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Dexmedetomidine in paediatric anaesthesia

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Learning objectives

By reading this article, you should be able to:

- Describe the benefits and potential adverse effects of using dexmedetomidine in children.
- Know the effective dose for dexmedetomidine for a wide range of uses.
- Anticipate the changes in heart rate and arterial blood pressure that occur with dexmedetomidine.
- Manage isolated bradycardia without other abnormal vital signs.

Key points

- The pharmacokinetics and pharmacodynamics of dexmedetomidine change markedly from neonate to infant to adult.
- Dexmedetomidine is a useful analgesic adjunct: it has opioid-sparing effects and prolongs the duration of regional anaesthesia.
- Dexmedetomidine allows for early extubation after paediatric cardiac surgery.
- Dexmedetomidine may provide neurocognitive protection to the neonatal brain exposed to volatile anaesthetics, but long-term follow-up studies are awaited.
- Intranasal dexmedetomidine has a promising role for preoperative sedation.

Dexmedetomidine (DEX) is a highly selective α_2-agonist that provides sedation which parallels natural sleep, anxiolysis, sympatholysis and an anaesthetic-sparing effect without clinically significant respiratory depression.[1] It produces this sedative effect via α_2 adrenoceptors in the locus coeruleus in the central nervous system. A single intraoperative dose without a subsequent infusion has been shown to reduce postoperative analgesic requirements, provide smoother emergence from anaesthesia and prolong regional anaesthesia.

Dexmedetomidine (Precedex) is currently approved by the United States Food and Drug Administration (FDA) for sedation via i.v. bolus and continuous infusion for up to 24 h in intubated adults and for sedation of non-intubated patients before or during surgical and other procedures. In the European Union, DEX (Dexdor) was approved in 2011 for the sedation of adult patients in an ICU without a time limit. Despite a strong evidence base for the use of DEX in paediatric anaesthesia, its use is currently 'off-label'.

The uses of a drug other than those listed on the prescription label are considered off-label uses. These include differences in dosage, patient group, and indication for use. Obstetric and paediatric patients are more likely to be

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Clinical scenario

A 5-year-old child with moderate autistic spectrum disorder presents for a brain MRI scan to investigate an abnormal gait that he has been experiencing over the last 6 months. He weighs 22 kg and has had previous general anaesthesia for dental extractions where a technique using oral midazolam premedication and an inhalational induction was unsuccessful, requiring physical restraint after other non-pharmacological interventions had failed. It was a traumatic experience for child and parent.

After preoperative assessment, and a simulation session using a mock MRI scanner, intranasal dexmedetomidine 2 μg kg^{-1} is given and after 45 minutes he achieves a Ramsay sedation score of 4. Intravenous access is obtained at this point, and this is atraumatic. He arouses briefly on transfer to the MRI table and scanner but is easily reassured by his mother and resumes an asleep state. He manages to complete the 20-minute MRI scan with ear headphones, a movie and the presence of his parent in the scanner. He is immediately awake once transferred to PACU.

prescribed medications for off-label use. The off-label use of medication is acceptable if there is no suitable alternative and if a physician feels confident that he or she is using the medication in accordance with current medical opinion.

Pharmacokinetics and pharmacodynamics in children

Dexmedetomidine is a highly lipophilic drug with a high volume of distribution (V_D) in both children and adults. Dexmedetomidine is predominantly bound to plasma proteins, primarily albumin and α_1 glycoprotein. It readily crosses and blood brain barrier and has a V_D in children older than 1 yr similar to adult values. It is thought to fit a two-compartment model with first order elimination.

