Review article

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Basics of paediatric anaesthetic pharmacology: a review based on practical challenges

Address for correspondence:
Dr. Sukhminder Jit Singh Bajwa, House No-27-A, Ratan Nagar, Tripuri, Patiala - 147001, Punjab, India.
Email: sukhminder_bajwa2001@yahoo.com

Sukhminder Jit Singh Bajwa[1], Smriti Anand[1], Hemant Gupta[2]

[1]Department of Anesthesiology and Intensive Care, Gian Sagar Medical College and Hospital, Ram Nagar, Banur, Punjab, India

[2]Department of Paediatrics, Civil Hospital, Solan, Himachal Pradesh, India

ABSTRACT

Pediatric patients have always been special patients, in fact the most challenging ones for the attending physicians. These tiny tots apart from being fun to deal with can be quite enigmatic and sometimes a nightmare for the healthcare provider. There exists definitive anatomical, physiological, developmental and pharmacological differences between the adult and pediatric patients and a failure to comprehend this can result in devastating albeit avoidable morbidity and mortality. Also occurrence of pharmacodynamic and pharmacokinetic differences between the adult and pediatric patients makes the safe drug therapy of these patients quite intriguing. However during the process of dealing with the pediatric patients one gains new insights which influence their overall management. The purpose of the present review is therefore to highlight pediatric pharmacology and the need of blending our practical experiences as regards to the pediatric drug therapy with the current available knowledge and literature so as to improvise the pediatric care delivery significantly by the attending physicians and the anesthesiologists.

Key words: Drugs, Paediatric patients, Pharmacodynamics, Pharmacokinetics

INTRODUCTION

Pediatric patients range from birth up to 18 years of age (Table 1) and it would not be appropriate to call them young adults. Differences related to pharmacokinetic and pharmacodynamic profiles amongst different pediatric age groups coupled with therapeutic challenges in the management of critically ill patients, makes pediatric pharmacotherapy quite challenging. Therefore it is of utmost importance to have a thorough knowledge of pharmacokinetic and pharmacodynamic principles in these patients to prevent mishaps in drug dosing. Moreover associated pathological and physiological factors can greatly alter drug handling.

Table 1: Classification of pediatric patients based on age

Terminology	Age group
Preterm newborn	Born before term gestation
Term newborn	(0-27 days)
Infants	(28 days-1 year)
Toddlers	(1-3 years)
Children	(4-10 years)
Adolescents	(1o-19 years)

PAEDIATRIC PHARMACOKINETICS

Pharmacokinetics is defined as the study of time course of drug absorption, distribution, metabolism and excretion. (Table 2) Clinical pharmacokinetics on the other hand is the application of pharmacokinetic principles to safe and effective therapeutic management of drugs in individual patients[1]. There exists a definite deviation in paediatric and adult pharmacokinetic variables, a thorough understanding of which is essential.

Absorption

Drug absorption is largely determined by the route of administration namely oral, rectal, mucosal, via the skin, intravenous and intramuscular.

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Oral route though the preferred route in children, is greatly influenced by the pH and volume of gastric secretions which attains adult values by two years of age as well as by the gastric emptying time the adult value of which is achieved by six to eight months of age[2]. These factors can significantly affect therapeutic plasma concentrations and requires dose adjustments.

Mucosal administration (buccal/nasal) is another time tested route of drug administration, the bioavailability via this route being higher than that in adults. Practical experience has shown that this route can sometimes become a reliable and lifesaving route in certain conditions like active seizures [3] where it can be used even in the prehospital setting. This route has also been explored for the therapeutic administration of desmopressin in children with enuresis [4].

Alternative route practiced in children is the rectal route eg. paracetamol and rectal suppositories, however this route is not reliable except rectal valproate where clinical experience has proved it to be beneficial in refractory seizures[5] as also rectal diazepam for the home management of seizures[6].

