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Pediatric Pharmacology, Clinical Applications, and the Safety Profile of Dexmedetomidine

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ABSTRACT:

Dexmedetomidine is an a2-adrenoceptor agonist having sedative, anxiolytic, and analgesic characteristics, and it is one of the most important drugs in the industry. Because it is effective and does not have any negative effects on the respiratory system, it is sometimes used in paediatric patients even though it is not approved for that usage. Adults run the risk of developing severe cardiovascular problems if they use dexmedetomidine. In spite of its widespread use, dexmedetomidine has not been subjected to a significant amount of research to determine whether or not it is safe for children. This article provides a comprehensive assessment of the most recent research (up to the year 2010), with a particular emphasis on the uses and safety of dexmedetomidine when it is given to young patients. What benefits are in store for the reader: In the paediatric critical care unit, as well as during diagnostic and therapeutic operations, dexmedetomidine is a helpful medicine that serves as both a sedative and an anxiolytic. Both low blood pressure and a slow heart rate are undesirable side effects of the drug dexmedetomidine. In addition, hypertension can appear during the "loading dosage" or when the infusion rate is too high. Dexmedetomidine may have detrimental effects on the cardiovascular system, despite the fact that it has a good respiratory profile. It is recommended that careful titration and close monitoring of the circulatory dynamics be performed. Additional research is required to better determine harmful effects during long-term infusions as well as in particular populations such pre-term newborns. These populations will require special attention.

Keywords*:* Adverse Effects, Dexmedetomidine, Indications, Pediatrics, Sedation

INTRODUCTION:

In 1999, the Food and Drug Administration (FDA) of the United States gave its initial approval for the use of dexmedetomidine in adult patients. Off-label use of the medication in paediatrics has become increasingly common as a result of its accessibility as a continuous intravenous (IV) infusion, which has little effects on respiratory function even when administered in sedative and anxiolytic doses [2]. However, injection of dexmedetomidine can result in substantial bradycardia and hypotension [1]. This is despite the fact that its

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adverse effect profile includes only moderate respiratory impairment. This article provides a review of the existing research that discusses the applications of intravenously administered dexmedetomidine as well as its potential side effects in the juvenile population.

The underlying working mechanism

Medetomidine's S-enantiomer, dexmedetomidine, has a higher specificity for the a2-adrenoceptor (a2:a1, 1620:1) than clonidine does (a2:a1, 220:1) [3]. It does this by connecting to a2 receptors in both the central nervous system and the peripheral nervous system.

The binding of a2-adrenoceptors in the locus ceruleus in the pons is what causes dexmedetomidine to have its sedative and anxiolytic effects in a patient. The inhibition of adenyl cyclase that is caused by G-proteins leads to a reduction in the amount of cAMP that is produced. This, in turn, stops the phosphorylation of proteins and changes the conductance of ion channels, which stops the release of norepinephrine. Because of this, the downstream regulation of a sleep-promoting pathway takes place, which involves inhibitory GABA neurotransmitters, resulting in sedation and anxiolysis [6-10].

Although the mechanism of its immunologic effects has not been delineated, adult literature suggests that dexmedetomidine reduces levels of TNF-a, IL-1, and IL-6 at doses up to 2.5 g/kg/h when compared to propofol which is administered in ICU patients [22,23]. This effect occurs at doses higher than those used in children. Both central and peripheral vasodilatation are involved in the anti-shivering effects of dexmedetomidine [24,25]. Centrally, it affects thermoregulation, and peripherally, it relaxes blood vessels.

Some Notes on Pharmacokinetics

In humans, dexmedetomidine has linear pharmacokinetics following intravenous injection within the dose range that is allowed by the FDA. At steady state, the volume of distribution, denoted by Vd, is 1.31 litres per kilogramme [26]. Dexmedetomidine has a protein binding affinity of 94% and undergoes almost full biotransformation to inactive metabolites through the processes of glucoronidation, hydroxylation via CYP2A6, and N-methylation, with an estimated clearance (Cl) of 39 litres per hour [26]. The urine is the primary route of excretion, and the elimination half-life (t1/2b) ranges from less than two and a half hours to more than two and a half hours [26]. The clearance in persons who have severe hepatic failure is reduced to 32% of what it would normally be [27]. In people who had significant renal impairment, there was no change in the clearance that was observed [28].