Dexmedetomidine is broken down by the hepatic enzymes uridine 5′-diphospho-glucuronosyl-transferase and cytochrome P450 (CYP2A6) to inactive metabolites and direct glucuronidation, which are excreted in bile and through renal pathways. Pharmacokinetic studies in adults show that DEX is rapidly distributed and has a short elimination half-life of 2.0 h. A population pharmacokinetic analysis study revealed that clearance changes considerably with age, with children out of infancy being similar to those described in adults (42.1 L h^{-1} 70 kg^{-1} *vs* 44.8–52.5 L h^{-1} 70 kg^{-1}). Clearance in neonates (42.4% of adult values, reaching 84.4% by 1 yr old) and infants is reduced, owing to immaturity of elimination pathways.[2] The maturation parameters for clearance are closely related to morphine maturation. Interestingly, average clearance in postoperative cardiac children was reduced by 27% in those receiving a prolonged infusion over 18 h. This could be attributable to a low hepatic perfusion period in the immediate postoperative period.[2]

There is a dose-dependent effect of DEX on MAP and HR. The median effective dose (ED_{50}) of i.v. DEX given over 5 s without significant haemodynamic compromise was found to be 0.49 μg kg^{-1} in healthy children receiving TIVA.[3] A similar modest reduction in systolic BP occurs when used with volatile maintenance anaesthesia. Transient DEX-induced hypertension appears to occur more frequently with repeated large boluses of 2–3 μg kg^{-1} and more likely to occur in infants than in older children.

A bradycardia of up to 30% from baseline should be expected with the use of DEX in children. In a large study of 747 patients where i.v. DEX was used as a sole sedative for children undergoing MRI, the incidence of bradycardia was 16%.[4] The use of anticholinergics to treat bradycardia resulting from DEX administration should be done with caution as there are even reports of profound transient hypertension when glycopyrrolate is used to treat DEX-induced bradycardia.[5] When a bolus of DEX 0.5 μg kg^{-1} was given with maintenance TIVA, 71% of patients had an HR <60 beats min^{-1} with a median maximum decrease of 20 beats min^{-1}.

Despite these changes in HR and MAP, haemodynamic collapse or need for pharmacological resuscitation has not been reported. Immediate action to treat bradycardia associated with α_2 adrenergic agonists in children is required only if concomitant vital signs are abnormal, if bradycardia is caused by a serious bradyarrhythmia, or both.[6] Resolution of adverse signs occurs with stopping or reducing the DEX infusion. Table 1 details the relative contraindications to using DEX in children.

Preoperative uses

Dexmedetomidine produces a cooperative and rousable sedative effect which can be ideal for the uncooperative or anxious child. The bioavailability of nasal (40.7%) and buccal (81%) DEX has been shown to differ quite markedly.[7] Oral bioavailability is very poor (16%). Intranasal DEX (i.n. DEX) is well tolerated and can be delivered either by the droplet method or via a mucosal atomiser device with equivalent bioavailability.[8]

I.N. DEX is a convenient, minimally invasive technique for sedation in children. A recent meta-analysis of i.n. DEX premedication in children concluded that it provided a more satisfactory sedation at parent separation and reduced the need for rescue analgesics compared with i.n. ketamine, oral and i.n. midazolam. The success rate of i.n. DEX varies with the age of the child. In a study by Li and colleagues,[8] the success rate of 3 μg kg^{-1} was 82.5% in children from 2 months to 3 yr undergoing transthoracic echocardiography. The time-to-peak effect of a dose of 2–3 μg kg^{-1} in a recent study was 45 min in children aged 0 to 11 yr, with no difference in the three different age groups.[9] Better acceptance of mask induction can be achieved with 2 μg kg^{-1} compared with 1 μg kg^{-1} of i.n. DEX.

Table 1 Relative contraindications or precautions to the use of dexmedetomidine (DEX) in children

Rapid bolus of dexmedetomidine with high blood concentrations of volatile anaesthetics
Cardiac conduction abnormalities
Septic shock
Concurrent treatment with digoxin, β-adrenergic blockers, calcium channel blockers, monoamine oxidase inhibitors or other agents that predispose to bradycardia or hypotension[13]
Chronic hypertension
Hepatic disease

I.N. DEX does not have the nasal irritation that is common with giving i.n. midazolam. The irritation can lead to poor drug effectiveness because of the associated coughing and sneezing. When lower doses of i.n. DEX are used (1 μg kg^{-1}), the authors have found that ~45 min is required for acceptable anxiolysis (Ramsay sedation score, 4). It is not unusual to have the child awake to external stimuli such as being moved or applying a facemask.[10] Buccal DEX, despite high bioavailability, has not been shown to be superior to i.n. DEX when used at a dose of 1 μg kg^{-1} 45 min before anaesthesia.[11]

I.N. DEX has the additional benefit of reduced postoperative nausea and vomiting and need for rescue analgesics.[12] The mechanism of action of its antiemetic effect is via decreased dopamine levels in the locus coeruleus and its analgesic effect, thereby reducing the need for opioids. A decrease in HR and arterial pressure within 20% of baseline occurs with i.n. DEX 0.5–3 μg kg^{-1}, which is less than the decreases seen with equivalent doses of i.v. DEX.[11] Continuous pulse oximetry, HR, and arterial blood pressure monitoring would be recommended after drug delivery.

