Drug Therapy

KETAMINE

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Children are by nature apprehensive and do perceive pain as adults do. But young children, do not always or readily complain vocally of discomfort. When chronic discomfort is punctuated by acute distress of diagnostic or therapeutic intrusions, relief may be obtained for some children by various analgesic-anesthetic agents. Although the ideal 'intravenous' analgesic-anesthetic agent is yet to be developed, clinical evaluation of ketamine has provided very encouraging results. Ketamine-a phencyclidine derivative has been employed as an anesthetic agent since 1965.

In this review we will discuss the basic pharmacology of ketamine and evaluate current clinical applications of this unique sedative, analgesic and anesthetic agent in children.

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Basic Pharmacology

Ketamine produces a so-called 'dissociative' anesthetic state which has been described as a functional and elcctrophysiological dissociation between thalamoneocortical and limbic system(l). The unique clinical anesthetic state produced by ketamine has been characterized as a state of catalepsy in which eyes remain open with a slow nystagmic gaze while corneal and light reflexes remain intact. Studies(2) have demonstrated excitatory activity in both thalamus and limbic systems without clinical evidence of seizure activity following administration of ketamine. Thus, ketamine would be an unlikely agent to produce generalized convulsions in patients with seizure disorder and in fact recent experimental data suggests that ketamine has anticonvulsant properties(3). Analgesic effect of ketamine is due to selective depression of medial thalamic nuelei and is seen even following subanesthetic doses of ketamine(4). The psychic sensations reported during emergence from ketamine anesthesia have been characterized as alteration in mood and body image, dissociative or extracorporeal (out of body) experience, floating sensations, weird dreams or illusions and occasionally frank delirium(5). These psychic emergence reactions occur secondary to ketamine induced depression of auditory and visual relay nuclei, leading to misperception and/or misinterpretation of auditory and visual stimuli(6). A variety of premedications have been evaluated in

attempts to prevent untoward emergence reactions following ketamine anesthesia. Diazepam (0.15-0.3 mg/kg IV) has been reported to significantly decrease the incidence of dreams and eliminate postoperative illusions when administered prior to induction with ketamine(7).

The cardiovascular effects of ketamine seen in humans are produced as a result of sympathomimetic actions primarily by direct stimulation of CNS structures(8). It produces a dose related increase in arterial blood pressure and heart rate. On the other hand in the absence of autonomic control ketamine, has direct myocardial depressant properties(9). Critically ill-patients occasionally respond to ketamine with an unexpected drop in blood pressure which may result from the inability of the sympathomimetic actions of ketamine to counterbalance its direct myocardial depressant and vasodilator effects(10). Because of its ability to prolong the relative refractory period, it may abolish epinephrine induced cardiac arrhythmias(11).

Ketamine produces an increase in cerebrospinal fluid (CSF) pressure which appears related to an increase in cerebral blood flow secondary to cerebral vasodilatation and a rise in systemic blood pressure(12). Hence, ketamine should be avoided in patients with abnormal CSF flow dynamic or other intracranial pathology.

Ketamine does not produce significant respiratory depression except in those situations when it is given as a rapid IV infusion. Salivary and tracheobronchial mucus gland secretions are increased by ketamine, necessitating prophylactic administration of an antisialogogue(13).

Biodisposition/Pharmacokinetics

Ketamine is metabolized extensively by hepatic drug metabolizing enzyme systems and although some biotransformation pathways are well established, others remain postulated. Peak plasma levels are achieved within one minute following intravenous administration of ketamine to animals and within five minutes following intramuscular injection(14). Ketamine acts rapidly on central nervous system after an intravenous dose of 2 mg/kg, consciousness returns between 10 and 15 minutes but full recovery may be more protracted. Tissue distribution and redistribution may play a major role in recovery of consciousness but undoubtedly metabolism by the liver is important for clearance of ketamine, since less than 5% of drug can be recovered from the urine in unchanged form(15).

Clinical Application

Ketamine has been used both for anesthesia as well as analgesia. When ketamine is used in critically ill patients it has been reported to provide good surgical anesthesia with a greater margin of safety and low incidence of side effects than conventional anesthesia(ll). Ketamine has been regarded advantageous for patients in hypovolemic shock secondary to acute hemorrhage because of very little effect on blood pressure or heart rate(16). Interesting case reports regarding the successful use of ketamine to treat severe bronchospasm refractory to conventional bronchodilators have appeared. Ketamine produced an increase in pulmonary compliance and a reduction in airway resistance(17). Because of salutary effect on airway resistance, ketamine may be the agent of choice for rapid induction of anesthesia in patients with reactive airway disease. Despite stimulation of secretions of salivary and tracheobronchial mucus glands, ketamine

has been used successfully for bronchoscopy in children without complication.

Low dose ketamine has been used successfully for brief pediatric oral surgery procedures lasting for 5 to 30 minutes, utilizing doses of 1-3 mg/kg IM and 0.5-1 mg/kg IV. Intramuscular ketamine, 5-10 mg/kg, has proved useful for diagnostic and minor surgical procedures which may not require intravenous cannulae or endotracheal intubation(18). Ketamine is widely used in children undergoing repeated anesthesias, including its use in radiotherapy. In children undergoing minor otolaryngological procedures, ketamine compared favorably with thiopental and althesin. The use of ketamine for ocular examinations under anesthesia is widely accepted inspite of occasional problems during the recovery phase. Although early clinical reports suggested that there was an increase in intraocular pressure with ketamine, more recent studies(19) have found this not to be the case. Finally, rectal ketamine 8 to 10 mg/kg; has been used successfully as an induction agent in pediatric anesthesia(20).

We have been using ketamine to do outdoor procedure like, endoscopy, bronchoscopy, bone marrow biopsy, and to achieve cooperation during various radiological procedures like CT-scan. The current clinical uses of ketamine as well as the contraindications to its use are summarized in *Table I.*

TABLE I—*Clinical Uses of Ketamine and Contraindications of its Use*

I. Indication for ketamine analgesia or anesthesia

- A. Poor risk patients
  1. Shock or cardiovascular instability
  2. Severe dehydration
  3. Respiratory failure or bronchospasm
  4. Severe anemia
  5. Cardiac tamponade or constrictive pericarditis
- B. Outpatient anesthesia
  1. Brief diagnostic and therapeutic procedures *(e.g.,* endoscopy, oral surgery, head and neck surgery, bone marrow biopsy, liver biopsy, ophthalmology, radiotherapy)
  2. Induction of anesthesia (e.g., intramuscular or rectal route)

II. Contraindications to the use of ketamine

- A. Cardiovascular disease
  1. Right or left heart failure
  2. Intracranial, thoracic, or abdominal aneurysms
- B. Central nervous system disorders
  1. Cerebral trauma
  2. Intracerebral mass or hemorrhage
- C. Open globe injury to eye or increased intraocular pressure*
- D. Otolaryngologic procedures involving pharynx, larynx and trachea*

* Indicates a relative contraindication to use of ketamine.

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