ORIGINAL ARTICLE

Opioids and Down's syndrome

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ABSTRACT

Opioids are used in clinical practice for sedation, anesthesia, and analgesia. Their effects depend on their pharmacokinetic and pharmacodynamic characteristics. The liver is the major site for the biotransformation of most opioids. The major metabolic pathway is oxidation. Metabolism influences distribution, clearance, onset, and offset of opioid drugs. Action also depends on the coupling of opioids with the class of receptors involved and on localization of specific receptors. Three major types of opioid receptors, designated as μ, δ, and κ, present in the central nervous system, are coupled to G proteins and inhibit adenylyl cyclase. Down's syndrome is a congenital condition characterized by mental retardation and particular physical features. Neurotransmission alterations are important. Alteration in the concentration of opioids in the cortex of these patients has been demonstrated. Neurobiological abnormalities and, in some, abnormalities in the neurotransmission systems, anxiety, and, in particular, nociception all suggest that structural and functional alterations of opioid receptors may be present. A clear knowledge of these multiple abnormalities is essential for skillful management of the perioperative period and for a good outcome for patients with Down's syndrome.

Key words: opioids, Down's syndrome, neurotransmission alterations, neurobiological abnormalities

INTRODUCTION

In the operating room and in intensive care, the anesthetist must provide unconsciousness, analgesia, and muscular relaxation.[1] Opioids have a predominant action regarding one of the components of anesthesia, analgesia. However, each agent, when used in combination, not only produces its own expected effect but can also modify the effect of another agent acting on a different component.[2] Their metabolism is closely related to their chemical structure. Opioids are subject to O-dealkylation, N-dealkylation, ketoreduction, or deacetylation leading to phase I metabolites. Phase II metabolites are formed by means of glucuronidation or sulfonation. Some metabolites of opioids have an activity themselves and contribute to the effects of the parent compound.[3]

Endogenous opioid peptides and opiates, like morphine, produce pharmacological effects through the membrane-bound opioid receptors.[4] Each class μ, δ, κ, and ε of opioid receptors has a characteristic distribution pattern in the nervous system, which may, however, exhibit differences in unlike species. The effects of opioid receptor stimulation depend on the class of receptors involved and on their localization.[5]

The development of selective receptor ligands and the recent cloning of each receptor have greatly contributed to our increasing knowledge of the neuropharmacological profile of each type of opioid receptor.[6]

All types of opioid receptors are coupled to G proteins, because agonist binding is diminished by guanine nucleotides and because agonist-stimulated GTPase activity has been identified in several preparations.[7] The consequences of activation of any of the opioid receptors in a given cell type depend more on the profile of the G proteins and effectors expressed than on the type of opioid receptor present in the cell.[8]

The use of opioids has long been accepted as the standard care in patients with cancer and acute pain. While the development of tolerance and physical dependence are known effects of opioids in cancer and noncancer pain populations, these patients cannot be regarded as addicted. However, long-term therapy with short-acting opioids predisposes to tolerance and addiction.[9]

CLINICAL USE OF OPIOIDS

Sedation and analgesia in intensive care unit

Sedation and analgesia are relevant aspects for the adequate treatment of patients in an intensive care unit (ICU). Recent drug developments and new strategies for ventilation provide improved sedation management, allowing better adaptation to the clinical background and individual needs of the patient.[10]

Opioids are used in the ICU for sedation and analgesia.

The main indications for opioid analgesia and sedation in the ICU include anxiety, pain, and agitation; immediate postoperative period after major surgery; short-term invasive procedures; cardiac protection; and neuroprotection.[11] The cytoprotective effects of opioids have recently been recognized. A new form of cytoprotection has been identified, where it has been observed that prior exposure to opioids provides protection against cell ischemia (opioid preconditioning). In the heart, this opioid preconditioning-induced protection has been well documented by multiple studies and may be mediated by δ receptors, G(i/o) proteins, protein kinase C, ATP-sensitive potassium channels, and free radicals. A study suggests that opioid preconditioning also induces neuroprotection that involves δ1 receptors, mitochondrial ATP-sensitive potassium channels, and free radical production.[12]

Opioids such as morphine, fentanyl, and remifentanil are considered first-line agents for treating pain. All of these agents are equally effective at equipotent doses, and the choice of agent depends on both drug and patient characteristics. Sedatives with amnesic properties are desirable to prevent or relieve anxiety and agitation.[13]

Use of opioids in anesthesia

Multiple drugs are used to provide anesthesia. Volatile anesthetics are commonly combined with opioids. Several studies have demonstrated that small doses of opioids (i.e., within the analgesic range) result in a marked reduction in minimum alveolar concentration (MAC) of the volatile anaesthetic, which will prevent purposeful movement in 50 percent of patients at skin incision.[14]