The pharmacokinetics of dexmedetomidine have only been explored in a small number of children and adolescents. Four pharmacokinetic investigations in which dexmedetomidine was given to children reported values that were comparable to those found in adults. These values were as follows: Vd 1.5 — 2.2 l/kg, Cl 0.56 — 1 l/kg/h, and t1/2b 1.6 — 2.7 hours [29-32]. An allometrically scaled two-compartment model provided the most accurate description of a pooled population pharmacokinetic study of the four studies indicated above

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[33]. The Vd value was 125.3 l/70 kg (1.8 l/kg), and the Cl value was 42.1 l/h/70 kg (0.6 l/kg/h). Clearance in neonates dropped to 18.19 l/h/70 kg after the reduction. This was ascribed to enzyme pathways that were not fully developed. By one year of age, values were getting close to what was reported for adults. In a different study, participants were given a dexmedetomidine loading dose of 0.35, 0.7, or 1 g/kg, which was then followed by a continuous infusion of 0.25, 0.5, or 0.75 g/kg/h [20]. The participants' ages ranged from 0.22 to 1.7 years, and their weights ranged from 5.1 to 11.9 kg. The participants had recently undergone cardiac surgery. Clearance rose with weight, age, and single-ventricle physiology, as demonstrated by an allometrically scaled two-compartment model with the following values: Vd 2.7 l/kg and Cl 40.7 l/h/70 kg.

CLINICAL USES:

When the FDA first approved dexmedetomidine, it was for the purpose of providing sedation to people who were initially intubated and were being mechanically ventilated in an intensive care unit (ICU) by a continuous infusion that did not exceed 24 hours. More recently, the use of dexmedetomidine for the sedation of non-intubated adults prior to and during surgical procedures and other treatments has also been given the green light. A loading dose of 1 g/kg administered over a period of 10 minutes and a continuous infusion of 0.2 — 0.7 g/kg/h are the dosages that are recommended for ICU sedation. For optimal procedural sedation, it is recommended to begin with a loading dose of 0.5 to 1 microgram per kilogramme, followed by a continuous infusion of 0.2 to 1 microgram per kilogramme every hour.

The Use of Sedatives within the PICU

In the Pediatric Intensive Care Unit (PICU), there have been two studies that prospectively compared and evaluated the efficacy of dexmedetomidine as a sedative. Starting doses of either dexmedetomidine 0.25 or 0.5 g/kg/h or midazolam 0.1 mg/kg/h were delivered to 30 patients who required mechanical breathing in a randomised trial comparing dexmedetomidine to midazolam [34]. The patients' ages ranged from 36 to 34 months to 44 to 54 years on average.

Patients who were given dexmedetomidine at a dosage of 0.5 micrograms per kilogramme per hour exhibited significantly better levels of sedation than those who were given midazolam. Furthermore, they required significantly fewer doses of supplemental morphine (20 versus 36, $p = 0.02$) and had higher Ramsay sedation scores. It was determined that a dose of 0.25 g/kg/h was equivalent to a dose of 0.22 mg/kg/h of midazolam. In a different trial of paediatric patients who had undergone heart surgery, 56 children were given dexmedetomidine at a dose of 0.4 to 0.6 g/kg/h, whereas 85 children were given chlorpromazine, midazolam, and/or fentanyl [34]. It was discovered that sedation with dexmedetomidine had a comparable level of efficacy, despite an increased incidence of bradycardia or hypotension (21.4 vs 8.2%, $p = 0.04$), but a decreased incidence of respiratory depression (0 vs 8.2%, $p = 0.04$) and involuntary movements (3.6 vs 15.3%, $p = 0.01$).

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Dexmedetomidine was used in both intubated and non-intubated PICU patients for primary sedation, failure of sedation with benzodiazepines and opioids, as a bridge to extubation, or for substance withdrawal in a number of other retrospective investigations. In these investigations, the dosage of dexmedetomidine varied from 0.1 to 2.5 micrograms per kilogramme every hour. The majority of patients in the study were able to experience successful sedation and analgesia, and they also required less benzodiazepine and opioid medication as a result of the study's findings. In addition, three trials revealed that up to fifty percent of patients were successfully extubated while they were being treated with dexmedetomidine.

