back to a near-conscious state and to maintain this state. We believe that because the drug is an analeptic and not a neutralizing agent, a continuous intravenous infusion will maintain the vital functions while the body detoxifies and eliminates the barbiturate. We have therefore employed an infusion containing 500 to 3000 mg. of ethamivan to 1000 c.c. of 5% dextrose in water. The concentration and rate of administration are dictated by the severity of the respiratory depression. If over 30 drops per minute of the infusion is required the concentration is increased, rather than risk overloading the patient with a large volume of intravenous fluid. As with noradrenaline, constant supervision over the infusion is mandatory. If both ethamivan and noradrenaline infusions are being employed, the concentrations of both are

adjusted so that a total infusion of 30 drops per minute is not exceeded. If ethamivan is given too rapidly, muscular twitching, laryngospasm or sneezing may occur. In our experience muscular twitching is the most common of these. The nurse in attendance is made aware of these side effects and instructed to slow the infusion if they occur. Having ascertained the rate of infusion necessary to support adequate respiration, the nurse is instructed to run the intravenous at the slowest rate that will maintain adequate respiratory exchange.

The patient's stomach is then lavaged. If a long interval has elapsed since ingestion of the barbiturate, the value of lavage might be questioned. However, there is often delay in gastric emptying in patients with barbiturate poisoning, and for this reason we have employed lavage in all cases. Because of the danger of aspiration an anesthetist has been consulted whenever possible and a gastric tube passed under direct visualization. An immediate danger is atelectasis and the development of pneumonia. Indeed, some patients have early pneumonia when first seen. For this reason the patient is postured from side to side each hour, a prophylactic antibiotic is administered, and a radiograph of the chest is taken. Attention is given to skin care, and a prophylactic eye ointment, such as neomycin with hydrocortisone, is applied hourly to prevent corneal scarring. An indwelling catheter is employed so that urinary output may be observed.

Clinical Experience

Nine cases of severe barbiturate poisoning were reviewed. The three more severe cases are reported and the remaining six are summarized in this communication.

CASE REPORTS

CASE 1.—A 64-year-old woman was admitted to the Victoria Royal Jubilee Hospital emergency department on October 4, 1961. She had been unconscious for an estimated seven hours after taking an unknown amount of Tuinal (a sedative containing equal parts of seconal and amytal). As she was being brought in, her respirations ceased. Mouth-to-mouth breathing was instituted until a pulmotor was obtained. Ethamivan 150 mg. was given intravenously over a period of one minute and spontaneous respiration resumed. Her pulse rate was then 100 per minute and her blood pressure was 120/70 mm. Hg, but she had neither corneal reflexes nor tendon reflexes and was completely flaccid. An intravenous infusion of ethamivan containing 500 mg. to 250 c.c. of 5% glucose in water was commenced; this was later changed to 1000 mg. of active agent per litre of fluid and run in at an average of 30 drops per minute over the following 12 hours. After approximately 12 hours of therapy the patient gradually recovered consciousness and her convalescence was uneventful. Approximately 3000 mg. of ethamivan was used during the course of treatment.

Comment.—The life-saving potential of ethamivan was dramatically demonstrated in this patient, for her respirations had ceased. It was also demonstrated that effective artificial respiration must be employed until the respiratory centre has been stimulated.

CASE 2.—A 34-year-old man was brought in to the emergency department of the Royal Jubilee Hospital on February 12, 1962, after consuming an unknown amount of meprobamate and secobarbital approximately 36 hours previously. On arrival he was comatose and deeply cyanosed, and had shallow respirations. The blood pressure was 95/80 mm. Hg. The pulse was rapid and weak. An airway with suction and oxygen was immediately employed and an intravenous infusion containing 1000 mg. of ethamivan in 500 c.c. of 5% glucose and water was started by means of a cut-down; 100 mg. of ethamivan was also given *via* the intravenous tubing. The colour of the patient improved considerably and the respirations became deeper. However, hypotension became more marked, with a low blood pressure reading of 64/40 mm. Hg. For this reason a noradrenaline infusion was also instituted. The concentration of noradrenaline used varied between four and 16 mg. per litre of 5% glucose and water, and it was given at rates varying from 10 to 15 drops per minute over the following 48 hours. Five hours after admission the patient had received 1100 mg. of ethamivan. He was still comatose but reflexes were present. Ethamivan, 2000 mg. per 1000 c.c. in 5% glucose and water, was being given at approximately 30 drops per minute. After a further three hours, twitching occurred and the ethamivan infusion was slowed down. This resulted, after a short time, in shallow respirations, and the rate of ethamivan infusion was increased until satisfactory respiratory exchange resulted. This was maintained with a further 4000 mg. of ethamivan over the next 35 hours—the rate of administration varying from 12 to 30 drops per minute of a solution containing 2000 mg. of ethamivan per 1000 c.c. of 5% glucose and water. Consciousness gradually returned. A further 2500 mg. of ethamivan was employed during the 14-hour period between return of consciousness and the time when the patient was coughing freely and was fully alert. The total amount of ethamivan used was 7600 mg. over a 54-hour period. It is interesting to note that when he was admitted the patient already showed clinical and radiological evidence of pneumonia in the right lung. Twenty-four hours after admission there was also atelectasis of the right base, but with antibiotic therapy and frequent positioning of the patient the signs had decreased considerably by 72 hours and eventually subsided.

