Dexmedetomidine, Application in Pediatrics: Paper Review

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ABSTRACT

Introduction: Dexmedetomidine is a drug with sedative, hypnotic, and analgesic properties. Its use in adult sedation was approved in 1999. In children, although the use has not been approved, its application by paediatricians is common. The drug offers many advantages in sedative procedures of paediatric patients. First, the half-life is relatively short. Second, it has little or no effect on respiratory management, and lastly, it is well tolerated by intensive care unit patients found with mechanical ventilation. Pharmacokinetics: 93% of the drug bonds with plasma proteins on absorption. Then, it undergoes a rapid phase of distribution with a half-life of 7 min. It has a depuration rate of 15 ml/kg/min, and half-life elimination rate of 2 h. Pharmacodynamics: The drug has antinociceptive action on α-2A adrenergic receptor of the spinal cord. It has hypnotic-sedative action, and inhibitory effect on central noradrenergic transmission. Applications: It is used as a premedication agent with the objective of getting better cooperation of the patient on starting anaesthetic procedures. Adverse reactions: Bradycardia and hypotension. Conclusion: Its use appears to have a promising future in paediatric population; however, it is pertinent that more controlled clinical studies be carried out in order to demonstrate its safety and efficacy.

Key words: Dexmedetomidine, Pharmacokinetic/pharmacodynamic, Paediatric patients, Adverse reaction, Applications.

INTRODUCTION

Anaesthesia refers to concomitant use of various drugs applied to get anaesthetic condition without triggering adverse effects.1 Presently, different anaesthetic drugs and co-adjuvant are used in daily practices. One of these co-adjuvant mostly used is dexametomidine (DX), a drug that possesses useful effects in general anaesthesia,2,4 with sedative properties similar to sleep5,6 and with advantages of fast recovery after use as well as its analgesic utility in the management of post-operative pain in patients subjected to long time procedures.7

DOI: 10.5530/ijper.50.2.31

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From several studies done in animals and in clinically controlled essays with volunteers and patients, it was possible to know the principal pharmacokinetic and pharmacodynamic data of dexmedetomidine and most importantly, the knowledge that the drug has sedative, hypnotic, and analgesic properties as well as the demonstration of its ability to reduce the requirement of other sedatives like propofol or midazolam, and analgesics like morphine with few discrete effects on the ventilation of the patients.8

The use of dexmedetomidine for sedation in adults was approved in 1999 by Food and Drug Administration (FDA) for intubated patients in intensive care unit (ICU) and in 2008 for non-intensive therapy patients; however, even when the use of DX has not been approved in children, it is being used in this population.9

Based on its efficacy in adults, (DX) is an alternative which could be combined with benzodiazepines and opioids in intensive therapy of paediatric patients. In 2010, its use in radiology, intervention medicine, endoscopy, surgery of the backbone, and instrumentation of airways was documented in paediatrics. It has advantages in sedative procedures in paediatric patients due to its relatively short half-life and few effects on respiratory management as well as being well tolerated in patients of intensive care with mechanical ventilation.10-13

Pharmacokinetic in adults

The metabolism of (DX) is principally in the liver by the action of Cytochrome P450 via CYP2A6, for aliphatic hydroxylation (3-hydroxy-dexmedetomidine and 3-carboxy-dexmedetomidine, inactive metabolites), N-methylated reactions, direct glucuronidation and nitrogenation (3-hydroxy-N-methil-dexmedetomidine and dexmedetomidine-N-methil-O-gluconide, are active metabolites without pharmacological activities).

