Editorial

Search for the ideal route of premedication in children.. far from over?

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Perioperative anxiety in children has often been associated with diverse implications like separation anxiety, emergence delirium, enhanced analgesic requirements and subsequent sequelae like behavioural changes leading to sleep disturbances, eating disorders and new onset enuresis.[1] Paediatric patients need premedication to reduce anxiety, improve compliance while providing amnesia for the process of induction, and reduce negative behavioural changes during the postoperative period.[2] Premedication is superior to the presence of parents or guardians during the induction or preoperative teaching programmes.[3] Good premedication should be easily applicable and have a rapid onset and short duration of action without significant short or long term side effects. Additionally, in this age group, it is desirable that there is no needle prick, is non-irritable, and is not painful. The search for the ideal premedication in children is far from over, especially in view of the diverse needs based on age and physiology, a plethora of pharmacologic agents available and varying routes available. The paediatric age group is different even within themselves anatomically, physiologically, as well as pharmacologically.[4]

Challenging in paediatric population, are the constant changes which impact the pharmacogenomics, pharmacokinetics, and pharmacodynamics of the administered medications.[5] To address this concern regarding paediatric medications, the International Conference on Harmonisation has proposed sub-classes for the paediatric population consisting of (i) Preterm new-born infants, (ii) Term new-born infants (0 to 27 days), (iii) Infants and toddlers (28 days to 23 months), (iv) Children (2 to 11 years), and (v) Adolescents (12 to 16/18 years, dependent on region).[5]

Clinical practice and literature remain undecided on the ideal route for the administration of premedication in children.[1] The routes traditionally used have been oral, nasal, rectal and intramuscular (IM). Over the time, transdermal, other transmucosal and intrapulmonary routes have also been explored. New drugs acting on the central nervous system (CNS) take a long time to develop. Premedication and anaesthetic drugs being intimately related to the CNS face such a challenge.[6]

This journal issue carries an original article by Shereef KM and colleagues, looking at the role of nebulised dexmedetomidine, midazolam or ketamine as premedication in preschool children undergoing general anaesthesia.[7] The authors conclude that nebulisation with dexmedetomidine showed easy parental separation, more satisfactory sedation and face mask acceptance with less postoperative agitation than nebulisation with midazolam or ketamine.[7]

PAEDIATRIC PREMEDICATION-THE JOURNEY SO FAR

Anticholinergics and antihistamines have been traditional premedication drugs. The anticholinergic

which had demonstrated promise was scopolamine, also known as hyoscine, for its sedative-hypnotic properties. While scopolamine can be used at doses of 0.005 to 0.010 mg/kg intravenous (IV) or intramuscularly, it is infrequently used in view of its adverse effects like vertigo, agitation, hallucination, blurry vision and dry mouth.[8] Scopolamine transdermal patch (STP) has been used in children with neurological disorders for the management of sialorrhea, but it is seldom used as a premedication for children.[9] Antihistamines are rarely used. Promethazine is contraindicated below two years of age and should be used with caution for those above two years in view of the risks of various adverse events like apnoea, respiratory depression, seizures and dystonia.[10] It is also known that many antihistamines also increase the QTc interval, and this is further aggravated by most general anaesthetics.[11]

The paediatric population has Trypanophobia, an intense fear of needles, and this means that the favoured approaches are intranasal, oral, and transmucosal. Synthetic opioids have been the preferred agents for their early onset and shorter duration of action. Oral administration of fentanyl and sufentanil are not viable options and they have been used via intranasal and oral transmucosal approaches.[12] Intranasal sufentanil in doses of (2 μg/kg) and intranasal fentanyl at 1.5 μg/kg have been used.[13,14] In fact, Chatrath V and colleagues found intranasal 1.5 μg/kg fentanyl to be better than intranasal midazolam 0.3 mg/kg and intranasal dexmedetomidine 1 μg/kg with regard to intravenous acceptance before induction of anaesthesia.[14] Oral transmucosal fentanyl (OTFC) has a shorter onset of action and better patient cooperation. However, due to its adverse effects like nausea, vomiting, over-sedation and oxygen desaturation, it has fallen out of favour and is now mostly used for breakthrough cancer pain.[15]