Alfentanil, fentanyl, and sufentanil are synthetic opioid analgesics acting on specific opioid receptors. These opioids are widely used as analgesics to supplement general anesthesia for various surgical procedures or as primary anesthetic agents in very high doses during cardiac surgery. Opioid analgesics are mainly administered intravenously. However, other techniques of administration, including epidural, intrathecal, transdermal, and intranasal applications have been demonstrated.[15]

The MAC reduction of isoflurane by remifentanil is similar to that produced by other opioids. Although remifentanil is given at extremely high concentrations in the absence of isoflurane, it does not provide adequate anesthesia. A 50 percent isoflurane MAC reduction is produced by 1.37 ng/ml remifentanil, as opposed to previously published plasma concentrations of fentanyl of 1.67 ng/ml or sufentanil of 0.14 ng/ml.[16]

The definition of TIVA is a combination of hypnotic agents, analgesic drugs, and muscle relaxants, excluding simultaneous administration of any inhaled drugs. Midazolam, ketamine, and propofol are used as hypnotic agents, and fentanyl, alfentanil, sufentanyl, or remifentanil is administered for analgesia during surgery. Based on pharmacokinetic studies, continuous intravenous administration of these agents is strongly recommended, and infusion pumps with or without computers may be used for this purpose.[17]

Use of opioids in pain management

Opioids are the oldest and most effective agents for the short- and long-term control of severe pain, particularly chronic cancer pain palliation.[18] A number of opioids are available for clinical use, including morphine, hydromorphone, levorphanol, oxymorphone, methadone, meperidine, oxycodone, and fentanyl, and their advantages and disadvantages for the management of pain have been, and are currently being, discussed. An understanding of the pharmacokinetic properties, as well as issues related to opioid rotation, tolerance, dependence, and addiction, are essential aspects of the clinical pharmacology of opioids for pain.[19]

Opioids are widely used as effective analgesic therapy for cancer pain. Despite years of controversy, their use has also been accepted in chronic noncancer pain. Compared with morphine, oxycodone has a higher oral bioavailability and is about twice as potent. Pharmacokinetic-pharmacodynamic data support oxycodone as a pharmacologically active opioid that does not require conversion to oxymorphone for pharmacological activity.[20] Hydromorphone can be a safe analgesic alternative for long-term intrathecal management of nonmalignant pain among patients where morphine fails because of pharmacological side effects or inadequate pain relief.[21]

As more extensive and painful surgical procedures (e.g., laparoscopic cholecystectomy, laminectomy, knee and shoulder reconstruction, hysterectomy) are being performed on an outpatient basis, the availability of sophisticated postoperative analgesic regimens is necessary to optimize the benefits of day surgery for both the patient and the healthcare provider. However, outcome studies are needed to evaluate the effects of these newer therapeutic approaches with respect to postoperative side effects, cost, and important recovery variables.[22]

The consequences of acute pain include clinical, economical, and patient-reported outcomes; therefore, advance in the treatment of postoperative pain has the potential of improving healthcare from a broad perspective. Opioids remain the cornerstone of treatment of postoperative pain. Multimodal analgesia also has the potential of improving the pharmacotherapy of postoperative pain.[23]

Anesthesiologists must therefore take preventive measures, as well as apply techniques during and after surgery, to diminish the intensity of pain and the incidence of nausea or vomiting.[24]

OPIOIDS AND DOWN'S SYNDROME

Down's syndrome (DS) is the most common genetic birth defect associated with mental retardation. The underlying mechanism of the neuropathology of DS is not completely understood. Different hypotheses have been advanced to explain this mystery, including the gene dosage effect, amplified developmental instability, and the molecular misreading concept.[25] Two different hypotheses have been speculated to better understand the disease. One maintains that increased gene dosage contributes to phenotypic abnormalities; the other correlates genetic imbalance with DS pathogenesis.[26]

Neurophysiological and functional information are needed to understand the mechanisms of mental retardation in DS. The trisomy-16 murine models provide windows into the molecular and developmental effects associated with abnormal chromosome numbers. The distal segment of murine chromosome-16 is homologous to nearly the entire long arm of human chromosome 21.[27] Trisomic mice present an overall depressed responsiveness to nociceptive stimulation.[28]

The most recent pain and anxiety control techniques employed in patients with DS are described in relation to how cooperative the patient is and what assessment is made of his or her general condition.[29] Pain assessment in people with intellectual disabilities is a frequent and difficult problem, especially for nurses working with people with intellectual disabilities on a daily basis. Nurses have used a wide range of indicators to assess pain in these patients. Functional abilities and the level of disability seem to influence the indicators used.[30]