After the (IV) administration in adults, (DX) undergoes through a fast distribution phase, with an average distribution life of approximately 6 min, presenting a linear kinetic in the recommended dose of 0.2–7 mcg/kg/h. The binding to plasma proteins is 94% (α1-acid glycoprotein). The distribution volume of the drug is 2-3 lt/K, depuration of 391/h, and the half-life elimination is 2-3 h. Patients with severe hepatic failure show a significant increase in distribution and in patients with renal insufficiency, the pharmacokinetics of the drug were similar to those found in healthy volunteers.14-16

Pharmacokinetic in children

In healthy children, dexmedetomidine bonds in 93% with plasmatic proteins and undergoes a fast redistribution phase with a half-life of 7 min, depuration of 15 ml/kg/min, and half-life elimination of 2 h. The bioavailability in oro-gastric administration is 16%; intranasal, 65%; orally, 82%; and IM, 104%.9

In different studies carried out starting in children, it was mentioned that the pharmacokinetic parameters are similar to that of adults. Although, in other studies, it was observed that there were differences in the pharmacokinetic in children in different ages, above all, in the distribution volume in inactive state with this being higher in older children than in younger ones.10,17-19

Pharmacodynamic

Action on nervous system

Dexmedetomidine is a drug that could have excitatory and inhibitory effects by itself with activation of different second messengers. This implies the stimulation of Guadinidine nucleotide protein bonders (Gi protein) which inhibits adenylcyclase causes low levels of AMPc that mediates the cellular effects and thereby leads to the activation of adrenergic receptors by disturbance in the activity of protein-kinase, the level of proteinic phosphorylation, and inhibition of voltage sensible of calcium channels. The reduced sympathicotone in the ceruleus locus stimulates the activation of GABAergic system (potentiating effect) and in the spine, reduces P substance release (analgesia and hypnotic-sedantac-tions).8,13,20

Its adrenergic action, alpha 2 agonist, blocks the afferent activity of A and C fibers associated with somatosympathic reflexes and spontaneous somatic flow and in this way offers protection against stress. It reduces preganglionicary cholynergic sympathic tone and regulates the reduction of other excitatory neurotransmitters as well as the secretion of noradrenaline and metabolic consumption of cerebral oxygen together with histamine liberation. Moreover, it activates the receptors in medular vasomotor center by reducing the norepinefrine with sympaticolytic effect which leads to the reduction of cardiac frequency and arterial pressure.21-24

It also makes that the decrease, not only in noradrenergic neurotransmission but also in serotoninergic, becomes associated with the transition from the awake state to sleepy state with production of hypnosis similar to slow sleep, and additive analgesia with an important neurovegetative blockade, a sedation which it produces at the level of (SN), described as cooperative, and used for wake-up agitation management in children without negatively prolonging or affecting in the recovery of anaesthesia with perfect conservation of immunological and cognitive functions.8,21-23
The administration of (DX) in combination with other anaesthetics and sedatives produces pharmacodynamic interaction which improves the sedation of the patient.8,10

**Action on cardiovascular system**

The cardiovascular actions of dexmedetomidine are due to the stimulation of α-2 adrenergic receptors at medulla, cerebral, and peripheral levels. On stimulating α-2 postsynaptic receptors at peripheral vascular level, an initial increase of arterial blood pressure is seen followed by hypotension, an event which is due to the action on peripheral vascular level, also mediates effects as antiarrhythmia for its sympatholytic effects.8,21,23

**Action on respiratory tract**

In respiratory function, dexmedetomidine has demonstrated having a favourable profile in terms of its effect on ventilation. Various studies have shown lack of detectable significant changes in respiratory parameters as well as in oxygen saturation after its administration.26

**Action on Endocrine system**

After (DX) administration, it was observed to have attenuating effect on stress response in a dose-dependent form in situations of intense stimulus such as laryngoscopy or surgery producing a minor increase of noradrenaline, adrenaline, and their metabolites as well as cortisol and beta endorphin.27

**Other effects of dexmedetomidine**

- Intestinal actions: The reduction in salivary flow is produced by the direct effect of α-2 agonists on α-2 adrenergic receptors of saliva glands and by inhibition of acetylcholine release. α-2 agonists reduce gastric secretions through the activation of presynaptic α-2 adrenoceptors of gastric parietal cells and by vagal inhibition.28