Comment.—The case demonstrated the importance of carefully titrating the rate of administration of ethamivan and noradrenaline. Excessive rate of administration of ethamivan resulted in muscular twitching, but too rapid withdrawal of the drug resulted in inadequate ventilation. Stimulation of the respiratory centre again occurred when the rate of administration was increased. The drug was also of value in the treatment of the continuing complication of pulmonary atelectasis and pneumonia.

CASE 3.—A 21-year-old man was admitted to St. Joseph's Hospital, Victoria, B.C., on December 12, 1961, approximately 24 hours after the ingestion of 60 grains of Tuinal and 10 "tranquillizer" tablets of unknown nature. He had been discovered in a hotel room in an unconscious state. On examination his face was flushed and slightly cyanotic, and his finger tips were cyanotic. Respirations were shallow and rapid. His pulse was 140 per min. and was thready. The blood pressure was 95/85 mm. Hg. No tendon reflexes were obtained. Examination of the chest showed basal rales. Axillary temperature was 103.8° F. Early pressure sores were present on the legs. The bladder was distended. An airway was inserted, the throat was suctioned and oxygen was administered. Ethamivan, 1000 mg. in 500 c.c. of normal saline, was given by intravenous drip at 20 to 30 drops per minute. A catheter was inserted into the bladder. Seven hours later the patient's respirations were becoming progressively more shallow with a respiratory rate of 56 per minute. The concentration of ethamivan was changed to 1500 mg. in 500 c.c. of 5% glucose and water, at 20 to 40 drops per minute. His colour improved, respirations becoming deeper and slowing to 44 per minute. Following this, metaraminol (Aramine), 5 mg., was given intramuscularly every half hour as required to keep the systolic blood pressure higher than 90 to 100 mm. Hg. This was necessary for the following 12 hours. Approximately 24 hours after admission the patient remained deeply unconscious. Antibiotics (penicillin and streptomycin) had been administered, his position was changed hourly from side to side, and suction was used as required. The patient received 5500 mg. of ethamivan. The drip containing 3000 mg. of ethamivan per litre of 5% glucose and water was continued during the following 12 hours and during this period a further 4500 mg. of ethamivan was used. In the evening of the patient's second day in hospital it was possible to reduce the dose of ethamivan to 500 mg. in 500 c.c. of intravenous solution; 500 c.c. of 5% glucose-saline was given to compensate for loss by visible perspiration. In the early morning of December 14, it was possible to reduce the ethamivan to 500 mg. in 1000 c.c. of 5% glucose in water, and when respirations appeared adequate at 10 drops per minute, a transfer to glucose and water was made. At this time the patient had begun to stir and had coughed out his airway. He gradually regained consciousness. Culture taken from throat suction on admission had grown *Staphylococcus aureus*. Following his return to consciousness, continuing treatment of the pulmonary infection remained a problem, but this gradually cleared with positioning, coughing, steam and antibiotics. His pressure sores gradually healed. A total of 10,000 mg. of ethamivan had been used.

Comment.—This patient required the greatest total amount of ethamivan used in this series of cases. It was well tolerated and consistently maintained deep respirations until consciousness returned. No side effects were noted.

The six other cases that were studied followed a pattern of response similar to that noted above. Five patients were women in their 30's and one was a woman of 73. All were unconscious on admission and had shallow respirations. Four of the six were cyanosed. In only one was hypotension a problem; this patient had ingested a tranquillizer, trifluoperazine, in addition to barbiturate. The hypotension responded to a noradrenaline drip. It was difficult and sometimes impossible to ascertain the exact amount of barbiturate taken. It appeared, however, that the more barbiturate ingested and the longer the time interval before treatment, the greater the amount of ethamivan required. Total dosage of ethamivan used for these six patients varied between 1000 and 3000 mg. given over periods ranging from four to 25 hours. The amount of barbiturate ingested was ascertained in only two cases: 36 grains of Amytal Sodium and 22 grains of phenobarbital by one patient, and 45 grains of Tuinal by the other. Four of the six showed minor muscular twitching as consciousness returned and one developed sneezing at that point. None developed convulsions.

DISCUSSION

Our experience with ethamivan has been favourable. It has become our mainstay in the treatment of severe barbiturate poisoning because we feel we can depend on it to maintain deep adequate respirations. Ethamivan has proved superior, in our experience, to amphetamine and picrotoxin therapy. We have not employed megimide (Bemegride), which is widely used in England. The actual value of analeptics in the management of barbiturate poison is the subject of much controversy.[8-10] Some workers believe that artificial respiration and general supportive care yield results as good as, or better than, those achieved with analeptics. Respirator care is not without its dangers and requires trained personnel. We did find that intermittent use of the Bird respirator was useful in the convalescent phase, when pulmonary atelectasis was present. Dialysis with the artificial kidney provides a means of directly eliminating the barbiturate. This, again, is not without danger and another disadvantage is the time required—usually at least two or three hours is required to get dialysis under way. The use of dialysis was considered in two of our more severe cases but preparations were abandoned when it became evident that adequate respiratory exchange was being maintained.

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