The initial treatment of pain should include agents such as acetaminophen, nonacetylated salicylates, celecoxib, or tramadol. If pain is not relieved, opioid analgesics should be considered. However, doses should be initiated at the lowest effective dosage and gradually increased, depending on response. Frequent monitoring for adverse outcomes should also be performed. If a daily opioid is needed, routine assessment of bowel function and use of a bowel regimen are recommended to prevent constipation.[31]

A 17-year-old boy with DS, weighing 48 kg, was scheduled to undergo laparotomy for duodenal obstruction and gastrostomy tube insertion. Combined general and continuous epidural anesthesia was selected as anesthetic. The patient awoke without distress and was discharged from the ward with subsequent good pain control from a continuous epidural infusion of bupivacaine 0.1 percent with 1 mcg/ml fentanyl at 4 to 6 ml/hr.[32]

A nine-year-old boy with DS was admitted to the pediatric ICU for treatment of septic shock and respiratory failure. Sedation was provided by continuous infusion of fentanyl and midazolam starting at 2 mcg/kg/hr and 0.05 mg/kg/hr, respectively. The doses were gradually increased up to a dosage of fentanyl at 4 mcg/kg/hr and of midazolam at 0.2 mg/kg/hr by the end of day four. The patient was enrolled in a study involving the correlation of the BIS with ICU sedation scale to demonstrate the development of tolerance to sedative drugs during sedation in the pediatric ICU. During the following five days, a two-fold increase in the dose of midazolam and a three-fold increase in the dose of fentanyl were required to maintain the same BIS value and desired level of sedation.[33]

Patients with DS are afflicted by multiple congenital anomalies, which affect almost all of their organ systems. Skillful management during the perioperative period is essential for a good outcome for patients with multiple congenital abnormalities in the cardiopulmonary and musculoskeletal systems.[34] A ketamine, midazolam, and vecuronium infusion was used for total intravenous anesthesia in a patient with DS with a ventricular septal defect and pulmonary hypertension. This simple technique, and ventilation with 100 percent oxygen, maintained tissue oxygenation and cardiovascular stability.[35]

There is a widespread clinical impression that it is difficult to achieve adequate sedation and that, following cardiac surgery, these patients require higher doses of morphine and additional sedative agents compared to patients without DS. It is in accordance with the report that DS patients are also more likely to receive additional sedatives and skeletal muscle relaxants.[36]

A seven-year-old Saudi boy with trisomy-21 was admitted to the hospital for dental surgery under general anesthesia. This was his first general anesthetic; there was no history of environmental allergies, respiratory tract diseases, or congenital heart malformation or any recent fever, cough, or sore throat. After connection of the monitors and before preoxygenation, a 50 mcg IV bolus of fentanyl (2 mcg/kg) was injected. Within 30 seconds, he began to cough explosively and struggled to a sitting position; the cough was unproductive and persisted in spasmodic bursts for a further two to three minutes until anesthesia was induced with propofol (60 mg) and atracurium (15 mg IV). After tracheal intubation and before surgery, numerous conjunctival and periorbital petechiae were noticed but had begun to fade by the end of the first postoperative day.[37]

Several recent reports have indicated that opioid blockers are effective in attenuating self-injurious behavior (SIB). In a study, four patients with SIB were challenged with four fixed doses (0, 25, 50, 100 mg) of naltrexone. The results suggest that endogenous opioids are implicated in SIB and that naltrexone is a powerful tool for examination of this treatment-resistant behavior.[38] Also, the data from another study on the effect of naltrexone on the frequency of SIB suggest that disturbances of the endogenous opioid systems may be involved in the pathophysiology of SIB of certain patients.[39]

An autistic eight-year-old boy with DS and unspecified

mental retardation was treated for SIB with naltrexone, which is a long-acting opioid antagonist. This treatment is based on the hypothesis that abnormal opioid systems mediate such behavior. The dose used on this patient was far above the consensus dose of 0.5 mg/kg to 2 mg/kg. After two weeks, the frequency of SIB had decreased.[40]

Endogenous opioids in the frontal cortex of adult patients with DS have been investigated, post mortem, in a study. The results of this study show that there is an increase in the levels of leu-enkephalin and dynorphin-A in the frontal cortex of patients with DS compared to the control group.[41]

Other alterations that involve neurotransmission in subjects with DS include the cholinergic system, which presents an important decrease; the GABA system; the noradrenergic system; and glutamate transmission. Moreover, another aspect that should be noted in the use of opioids in patients with DS is the special drug metabolism of this syndrome. Alterations in hepatic and kidney functions modify the pharmacokinetics and pharmacodynamics of drugs.