Uses for surgical and non-surgical procedures

Ear, nose, and throat surgery

Rigid bronchoscopy for foreign body retrieval in children frequently requires a spontaneous breathing anaesthetic technique, which can be achieved with an inhalational agent or TIVA. The depth of anaesthesia in this procedure is critical to avoiding apnoea, coughing, and interruption to surgery. The additional of i.v. DEX may offer some alternatives in reducing the doses of propofol/remifentanil/inhalational agent, and potentially reduces the incidence of coughing, interruption of surgery and apnoea.[13]

Chen and colleagues[13] compared propofol–remifentanil and propofol–DEX in 77 patients and found no difference in the incidence of breath holding. This study did use an inhalational induction and gave a bolus dose of DEX 4 μg kg^{-1} followed by infusion of 1–2 μg kg^{-1} h^{-1}. As expected, they found significantly prolonged duration of stay in PACU in the DEX group. It should be noted that despite these higher than recommended doses of DEX, and co-administration of propofol at 200 μg kg^{-1} min^{-1}, spontaneous ventilation was maintained with no airway collapse. We commonly use DEX in these procedures to reduce the dose of propofol and remifentanil and to reduce the risk of apnoea.

The potential benefits of DEX use in children with obstructive sleep apnoea (OSA) have been extensively studied. These children are at particular risk of propofol, volatile inhaled anaesthetic, or opioid-associated implications. Children with OSA undergoing adenotonsillectomy present a challenge to anaesthetists because of potential postoperative airway compromise and optimisation of analgesia. Dexmedetomidine has been shown to provide satisfactory intraoperative conditions for adenotonsillectomy without adverse haemodynamic effects when a 2 μg kg^{-1} bolus is given followed by an infusion of 0.7 μg kg^{-1} h^{-1}, combined with volatile anaesthesia for maintenance of anaesthesia. Postoperative opioid requirements were significantly reduced and there were fewer episodes of desaturation when compared with a group receiving fentanyl 1 μg kg^{-1}.[14] There was no difference in the time to awakening and time to extubation in the DEX group despite the relatively high doses. This is an interesting study in a group of patients likely to benefit from a reduction in opioid consumption. They demonstrated a total fentanyl use of 2 μg kg^{-1} in the non-DEX group, and rescue fentanyl dose of 0.73 μg kg^{-1} in the DEX group; these were not statistically significant. In our experience, a lower dose of i.v. DEX (0.5 μg kg^{-1} with fentanyl 1 μg kg^{-1} during induction) in combination with a TIVA technique using remifentanil 0.1 μg kg^{-1} min^{-1} provides effective intraoperative conditions, emergence and postoperative analgesia.

The use of DEX in combination with ketamine in patients at risk of fatal airway collapse with anterior mediastinal mass with SVC compression has been described.

Cardiac surgery

The use of DEX in children after cardiac surgery has been described since 2006.[15] The pharmacokinetics of DEX are dramatically affected by age, weight, total bypass time and intracardiac shunting.[16] For example after a Glenn procedure, clearance of DEX in children is increased by 24% because of the right-to-left intracardiac shunt and recirculation of blood through the liver.[16] However, despite this, distinct advantages have been shown in using DEX in the right groups of paediatric cardiac patients.

The recent Pediatric Heart Network Collaborative Learning Study has demonstrated that giving DEX during surgery was independently associated with early extubation in haemodynamically stable children undergoing coarction and tetralogy of Fallot repair.[17] This is largely attributable to the reduced need for opioids and benzodiazepines, with no change observed in the use of volatile anaesthetic agents. There was an increased incidence of junctional arrhythmias requiring therapy in the DEX group (14% *vs* 6%).