**Applications of dexmedetomidine in pediatrics**

Dexmedetomidine has been used, alone or combined with other drugs, as a premedication agent in paediatric anaesthesia in different scenarios with the fundamental objective of obtaining adequate cooperation from the patient at the time of starting anaesthetic procedure. Premedication. Children that would be subjected to any procedure, be it surgery or diagnosis, always have anxiety, fear, and distress of their separation from their parents. Moreover, it is possible not to have permeable endovenous via in this stage, and for this reason, a series of drugs like DX have to be administered in order to obtain the benefit derivable from the same drug on anaesthetic induction (reduction in induction time) and sedation.

Transanaesthetic. In this phase, it should be emphasized that the use of dexmedetomidine should be aimed at achieving one or various effects that could represent a benefit for every patient depending on his or her present state and the type of surgery as well as the chosen anaesthetic technique.

Image diagnostic procedure. Recently, dexmedetomidine was proof-tested in sedation process in paediatric patients subjected to image diagnostic procedures with the good sedative outcome demonstrated in computerized tomography (CT) and nuclear magnetic resonance (NMR) procedures.29,30 This drug reduces brain blood flow in children and adults which favours the decrease of cerebral oxygen consumption thereby benefitting children with brain damage. It presents a decrease in anaesthetic recovery time.31

Intensive Care Unit. Based on its efficacy in adults, dexmedetomidine is presently being studied as an alternative or complement to benzodiazepines and opioids in paediatric population in intensive care units. The efficacy and safety of dexmedetomidine in lactants and children were evaluated in several studies with the result that the use of DX reduces the dose of other sedative agents which is a benefit to children with neurological damage. These publications also suggest that DX offers a good opportunity for sedation in children that receiving ventilatory support in intensive care units that require sedative procedures.32 When compared with midazolam, it was reported that DX provides a better sedation, shows that minor dose of morphine is needed, and decreases the requirements of the morphine as well as producing at decrement in the number of evaluation points in the Ramsay scale.10,19,33

**Adverse reactions**

**Cardiovascular**

The most frequently presented adverse reactions with the use of DX are hypotension and bradycardia which is as a result of its sympathetic activity. It produce dose-dependent systolic pressure fall with hypotension whose severity directly varies with the dose applied. This effect begins with a small initial response of peripheral vasoconstriction that leads to transitory systemic hypertension and a fall in cardiac frequency.17,18 The hypertension as well as bradycardia have been reported in various paediatrics studies, although these rarely produce important clinical changes that could require corrective intervention.6,34

In a retrospective study of 747 children where the efficacy and safety in prolonged infusion therapies were evaluated, an adequate sedation in 97% of the patients...
was reached with a 16% incidence of bradycardia and without finding differences with the patients that received pentobarbital.\textsuperscript{36}

Prolonged dose of DX (2-3 \text{ug/kg/h}) followed by continuous infusion of 2 \text{ug/kg/h} produce 16% of bradycardia incidence with frequencies of less than 30 pulses per min. This is more frequent in young infants than in older children. Also, bradycardia has been reported in children after undergoing a moderate hypothermia and who were in sedation with DX.\textsuperscript{36,37}

**Respiratory**

In general, dexmedetomidine has a favourable profile in terms of its effect on ventilation. With dose higher than 2 \text{ug/kg}, a mild respiratory depression is produced and its effect on oxygen saturation and respiratory frequency are similar to that caused by diclofenac.\textsuperscript{8,38}

**Neurological**

The appearance of neurological symptoms such as agitation, abnormal speech, and irritability as well as tachycardia has also been reported when the prolonged infusion of DX is suddenly suspended. For this reason, it is suggested to monitor the patient between 12 and 24 h after retiring the infusion.\textsuperscript{39}