The use of sedation for operations that are not invasive

During diagnostic techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalogram (EEG) recording, dexmedetomidine may be given to the patient. Subjects were randomly assigned to receive a loading dose: continuous infusion regimen of either dexmedetomidine 1 g/kg over 10 minutes followed by 0.5 g/kg/h or midazolam 0.2 mg/kg followed by 0.36 mg/kg/h in a study involving 80 children undergoing MRI. The loading dose was administered as a single dose. The research found that the dexmedetomidine group had a greater rate of sufficient sedation (80%), better MRI quality, and a shorter onset time to sedation than the midazolam group (20%) (p 0.001). In a trial that was quite similar, the sedative effects of MRI were evaluated using either dexmedetomidine (1 g/kg over 10 minutes followed by 0.5 g/kg/h) or propofol (3 mg/kg followed by 100 g/kg/min) on 60 children. The authors concluded that there was no significantly different quality of MRI and adequate sedation between the two groups. When compared to dexmedetomidine, it was discovered that propofol had a quicker onset (four minutes versus eleven minutes) and recovery time (eighteen minutes versus twenty-seven minutes; p 0.05). Patients who were given propofol, on the other hand, had a significantly increased risk of hypotension and oxygen desaturation.

The use of sedation in conjunction with invasive operations

However, there are very few studies that support the use of dexmedetomidine for sedation during invasive procedures such as cardiac catheterization, gastroenteric endoscopy, and bronchoscopy. Despite this, the medication has been used. A randomised study comparing dexmedetomidine-ketamine to propofol-ketamine in 44 infants and children undergoing cardiac catheterization found that dexmedetomidine-ketamine provided less adequate sedation and analgesia along with a longer recovery time. The researchers attributed these findings to the fact that dexmedetomidine-ketamine was administered more slowly. Loading doses of dexmedetomidine and ketamine were given to the dexmedetomidine-ketamine group, which were 1 g/kg and 1 mg/kg over a period of 10 minutes, respectively. This was then followed by continuous infusions of 0.7 g/kg/h and 1 mg/kg/h, both of which were given. The participants in the propofol group received the same dose of ketamine as those in the other groups, in addition to 1 mg/kg of propofol, which was then infused at a rate of 100 g/kg/min. The need for ketamine rescue medication was considerably higher in the

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dexmedetomidine-ketamine group in comparison to the propofol group (2.03 vs 1.25 mg/kg/h, p 0.01), and patients in the former group had a longer recovery time (49.54 vs 23.16 min, p 0.01) than those in the latter group.

In a research in which 24 children were undergoing esophagogastroduodenoscopy (EGD), the effect of dexmedetomidine on the median effective concentration (EC50) of propofol was investigated. A target-controlled infusion (TCI) system was utilised to provide a continuous infusion of propofol to the control group beginning five minutes before the beginning of the EGD procedure.

Emergence delirium

Dexmedetomidine has been the subject of a number of randomised and controlled studies to see whether or not it is effective in preventing emerging delirium in patients who have undergone inhalational general anaesthesia. When compared to saline placebo, all studies demonstrated a reduction in the incidence of emergence agitation when dexmedetomidine was administered either as a single dose after induction (0.3 — 1 g/kg), prior to the end of surgery (0.5 g/kg), or as a continuous infusion (0.2 g/kg/h). This reduction ranged from 10 to 26%, whereas the incidence of emergence agitation was between 37 There were no clinically significant differences between the groups in the amount of time it took for patients to open their eyes, be extubated, or be released from the recovery room. In these investigations, the analgesic effects of dexmedetomidine were inconsistent. Two of the studies reported that there were no significant differences between dexmedetomidine and the placebo, while the third research reported a decrease in pain scores.

Additional uses in paediatric medicine

Dexmedetomidine has been used in the peri-operative care of paediatric patients in a range of settings. This is in addition to its use in the avoidance of emerging delirium, which can occur in a number of different circumstances. It has been determined that dexmedetomidine can be safely administered as an adjuvant to total intravenous anaesthetic that is based on propofol during spinal fusion surgery. Dexmedetomidine loading dose-infusion, 1 g/kg - 0.5 g/kg/h, had no significant effect on somatosensory or motor evoked potentials (amplitude or duration) with appropriate propofol dosing adjustment and can be administered as a component of total intravenous anaesthesia, according to the findings of a retrospective study that included nine adolescents as patients. There have also been case reports of the successful use of dexmedetomidine during awake craniotomy at doses as high as 0.7 g/kg/h. Other, less prevalent applications of dexmedetomidine in children include its usage as an opioid-sparing postoperative analgesic, as a therapy for tachyarrythmias, and as an anti-shivering agent. Last but not least, a number of case studies detail how dexmedetomidine was successfully utilised in the therapy of withdrawal from substances.