Skin though a widely used route in adults can be hazardous especially in neonates as their skin is very thin leading to enhanced drug absorption with resultant toxicity[7]. This has been seen with percutaneous administration of drugs like lidocaine and corticosteroids[8]. Also any factor causing increased vascularity of skin e.g., fever will increase its uptake. However percutaneous theophylline gel has been used for the treatment of apnoea in newborns[9].

Intravenous route is the preferred route of drug delivery in critically ill children (because of decreased gut perfusion) and those recovering from the effects of anesthesia (due to decreased gut function). Intramuscular route is painful for the child and should ideally be avoided. Sometimes non-traditional routes of drug delivery need to be practiced for instance the intraosseous route for difficult intravenous access, endotracheal route for administering atropine, epinephrine, naloxone or lignocaine with proper dose adjustments.

Distribution

The drug distribution is directly related to the lipid solubility and inversely related to the protein binding. Premature and full term neonates have greater proportion of body weight in the form of water (90% and75% respectively) and they have been rightly called as "little bags of water". Consequently the volume of distribution of water soluble drugs is higher in neonates. Deficiency in muscle and fat content in neonates results in prolonged clinical effect of the drugs like thiopentone which redistribute in muscle and fat. Also the concentration of both albumin and alpha$_1$ acid glycoprotein which bind to the acidic and basic drugs respectively is decreased in neonates thereby requiring great caution when administering drugs like phenytoin, theophylline and certain antibiotics which are otherwise highly protein bound[10,11]. Immaturity of blood brain barrier in neonates also increases the risk of toxicity of otherwise lipid insoluble drugs like morphine.

Metabolism

Liver is the principle site for the synthesis of drug metabolizing enzymes. This biological machinery is however deficient in neonates reaching adult values by one year of age and manifesting as slower rate of drug metabolism[12].

Excretion

This is largely the domain of the kidneys attaining maturity by two years of age. So the drugs primarily excreted via kidneys in neonates will exert prolonged half life.

Table 2: Salient features of pediatric pharmacokinetics

- *Delayed gastric emptying time in neonates reaching adult values by 6-8 months.*
- *Decreased gastric acidity in neonates reaching adult values by 2 years of age.*
- *Oral route for drug administration is the preferred route in children and intravenous route is preferred in critically ill children.*
- *Volume of distribution of water soluble drugs is increased in neonates and infants because of increase in total body water resulting in higher doses in mg/kg to attain therapeutic levels.*
- *Concentration of drug binding proteins is decreased in neonates attaining adult values by 10-12 months of age.*
- *Hepatic enzymatic machinery is deficient in neonates reaching adult values by one year of age.*
- *Drug elimination is primarily by kidneys which attain functional maturity by 2 years of age.*

PAEDIATRIC PHARMACODYNAMICS

Pharmacodynamics deals with the reactions between drugs and living systems. The child's response to drugs is affected by maturity of the targeted receptor, immature

transduction of drug-receptor interaction into intracellular messages as well as by the incapability of the immature tissue or the organ to respond to the message. These pharmacodynamic alterations influence not only the therapeutic action but also the adverse reactions. An example is the presence of immature gamma-aminobutyric acid GABA receptors which exhibit excitatory rather than inhibitory response with benzodiazepines like midazolam in preterm and newborn infants manifesting as paradoxical seizures[13]. Also there may be age related variation in the site or function of receptors eg. mu opioid receptor (present in pons and medulla of the newborns) as elucidated by the increased susceptibility to the respiratory depressant effect of opioids in the experimental rats[14].

PHARMACOGENETICS

Pharmacogenetics which deals with the effect of genetic factors on reactions to drugs, has revolutionized personalized medicine[15]. Incorporation of pharmacogenomics in clinical trials has tremendously improvised management of pediatric acute lymphoblastic leukemia[16]. It has also optimized management of asthma in pediatric patients[17].

Much of the studies so far have been directed on the pharmacokinetic variables. However how the drug exerts its overall effect is a complex interplay of the pharmacokinetic and pharmacodynamic principles influenced by the physiological and pathological parameters as well as pharmacogenomics and modified from time to time by the vast clinical experience.