Neonatal anaesthesia

It is well known that neonates, with immature cardiovascular, central nervous and respiratory systems, are vulnerable to the adverse effects of anaesthetic drugs and tracheal intubation. Dexmedetomidine has been shown to attenuate isoflurane-induced neurocognitive impairment in rats.[18] The use of DEX sedation in this age group in combination with caudal anaesthesia in open inguinal hernia repair has been described.[19] Bong and colleagues[19] randomised 104 infants to receive sevoflurane general anaesthesia or DEX sedation and caudal epidural analgesia for inguinal hernia surgery. A bolus of DEX 3 μg kg^{-1} i.v. over 20 min was given, followed by caudal anaesthesia using levobupivacaine 2.5 mg kg^{-1} diluted to a total volume of 1.25 ml kg^{-1}. This was followed by an infusion of DEX 0.2–1 μg kg^{-1} h^{-1} i.v. targeting a Ramsay sedation score of 3–4.

There were two infants (2/51) who required temporary bag mask ventilation without requiring intubation and overall a greater than 90% success rate. This study provides further evidence for the safety profile of i.v. DEX and avoids the need for tracheal intubation in these high-risk neonates (severe lung disease of prematurity). Despite the relatively high doses of DEX used, there was greater haemodynamic stability in the DEX group than GA with caudal.[19]

Neurosurgery

The use of DEX in awake craniotomy in children is well described. Brain mapping and neurophysiological testing in

patients with brain tumours undergoing epileptic seizure foci resection utilises subdural electrocorticography (ECoG) to guide surgical resection. Electrocorticography allows direct localisation of lesion boundaries by direct recording of cortical potentials but can be adversely affected by anaesthetic agents. Inhalational agents reduce the amplitude and frequency of EEG, and benzodiazepines are contraindicated because of their antiepileptic properties. Propofol does not appear to interfere with spontaneous interictal epileptiform activities (IEAs) as long as it is discontinued 20 min in advance of ECoG. High doses of all opioids can cause interictal high spikes.

Conversely, DEX at low doses does not adversely affect ECoG.[20] Doses of 0.1–0.2 μg kg^{-1} h^{-1} after an initial bolus of 0.5 μg kg^{-1} have allowed children to participate in awake testing intraoperatively (Table 2). The fact that DEX does not reliably induce amnesia is a potential cause for concern in these patients. Most regimes for awake craniotomy will include co-administration of a low-dose opioid in the form of fentanyl boluses or remifentanil infusion.

Emergence delirium

Dexmedetomidine and clonidine have been shown to reduce the incidence of emergence delirium (ED) but with anticipated prolonged duration of PACU stay in some studies. The dose required to reduce the incidence has been shown to range from 0.3 to 1 μg kg^{-1} in studies looking at MRI (1 μg kg^{-1}), adenotonsillectomy (0.5 μg kg^{-1}), superficial lower abdominal and genital surgery (0.3 μg kg^{-1}).

Sevoflurane anaesthesia in children for MRI has been shown to have an incidence of ED of 40%.[21] Bong and colleagues found no difference in the incidence of ED when propofol or DEX (0.3 μg kg^{-1}) was given compared with a control group. However this study showed that for every minute longer the child took to emerge from anaesthesia, the odds of ED were reduced by 7%.[21] These results could be attributable to the different ED assessment score used or that when a sevoflurane inhalational technique is used in isolation, a higher dose of i.v. DEX is required to reduce the incidence of ED.

Procedures in radiology

Sedation of children in radiology suites ranges from short non-stimulating CT scans to stimulating MRI sequences that require a child to be motionless for more than an hour. The Boston Sedation Protocol (3 μg kg^{-1} loading dose over 10 min, followed by 2 μg kg^{-1} h^{-1} infusion) is an established technique with a robust safety record.[4] It should be noted that airway management described in these studies consist of oxygen via nasal prongs with spontaneous ventilation and is a nurse-administered sedation service under the supervision of a consultant anaesthetist. The rationale for using DEX as the sole agent is to reduce the risk of critical adverse outcomes, which increase with the use of adjuvant sedative drugs. HR and MAP changes were found to be similar to those seen when propofol or inhalational anaesthetics are used alone to achieve anaesthesia. A similar service for MRI sedation in children has been described in the UK.[22]

The duration of PACU stay after MRI under sedation using propofol infusion as a sole sedative agent ranges from 28 to 35 min compared with 25 min with i.v. DEX. However, the incidence of airway interventions is 7–8% during propofol infusion compared with no airway interventions reported when using the Boston Sedation Protocol.[4] It may be that a bolus dose of DEX combined with a lower dose propofol/remifentanil infusion offers a good compromise.