**Endocrine-metabolics**

It has been demonstrated that DX presents a biphasic effect on oxygen consumption with an initial rise of up to 16% followed by a pronounced fall. These endocrine-metabolic effects are principally related to the inhibition of sympathetic flow and to the decrease in circulating plasmatic chetocolamine levels. In healthy volunteers, a dose-dependent fall of up to 92% in plasmatic noradrenaline concentration has been demonstrated. It attenuates stress response from strong stimuli like orotracheal intubation or surgery by producing a minor increase of noradrenaline, adrenaline, their metabolites, cortisol, and beta endorphine. It also produces an increase in the levels of dose-dependent glycemia.\textsuperscript{8}

**Other effects**

Other effects include nausea, auricular febrile, anaemia, pulmonary edema, fall in intraocular pressure, diuretic action, oliguria and natriuretic. Moreover, it decreases brain blood flow, inhibits gastric emptying and gastrointestinal movement, mouth dryness, and thirst.\textsuperscript{8}

**DISCUSSION**

Dexmedetomidine is a sedative drug useful in intensive care units, diagnostic procedures, and paediatric therapies. It produces sedation very similar to real natural sleep and presents a favourable action on respiratory apparatus but adverse cardiovascular effects like hypotension and bradycardia.\textsuperscript{40}

Presently, it is approved by FDA for use as sedative in adults but yet to be approved for use in paediatric patients.

Few studies have been carried out to evaluate its safety in paediatrics. The majority of the publications are reports of series of sedation cases in children with respiratory support as well as the characterization of its pharmacokinetic and pharmacodynamic in this population which is still deficient.\textsuperscript{19,32,40}

It has been demonstrated that DX could provide a viable and efficient method of sedation in children subjected to diagnostic studies. Effects on the basal respiration were not found since there was no alteration on respiratory frequency and the values of expired CO\textsubscript{2}.

The decrease in cardiac frequency and arterial pressure are clinically acceptable for paediatric population. However, a close monitoring of circulatory dynamic and an appropriate evaluation of paediatric patient on administration of DX is recommended. Also, more studies on the pharmacokinetic and pharmacodynamic in different paediatric ages should be conducted in order to guarantee results, and investigate the adverse effects after a long term infusion as well as a study on special populations like premature babies.\textsuperscript{40}

**CONCLUSION**

In this review work, we found that DX is a good option to be used by anaesthesiologist in various scenarios to improve the quality of attention of patients in preanesthetic, transanesthetic, and in radio diagnostic, non-invasive, invasive, therapeutic, as well as in surgical procedures, including patients in critical state due to its sedative actions similar to real sleep. It has few effects on respiratory apparatus and reduces the requirement of other drugs. Moreover, it could function as a co-adjuvant of analgesics. The hemodynamic effects presented do not require pharmacological treatment and the drug is well tolerated.

Unfortunately however, there are few studies on the use of DX in paediatric patients, a use which has not been approved by FDA. Nevertheless, the use seems to have a promising future in paediatric population, but it is necessary to carry out controlled clinical assays to demonstrate its safety and efficacy so as to be authorized in this population.
ACKNOWLEDGEMENT

Thank the doctor Natalia Barradas for his support.

CONFLICTS OF INTEREST

No conflict of interest.

REFERENCES

**SUMMARY**

- Dexmedetomidine is a drug with sedative, hypnotic, and analgesic properties.
- Its use in adult sedation was approved in 1999.
- In children, although the use has not been approved, its application by paediatricians is common.
- The drug offers many advantages in sedative procedures of paediatric patients.
- The half-life is relatively short.
- It has little or no effect on respiratory management, and lastly, it is well tolerated by intensive care unit patients found with mechanical ventilation.

**ABBREVIATIONS USED**

- DX: dexmedetomidine
- FDA: Food and Drug Administration
- ICU: intensive care unit
- IV: intravenous
- SN: nervous system
- CT: computerized tomography
- NMR: nuclear magnetic resonance

**About Authors**

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