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UNFAVORABLE CONSEQUENCES

The most common adverse consequences

In clinical trials involving adults, hypotension and bradycardia were the most often seen adverse effects of dexmedetomidine. The incidence and frequency of each condition are highly variable depending on the parameters that are utilised. In the adult intensive care unit population, the drug maker reported an overall incidence of hypotension of 25%, whereas the placebo group reports an incidence of 12%. However, in the adult procedural sedation population, the incidence was 54 versus 30%, respectively. In patients admitted to the intensive care unit (ICU), the incidence of bradycardia was 5%, compared to 3% in the placebo group; nevertheless, it was 14% under procedural sedation. Hypertension during the loading dosage was transitory and dose-dependent.

During the loading dosage, nine percent of patients in both the placebo and dexmedetomidine groups experienced hypertension. In comparison to the placebo group, those given dexmedetomidine experienced just fleeting hypertension that lasted less than ten minutes (up to 4 h).

Cardiovascular

The a2-agonist characteristics of dexmedetomidine are responsible for the majority of the drug's effects on the cardiovascular system. Its central sympatholytic capabilities are responsible for the side effects of low blood pressure and slow heart rate. The stimulation of peripheral a-receptors and the associated vasoconstriction can lead to a condition known as transient hypertension. This condition typically manifests itself during bolus dosage or rapid infusion.

Blood pressure effects

In children, studies that evaluate the blood pressure response to dexmedetomidine given as a single bolus dose produce inconsistent results. A single dosage of dexmedetomidine (0.33, 0.66, or 1 g/kg given over a period of ten minutes) was given to each of the 36 children in the trial who were about to have urologic, lower abdominal, or pelvic surgery [29]. The systolic blood pressure (SBP) was found to be inversely linked with dose (p 0.028) and time (p 0.029) following administration of dexmedetomidine. The decrease in SBP was measured in the first hour after dexmedetomidine was administered, and it was found to be 25% lower than at baseline. The diastolic blood pressure went down over the course of the study ($p = 0.02$) When compared to the control group, the results of a randomised controlled trial (RCT) that administered dexmedetomidine at a dose of 0.5 micrograms per kilogramme of body weight over the course of five minutes to thirty children who had just undergone tonsillectomy and adenoidectomy showed a marginally lower blood pressure.

It was discovered that the group receiving dexmedetomidine and midazolam had a higher SBP at 20 minutes when compared to baseline (p 0.02), whereas the group receiving propofol had considerably lower blood pressure measures when compared to baseline and

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dexmedetomidine (p 0.0003). According to the research that has been conducted thus far, the incidence of hypertension following the injection of dexmedetomidine can range anywhere from 0% to 8%.

Effects on the Rate of the Heart

The effects of dexmedetomidine on the electrophysiology (EP) of the heart have been the subject of a number of studies, with varying degrees of success.

An electrophysiology research was conducted on a group of 12 children who were undergoing cardiac catheterization. The effects of dexmedetomidine on conduction were evaluated after a loading dose of 1 g/kg and a 10 minute infusion at 0.7 g/kg/h. The function of the sinus node was impaired, as seen by an increase in recovery time from baseline, which was 293 ms as opposed to 212 ms.

In a study involving 36 children, dexmedetomidine was given as a single dose of either 0.33, 0.66, or 1 g/kg over a period of ten minutes. This was done in comparison to control subjects who did not receive any drug [29]. Dexmedetomidine was found to have a negative correlation with both dose (p 0.00008) and time (p 0.025), which resulted in a decrease of 15% in heart rate in the first hour after administration of the drug when compared to the baseline value. Following a bolus dose of up to 1 g/kg, the results of two other prospective studies showed findings that were comparable, with a significant slowing of the heart rate in comparison to the baseline value. Several \srandomized controlled studies of dexmedetomidine provided as a bolus dosage (maximum 1 µg/kg over 2 min) to children \sshowed no significant effect on heart rate. None of these studies found any bradycardia that might be considered clinically significant.