ANTIBIOTICS

Antibiotics are the commonest and most widely prescribed therapeutic medications to the children. There are certain pharmacokinetic and pharmacodynamic considerations to be taken care of while administering antibiotics to the children:

- ***Calculation of the therapeutic dosages-*** Most of the pediatric drug dosing of the antibiotics is done as per the body weight in contrast to the antineoplastic agents where body surface area is employed for computing the drug dose. Also the gestational age has to be taken into consideration especially so in newborns for drug dosing. This is particularly important in the pharmacokinetics of gentamycin in newborns[18].

- ***Hepatic and renal immaturity at birth-*** Increased levels of unconjugated bilirubin has been seen in newborns due to immaturity of hepatic enzymes[19]. Antibacterial agents like sulphonamides and ceftriaxone by displacing bilirubin from albumin can elevate the levels of unconjugated bilirubin which can lead to kernicterus. So these drugs should ideally be avoided in children. Also immaturity of the renal function necessitates caution while prescribing aminoglycosides and β-lactams.

- ***Underlying disease pathology*** also alters drug dosing and disposition. For instance patients with cystic fibrosis have large volumes of distribution for certain antibiotics like aminoglycosides and beta lactam antibiotics requiring increase dosages in per kilogram body weight to the extent of 20-30% to attain the therapeutic concentrations[20]. Also there is increased clearance of drugs in these patients.

- ***Concomitantly administered drugs-*** Polypharmacy with antibiotics can result in drug interactions which can manifest as therapeutic advantage or treatment failure. [21] An example of the former is the use of sulfamethoxazole and trimethoprim combination to treat pneumocystis pneumonia, ottitis media and urinary tract infections in children. Also antibiotics when given in combination with warfarin cause an increase in International Normalized Ratio (INR) in children[22].

- ***Drug toxicities-*** Diarrhea is the most common side effect reported with antibiotic therapy in children. Other observed toxic effects are neurotoxicity with cephalosporins[23], bone dysfunction with tetracyclines[24], gray baby syndrome with chloramphenicol, immunosuppression, allergic manifestations ototoxicity and nephrotoxicity by aminoglycosides and antibiotic resistance.

- ***Physiological factors-*** Children are in a continuous phase of growth and development and any drug interfering with this process has to be avoided. A classic example of this is that of the tetracyclines which when used below the age of 10 years causes bone dysfunction and teeth discolouration[24].

- ***Pathological factors*** like obesity can markedly alter drug dosing e.g., vancomycin, a moderately fat soluble drug when administered as per ideal body weight can result in under treatment. So dose calculation using total body weight is recommended when calculating the dose of vancomycin in children[25]. Similarly the dosing of aminoglycosides, a water soluble drug, when done in accordance with the total body weight in obese children will result in sub therapeutic levels,

hence employing adjusted body weight (using total body weight and ideal body weight) is recommended for dosing of aminoglycosides in obese children[26].

- ***Route of administration***- Oral route remains the preferred route in children especially syrup formulations. Intravenous antibiotics are given in critically ill children. Intramuscular route being painful should ideally be deferred. A rectal suppository of antibiotics is another route explored in children especially for beta lactams and antibiotics [27].

ANAESTHETIC DRUGS

- ***Inhalational anesthetic agents***

Because of the increased alveolar ventilation and enhanced cardiac output, the uptake and excretion of the inhalational anesthetic agents is rapid in infants and children. The Minimum Alveolar Concentration (MAC) of inhalational anesthetics especially to induce anesthesia than to inhibit cardio-respiratory system is also higher in infants than in older children and adults thereby narrowing their safety margin. Sevoflurane is the anesthetic agent of choice in children because of its rapid uptake and recovery. However halothane, isoflurane and desflurane have also been used.