Midazolam, a water-soluble benzodiazepine with rapid onset and shorter duration of action, can be administered orally and transnasally and has become the preferred choice amongst most paediatric anaesthesiologists.[16] It is typically administered orally at a dose of 0.5–0.75 mg/kg, up to a maximum of 20 mg, after which sedation and anxiolysis are reliably achieved within 20 min.[1] The bitter taste can be masked by sugary or fruity syrups. Though intranasal and sublingual midazolam (0.3 mg/kg) have a rapid onset of action (10 minutes), they are poorly accepted due to the burning and stinging sensation experienced by children.[17] Rectal midazolam (0.5-1 mg/kg) can also achieve adequate anxiolysis, however, this route is not preferred by parents and may be ineffective due to expulsion. 0.2 mg/kg nebulised midazolam has also been used recently. Rapid absorption through respiratory, nasal or buccal mucosa has the additional advantage of better acceptability and clinical efficacy.[18] It should be noted that midazolam premedication can worsen post anaesthesia cognitive function leading to elevated mean reaction time in the immediate postoperative period.[19] Satisfactory results with midazolam are seen in only 60-80% of the cases.[20]

Ketamine has 12% protein binding and significant lipid solubility. It gets extensively distributed in the body after rapid absorption when administered through IV (1-2 mg/kg), IM (3-7 mg/kg), oral (5-10 mg/kg), rectal (5 mg/kg), intranasal (6 mg/kg) or through nebulisation (2 mg/kg).[21] While oral, intranasal or nebulised ketamine is preferred, there is no ideal route for ketamine premedication. Hypersalivation, the emergence of delirium and prolonged recovery are known adverse effects.

Clonidine and dexmedetomidine have been widely used to have a "calm and cooperative child" at induction of anaesthesia, reducing anaesthetic requirements and post-operative nausea and vomiting.[22] Clonidine can be used orally (3-5 μg/kg) and intranasally (2 μg/kg). It is non-irritating to the nasal mucosa, but is erratically absorbed, and takes 1.4 to 3 hours to reach peak plasma concentration.[23]

Dexmedetomidine, with its pharmacological profile, is an ideal premedication drug in children but is yet to be approved by the US Food and Drug Administration (FDA) for use in the paediatric population.[6] Dexmedetomidine has been used orally (1 μg/kg), intranasally (1 μg/kg), and more recently through inhalation of nebulised solution of dexmedetomidine (2 μg/kg).[7]

Both the alpha 2–adrenergic agonists are associated with the potential risk of bradycardia, drymouth and nausea, rarer arrhythmias, heart block, bronchospasm and respiratory depression.[24]

Melatonin has the potential to be used as an anxiolytic preoperatively. Compared to other anxiolytics, melatonin has insignificant sedative effects. Melatonin facilitates gamma-aminobutyric acid (GABA) transmission to produce anxiolysis.[25] Despite melatonin's safety profile without significant

side effects and benefits of improved emergence behaviour, a recent systematic review did not find enough evidence for its use in the paediatric setting.[26]

Multimodal premedication techniques using melatonin have reduced anxiety and emergence delirium in children.[27]

PAEDIATRIC PREMEDICATION - ROUTES OF ADMINISTRATION OF DRUGS

When a child has an IV cannula *in situ* coming into the operating area, it is the preferred route for drug administration. Drugs like midazolam, lorazepam and propofol in sedative doses with close monitoring have been used to calm a child. It is not ideal that IV access should be solely established for the purpose of premedication and alternative routes for administration should be sought.

The IM route is convenient in many cases to sedate an agitated child. IM ketamine is frequently used in India. The external thigh, vastus lateralis muscle zone which accommodates about 5 ml of drug is recommended in children.[28] The gluteal zone carries a high risk of nerve damage in children due to reduced muscle development at that age. IM may be a safer route than IV, but complications such as nerve damage, infection, pain, and scar at the site of injection are all possibilities.[28]

Oral administration is convenient and economical and is the first choice as a route for the administration of drugs across all paediatric age groups. Oral midazolam is the most commonly used paediatric premedicant. The taste of the drug plays an important part and therefore bitter drugs like midazolam need to be laced in honey or a sugar solution. Drug absorption in young children and neonates is significantly reduced because they possess lower gastric emptying rates, lower acidity, lesser volume of GI fluids, lower surface area and intestinal blood flows.[29] The luminal pH, motility, transition time and gut morphology and variance of enzymes and transporters play a part in the variable absorption.[30] In older children, many drugs such as triclofos, clonidine, and ketamine have been tried. Ketamine and dexmedetomidine have been comrades on an eternal journey.[6]

The sublingual route produces rapid onset of action due to high blood and lymphatic flow, the absence of keratinised epithelia in that area.[28] Additionally, there is a first-pass effect. Palatability of the drug is again a factor by this route. Regulating bodies nationally and internationally are yet to approve the use of common premedicant drugs by this route in children.