Respiratory

During administration of dexmedetomidine, the results of a number of prospective studies indicate either a modest or nonexistent change in respiratory function. It was shown that dexmedetomidine did not elicit alterations in respiratory function when it was administered as a single bolus dosage of up to 1 g/kg over a period of 2 minutes. Minor alterations in respiratory function were recorded, but they were not clinically significant when the drug was given as a continuous infusion of up to 2 micrograms per kilogramme per hour.

It was discovered that modest CO2 retention caused respiratory rates to drop by a maximum of 8%, and that maximal transient end-tidal CO2 measurements reached a value of $ 57 mmHg. There was no association found between dexmedetomidine and hypoxemia in any of the investigations.

When compared to midazolam, dexmedetomidine did not exhibit any differences in respiratory function; however, when compared to propofol, dexmedetomidine was associated with a smaller decrease in respiratory rate as well as no episodes of desaturation. This is in contrast to the propofol group, which experienced four episodes of desaturation. It does not

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appear that dexmedetomidine plays a role in the development of laryngospasm or bronchospasm.

Isolated incidences of oversedation and subsequent respiratory depression have been documented following the administration of dexmedetomidine at therapeutic doses. This is the case despite the fact that controlled investigations showed negligible alterations in respiratory function. One patient who was given a single bolus dose of dexmedetomidine at a rate of 1 microgram per kilogramme per kilogramme over ten minutes was found to be well sedated and exhibited respiratory depression with hypoxemia reaching 94% while they were breathing air [29].

Neurologic

Effects of dexmedetomidine on the central nervous system have not been researched in youngsters. In adults, the effects it has on the seizure threshold provide contradictory results. Only one research study involving the use of dexmedetomidine in paediatric patients showed the occurrence of seizures as a negative side effect. In a randomised clinical trial with 44 patients undergoing cardiac catheterization, 22 children with congenital heart disease were given dexmedetomidine at a dose of 1 microgram per kilogramme (mcg/kg) followed by 0.7 mcg/kg per hour. The other 22 children were given propofol at a dose of 1 milligramme per kilogramme (mg/kg) followed by 100 micrograms per kilogramme per minute. Both of the groups were given ketamine at a rate of 1 mg/kg simultaneously, followed by 1 mg/kg/h.

Other

It would appear that dexmedetomidine does not have any effects on the endocrine system that are clinically important. A suppression of the adrenal glands has not been found to be linked with the administration of dexmedetomidine [20,21]. When pre- and post-infusion measurements are compared, the results of an investigation into the effects of dexmedetomidine on serum glucose levels demonstrate that there is no change in the level of serum glucose. In a similar vein, there is no evidence that dexmedetomidine causes an increased risk of gastrointestinal adverse effects, such as emesis, ileus, or an elevation in hepatic transaminase [20,21,32]. In the adult literature, there is only one case report of what is suspected to be drug fever.

Patience and reluctance to engage

Although dexmedetomidine is routinely given as a protracted infusion lasting more than 24 hours, it has not been adequately researched in either adult or paediatric patients how tolerance develops during administration or how withdrawal symptoms manifest after dexmedetomidine treatment is stopped.

Overdose

In the research that has been published, there are two case reports that describe the delivery of dexmedetomidine as massive and rapid infusions. Following sedation with 4 g/kg of

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intranasal dexmedetomidine and 0.5 mg/kg of midazolam, a boy who was 3 years old was given dexmedetomidine at a rate of 1 g/kg/min for 10 minutes in order to prepare him for an MRI. The patient experienced hypertension that reached 135/75 mmHg as well as persistent sedation that lasted for more than four hours. There was no discernible decrease in respiratory capacity. The second case report describes a girl who was 20 months old when she underwent cardiac catheterization and received 1 microgram per kilogramme per minute for 36 minutes. When compared to the patient's baseline heart rate of 126 beats per minute, this patient's heart rate dropped to a nadir of 84 beats per minute 1.5 hours after the infusion was completed. After 20 minutes of the infusion, the patient's hypertension reached its maximum level of 152/85 mmHg. The patient did not experience any respiratory depression despite the large rapid infusion that was given to them. The extended sedation persisted for more than seven hours. The patient also had two seizures owing to hypoglycemia, with serum glucose levels of 26 mg/dl. These seizures happened after 14 hours of fasting, and the relationship between them and the dexmedetomidine is unknown.