Multiple recent studies have shown successful sedation and completion of MRI scans in children of varying age groups using i.n. DEX with the use of adjuvant sedatives.

Use as an analgesic adjunct

Clonidine and DEX have both been shown to prolong the duration of action of a caudal epidural when given caudally for up to 12 h. A recent study has shown that caudal and i.v. DEX 1 μg kg^{-1} prolong the duration of caudal analgesia similarly in infants undergoing open inguinal hernia repair. Administration of neuraxial DEX is off label, and safety has not been established in humans.

A prospective double-blind RCT showed that addition of perineural DEX 0.3 μg kg^{-1} as an adjunct compared with plain ropivacaine 0.197% in ilioinguinal/iliohypogastric nerve block resulted in lower pain scores and longer time to first demand for supplementary analgesia in children undergoing inguinal hernia repair.[23] An adult volunteer study showed DEX 20 μg as a perineural adjunct with 3 ml ropivacaine 0.75% to the ulnar nerve prolonged sensory and motor block by 60% compared with systemic DEX at the same dose. This is a small dose of i.v. DEX per kg, and therefore one could expect a greater response with an equivalent dose of 0.5 μg kg^{-1}. We would therefore argue that i.v. DEX as an analgesic adjunct in those receiving a peripheral or neuraxial regional anaesthesia be given until the safety profile of perineural DEX is fully elucidated.

High-dose opioid infusions have been the mainstay of analgesia for significant pain from targeted immunotherapy

Table 2 Examples of dosing regimens for dexmedetomidine use in children

Application	Route	Dose range
Preoperative anxiolysis	Intranasal	1–2 μg kg^{-1}
Intraoperative applications		
• ENT – obstructive sleep apnoea	Intravenous	0.5 to 1 μg kg^{-1} bolus
• Cardiac	Intravenous	No loading bolus 0.3–0.5 μg kg^{-1} h^{-1}
• Neurosurgery (awake craniotomy)	Intravenous	0.5 μg kg^{-1} bolus followed by infusion of 0.1–0.2 μg kg^{-1} h^{-1}
Postoperative benefits		
• Emergence delirium	Intravenous	0.5 μg kg^{-1}
Analgesic adjunct-acute pain management	Intravenous	0.2–0.5 μg kg^{-1} h^{-1}
Prolong regional anaesthesia	Intravenous	0.5–1 μg kg^{-1}

for neuroblastoma. Our pain management strategy to manage discomfort during the treatment of high-risk neuroblastoma with ch14.18-based immunotherapy includes the use of DEX infusion 0.1–0.6 μg kg^{-1} h^{-1} in conjunction with a hydromorphone infusion 2–8 μg kg^{-1} h^{-1}. This pain management strategy resulted in dramatically reduced opioid consumption compared with reports in the literature whilst remaining a safe technique in the setting of an oncology ward.[24]

Future applications

Some have justifiably advised caution with the initial enthusiasm with DEX because some important questions remain unanswered.[25] We have found a large interindividual dose response that is dependent on age. The use of DEX in rare metabolic disorders is a natural choice; however, evidence to support its use in these children remains in the form of case reports. We also await further studies looking at long-term follow-up of early anaesthetic exposure to DEX and evidence of its neuroprotective effects.

Conclusions

Despite the increasing evidence for the applications of DEX as described in this article, the uptake of anaesthetists using DEX in children is variable. We are learning more about its pharmacokinetics and pharmacodynamics in neonates, infants, and in congenital cardiac conditions. DEX is finding its place in paediatric anaesthesia, but there are still some gaps in knowledge and more work is warranted.

Declaration of interests

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) are accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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