Rectal administration is also a viable alternative. However, it has the risk of low or unpredictable bioavailability.[17] and is often associated with erratic absorption and unpredictable action.[1] Additionally, parents rate it to be the most unpleasant route for drug administration in children and there is a significant chance of expulsion of the administered drug.[1,31]

The nebulised pulmonary route (NPR) is a non-invasive method that allows a rapid onset of drug action and good bioavailability because of a large available area of mucosal absorption.[32] Nebulised route is better accepted and tolerated by paediatric patients than gargles or even the oral route. Unlike the oral route, the taste is not a factor and there is no risk of aspiration. However, nasal irritation may precipitate bouts of cough or sneezing.[33] Sneezing may also reduce the absorption of the drug. Droplet sizes produced by the nebulising device influence the absorption of the nebulised drug. Large droplets of size >10 μm are most likely to deposit in the mouth and throat. Drops with diameter of 5-10 μm get deposited from mouth to upper airway and those with size <5 μm are likely to get deposited in the lower airways. This may have a marked effect on the therapeutic response. One cannot assume that different drugs nebulised under identical conditions will have the same output characteristics. The nebulisation time may not be the same for dexmedetomidine, ketamine and midazolam.[18] This basic information is very important both to the researchers conducting research on nebulisation routes and to the clinicians using nebulisation routes. In preschool children, nebulised dexmedetomidine has shown more satisfactory sedation, less parental separation anxiety and emergence agitation than those who received nebulised ketamine or midazolam.[34] This route to awaits approval from regulatory bodies. Mask anxiety and mask fit are also practical issues in this age group. Only 10% of the drug that is nebulised may reach the lungs. The breathing pattern of the child affects nebulised drug delivery. When the groups of children are compared, this can act as a confounding factor.

The intranasal route ensures a rapid onset of action. An ideal drug for intranasal administration should be non-irritating and should not be associated with

burning or stinging and should not leave a bitter or poor after-taste.[17] Intranasal midazolam, dexmedetomidine and ketamine have been tried in children. Ketamine alone has not been shown to be efficacious for sedation requiring very high doses (upto 9 mg/kg). However, a combination with dexmedetomidine has shown possible utility in children. A meta-analysis has reported that intranasal dexmedetomidine provides better sedation and parental separation than other intranasal (midazolam, clonidine, ketamine) or oral premedicants (midazolam) with reduced nasal irritation.[35] In small children, application may be difficult due to small nasal apertures. Lack of cooperation and spillage loss are challenges encountered while using this route. Nasal applicators may be useful.

Transdermal drug delivery in paediatrics offers a convenient modality for drug delivery. Very few patches are supported by paediatric labelling and most are used unlicensed. Rapid changes in the skin barrier function in premature neonates and challenges in designing a delivery mechanism for paediatric population which does not carry the risk of overdose is likely to remain. Innovative mechanisms like microneedles and sonophoresis are currently under trial.[36] Microneedle arrays (MNA) have to be considered safe before they become acceptable in clinical practice as alternative modalities to traditional drug delivery techniques. Pain, local reactions like erythema, inflammation and irritation along with infection are the undesirable effects that may be encountered.[37]

Multimodal premedication using different routes of administration has been advocated by some authors. 2 μg/kg intranasal dexmedetomidine and 3 mg/kg oral ketamine when combined, facilitated easier separation from parents, intravenous cannula placement and acceptance of the face mask.[38] The two drugs when combined complement each other haemodynamically and the quick onset of action of ketamine covers up the slower onset of action of dexmedetomidine.[38]

The route of drug administration is the pathway of getting the chosen drug onto or into the body. The chosen route should ensure the speed and efficiency of drug action. To exert its effect, the drug needs to be well absorbed. For absorption, the drug must be administered in the proper manner. Therein lies the challenge of finding the best route for the premedicant drug to get into the system of a paediatric patient. This leaves one wondering as to which will be the next drug that will be tried for premedication in children, and which newer route of premedication will be tried.

Will the search never come to an end?

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