- ***Intravenous anesthetic agents***

Propofol: There is increased requirement of induction dose of propofol in children because of larger central volume of distribution and higher clearance rate. However its safety in children <2years of age is doubtful, particularly in preterms and neonates [28]. Also prolonged propofol infusions when administered > 48 hours at doses >5mg/kg/hr in critically ill pediatric patients results in propofol infusion syndrome which manifests as metabolic acidosis, rhabdomyolysis, cardiac and renal failure[29].

Sodium thiopentone: Sodium thiopentone 2.5% in a dose of 5-6mg/kg induces anesthesia in healthy children. Redistribution into muscle and fat terminates its effect. Dose adjustments are therefore required in undernourished and in neonates who have reduced fat stores (2-4 mg/kg). Intravenous induction dose is 5-7 mg/kg in children in contrast to 3-5 mg/kg in adults[30]. Rectal sodium thiopentone has also been used in pediatric patients for sedation purposes[31].

Ketamine- Ketamine produces profound analgesia and dissociative anesthesia. In neonates the clearance is decreased but the volume of distribution is enhanced[32] thereby increasing the doses required in neonates to more than fourfold than in a 6 year old child[33]. Also the bioavailability after intramuscular administration is increased[34]. Ketamine has been used in children for premedication as well as for inducing anesthesia and sedation. All routes have been explored for its administration i.e., oral, nasal, rectal and caudal[35], however preservative free formulations are preferable for nasal as well caudal routes because of the theoretical risk of neurotoxicity with the preservative[36]. The most common side effect reported in children is Postoperative Nausea and Vomiting (PONV) the incidence of which can reach upto 33%[37] and postoperative hallucinations[38] which in turn can be prevented with prior administration of benzodiazepines[39].

- *Muscle relaxants*- In adults the neuromuscular junction comprises of five sub units two α and one β, δ and ε sub unit while in preterms the ε sub unit is replaced by γ sub unit[40]. Intense neuromuscular blockade is seen in neonates than in children and dose requirement is also decreased because of immaturity of neuromuscular junction[41]. Onset of action of neuromuscular blocking drugs in neonates is more rapid than in adults. Clearance which is via renal (alcuronium) and/or hepatic pathways (pancuronium, rocuronium, vecuronium) is markedly reduced in neonates[42]. On the other hand clearance of succinylcholine which is hydrolyzed by butyrlcholinesterase also decreases with age[43]. However the clearance of atracurium and cisatracurium is enhanced in neonates.

Succinylcholine is the only depolarizing muscle relaxant used in children. It can be given intravenous, intramuscular as well as sublingual or intralingual injection. Prolonged infusions can result in tachyphylaxsis (3mg/kg) and phase II block (4mg/kg)[44]. Metabolism by pseudo cholinesterase enzyme results in succinylmonocholine derivative. There are five alleles which encode for the cholinesterase enzyme and children who are homozygous for the silent gene have prolonged duration of action with scoline upto 6-8 hours. The incidence of bradycardia and asystole after a single dose of succinylcholine is significant in pediatric patients which necessitates the use of vagolytic agent like atropine. Also hyperkalemic cardiac arrest after a single intravenous dose of succinylcholine has been reported in children of burns, sepsis, neuromuscular diseases and neuropathies because of proliferation of extrajunctional receptors, immature γ receptors and nicotinic acetycholine receptors so that potassium is released from entire muscle during depolarization[45]. Also succinylcholine with halothane can trigger malignant hyperthermia in genetically susceptible children[46].

Infants are more sensitive to the action of vecuronium reaching adult values during adolescence[47]. Rocuronium another non depolarizing neuromuscular blocking agent has slightly faster onset in infants than older children with 600µg/kg dose. It can also be given via intramuscular route. Pancuronium is used for cardiac and high risk procedures in infants and children and is associated with long elimination $t_{1/2.}$

To antagonize neuromuscular blockade neostigmine with anticholinergic combination is given. The volume of distribution of neostigmine in children is the same as adults; however elimination half life is less.