The "Down's syndrome critical region" (DSCR) is a chromosome 21 segment purported to contain genes responsible for many features of DS.[42] Neither the pathogenesis nor the etiology of DS is clearly understood. Numerous studies have examined whether clinical features of DS are a consequence of specific chromosome 21 segments being triplicated.[43]

Although numerous biochemical abnormalities accompanying the syndrome have not yet been completely clarified, the antioxidant defense system enzymes have been shown to be altered due to increased gene dosage on chromosome 21 and overproduction of superoxide dismutase (SOD-1 or Cu/Zn SOD).[44] It has been emphasized that increased oxidative damage may be present in DS and that SOD-1 seems to play a role in the pathogenesis of this disorder.[45] This is an example of a consequence of genetic anomalies in DS.

The human liver-type subunit of the key glycolytic enzyme, phosphofructokinase (PFKL), is encoded by a gene residing on chromosome 21. This chromosome, when triplicated, causes the phenotypic expression of DS (trisomy 21). Increased PFKL activity, a result of gene dosage, is commonly found in erythrocytes and fibroblasts from DS patients.[46]

Transient myeloproliferative disorder (TMD), an acute leukemia-like disorder in neonates with DS, is characterized by spontaneous regression of abnormal blast growth.[47] Knowing the cellular mechanism of hepatic fibrosis and its modulation by growth factors (e.g., platelet-derived growth factor), a pathogenetic link between TMD and the development of liver fibrosis in DS neonates seems probable. An association of this triad of findings no longer appears to be accidental.[48]

A range of renal diseases has been previously described in patients with DS. With increased survival, it appears that a growing number of these patients present with chronic renal failure. Definition of underlying causes of renal failure could potentially lead to prevention of progressive renal dysfunction in this population.[49] A variety of urological abnormalities and glomerulopathies have been reported in this population, and some DS patients develop chronic renal failure. Renal disease in patients with DS is not as rare as previously thought, although the majority of findings are of minor relevance. According to the variety of pathologies, and in order to detect early irreversible renal injury, it seems quite reasonable to perform regular monitoring of renal function in these patients.[50]

Sleep apnea syndrome occurs when, during sleep, breathing stops for 10 seconds or longer, with an index of five times an hour or more. It is clinically characterized by loud snoring at night, either continuous or interrupted by pauses, followed by loud breathing. Sleep is fitful, broken by arousals, and yields little rest.[51] This syndrome has many implications for the anesthetist because patients are exquisitely sensitive to all central depressant drugs, with upper airway obstruction or respiratory arrest occurring even with minimal doses, and because patients with sleep apnea syndrome have a potentially difficult airway to manage. Perioperative risks that patients with sleep apnea syndrome face emphasize the importance of detection and perioperative evaluation and planning.[52] Steroids may be used to decrease the amount of airway swelling. Supplemental oxygen should be used in patients who demonstrate desaturation. Opioids and sedatives should be avoided, as should other drugs that have central and sedating effects. Postoperative pain is effectively controlled with acetaminophen and topical anesthetic sprays. Postoperative monitoring for apnea, desaturation, and arrhythmias is a necessity in sleep apnea patients.[53] Obstructive sleep apnea has been reported in 20 percent to 50 percent of children with DS.[54] The causes, severity, and presentation of upper airway obstruction in children with DS are related to the age of the child and to associated comorbidities. The treatment of comorbidities and secondary ear, nose, and throat disorders is an integral component of the surgical management of upper airway obstruction in such cases.[55]

While the prevalence of obstructive sleep apnea syndrome among children with DS is reported to vary from 30 percent to 50 percent, the nocturnal respiratory pattern of adults with DS is not well known. According to the literature, and in conjunction with the current study's results, it could be hypothesized that the nocturnal respiratory pattern of adults with DS depends on several pathogenetic factors such as age, severity of upper airway abnormalities, body mass index, other pathological conditions, and age-related brainstem dysfunction.[56] The

sleep apnea syndrome in DS patients must be evaluated when using opioids in order to avoid respiratory arrest.

CONCLUSION

DS is a condition characterized by mental retardation and associated with multiple congenital anomalies. Neurotransmission abnormalities involve opioid receptors and pain transmission, with repercussions on pharmacodynamic and clinical aspects. Therefore, in these patients, a clear knowledge of the structure and function of opioid receptors is vital for the use of these drugs in performing safe and adequate procedures.

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