SPECIAL POPULATIONS:

Cardiac

Because of its ability to both sedate and calm anxious patients, dexmedetomidine is a common medication used in cardiac intensive care units (ICUs). Due to the fact that it has very few affects on a person's ability to breathe, it is an excellent complement to more conventional drugs like fentanyl and midazolam. After heart surgery, it is critical to administer appropriate sedation and begin weaning the patient from mechanical ventilation as soon as possible. A continuous infusion of dexmedetomidine at a dose of 0.2–2 g/kg/h was given to 54 children ranging in age from 1 day to 16 years as part of a third study [21], which indicated that there was no change in blood pressure during the infusion when compared to the values at baseline and after the infusion. Dexmedetomidine administration was not associated with increased pulmonary artery pressure, as measured by transthoracic echocardiogram, in an observational study involving 22 children who had undergone cardiac surgery and received a loading dose of 0.5 — 1 g/kg of dexmedetomidine, followed by an infusion of 0.1 — 1.5 g/kg/h titrated to effect. The study was conducted after the children had recovered from the surgery.

Obstructive sleep apnea

High-dose dexmedetomidine, with a loading dosage of 2 g/kg followed by an infusion of 2 g/kg/h, was compared with propofol in a trial that involved 85 patients with obstructive sleep apnea who were receiving sedation for MRI. These patients were between the ages of 5 and 15 years old. The delivery of dexmedetomidine resulted in a slower heart rate and a smaller fall in blood pressure when compared to the administration of propofol, but there was no indication of bradycardia or hypotension. Patients who were given dexmedetomidine had a much lower likelihood of requiring advanced airway techniques or the installation of oral or nasal airways to relieve obstruction (15 versus 46%, p = 0.01).

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Conditions related to child development and behaviour

The sedative effect of dexmedetomidine is comparable to that of stage 2 natural sleep [11,12]. When compared to several other sedatives, dexmedetomidine's singular quality offers a significant benefit in the context of an electroencephalogram (EEG) examination. Patients diagnosed with autism or extensive developmental problems frequently require EEGs for the examination of seizure activity; yet, these patients have traditionally been difficult to sedate. There are now two studies being conducted that look at the use of dexmedetomidine for the purpose of procedure sedation in patients who suffer from pervasive developmental and behavioural abnormalities.

Neonates Born Prematurely

There has been no research done on the effects of giving dexmedetomidine to pre-term newborns. One case report recounts how dexmedetomidine was successfully used in the treatment of a premature infant who was 24 weeks old.

Following the administration of a loading dose of dexmedetomidine at a rate of 0.5 micrograms per kilogramme, the patient received a continuous infusion of the drug, which was gradually increased to a maximum rate of 0.7 micrograms per kilogramme per hour over the course of 19 days. The administration of dexmedetomidine produced sufficient drowsiness, which made it possible to wean the patient off of various sedatives and analgesics as well as mechanical ventilation assistance. After the patient was extubated, the infusion was gradually stopped. During the injection of dexmedetomidine, the patient had one episode of hypotension due to relative adrenal insufficiency. This condition is assumed to be a consequence of the patient's severe premature birth.

CONCLUSION:

In a number of different clinical contexts, dexmedetomidine is administered to paediatric patients. Because it has just a small impact on the patient's ability to breathe, it is an attractive option for use as a sedative in the paediatric intensive care unit (PICU), during procedural sedation, and for the prevention of emerging delirium associated with general anaesthesia. Dexmedetomidine has recently found use in the treatment of withdrawal symptoms associated with substance use as well as in the medical management of trembling. The administration of dexmedetomidine almost always results in a reduction of both blood pressure and heart rate; however, in the vast majority of instances, these changes are not clinically meaningful. During bolus dosage or rapid infusion, dexmedetomidine can cause temporary hypertension in addition to hypotension and bradycardia. These are the most prevalent adverse effects associated with the administration of dexmedetomidine. The administration of dexmedetomidine in specialised patient groups, such as infants and children born prematurely or with congenital heart disease, has not been subjected to extensive research. In a similar vein, it is unknown whether or not patients who receive lengthy infusions of dexmedetomidine will eventually acquire a tolerance or go through withdrawal.

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