Antibiotics like aminoglycosides especially gentamycin and tobramycin prolong the neuromuscular blockade and doses have to be accordingly modified.

- *Opioids*- Morphine is frequently used in pediatric patients. It is poorly lipid soluble drug. Increased sensitivity to morphine is seen in neonates because of immaturity of blood brain barrier BBB, altered regional blood flow and increased uptake[48]. It is also associated with nausea and vomiting.

Fentanyl is the most commonly used opioid anesthetic in children and has a rapid onset and shorter duration of action in children. It can be given via intravenous, intramuscular, oral and transdermal routes.

Tramadol is a weak opioid used for moderate to severe pain in children especially after tonsillectomy in children with obstructive sleep apnoea[49]. It is also given caudally.

- *Benzodiazepines* Midazolam is the only benzodiazepine approved by FDA for use in children, commonly used for sedation, anxiolysis as well as induction of anesthesia. It can be administered orally, nasally, intramuscularly, intravenously and rectally[50].

Diazepam has been used for sedation, amnesia as well as antiepileptic agent and can be administered intravenously, intramuscularly as well as rectally. It has decreased half life in adolescents and children.

- *Chloral hydrate*- It is commonly used for sedation purposes in non painful conditions. Its use is curtailed in neonates because of its interference with binding of bilirubin with albumin with consequent accumulation of toxic metabolites manifesting as metabolic acidosis, renal failure and hypotonia[51].

- *Local anesthetic agents*- Regional anesthesia is routinely practiced in pediatric patients for sedation, analgesia as well as anesthesia[52,53]. Metabolism and clearance of amide local anesthetic agents is diminished in neonates attaining maturity at 3-8 months[54]. Amino esters which exhibit esterase metabolism are rapidly cleared. Also increased plasma concentration of α_1 acid glycoprotein seen in neonates results in elevated levels of unbound fraction of bupivacaine. Lignocaine, chlorprocaine, bupivacaine, articaine, levobupivacaine and ropivacaine have all been used[55,56]. Prilocaine is associated with methemoglobinemia and its use is therefore restricted to topical application of EMLA cream (a euctetic mixture of lignocaine with prilocaine).

- *Adjuvants*- Various adjuvants have revolutionized the practice of anaesthesia as they not only decrease the dose of local and general anaesthetics but provide stable haemodynamic environment besides prolonging the post-operative analgesia with smoother recovery[57,58]. Though not used extensively in paediatric population, dexmedetomidine has been successfully used in adults for attenuation of stress response during induction and intubation as well as for prevention of shivering in post-operative period[59,60].

Table 3: Dosage regime for the commonly used agents in pediatric anesthesia

DRUG	DOSAGE	USES	SIDE-EFFECTS
Sodium thiopentone	For induction- < 1 month 3-4mg/kg i.v < 1 year 5-8 mg/kg i.v 1-12 years 5-6 mg/kg i.v >12 years 3-5 mg/kg i.v	-Induction and maintenance of anesthesia -In seizures	-Respiratory depression -Myocardial depression -Laryngospasm -Anaphylaxis

Propofol	2.5 mg/kg i.v for induction. 0.125-0.3mg/kg/min for maintenance	-Induction of anesthesia (≥ 3 years) -Maintenance of anesthesia (≥ 2 months of age)	-Bradycardia and asystole. -Propofol infusion syndrome. -Anaphylaxis
Ketamine	For induction- 4-5mg/kg i.m 1-2mg/kg i.v For sedation- 6-10mg/kg per oral to be mixed with 0.2-0.3ml/kg beverage to be given 30 minutes before procedure. 5-10µg/kg/min to be titrated.	-Balanced anesthesia by combination with other agents like oxygen and nitrous oxide.	-Tachycardia and hypertension -Respiratory depression -Seizures -Increased intraocular pressure
Muscle Relaxants			
Succinylcholine	To facilitate intubation- 2mg/kg i.v for infants and small children. 1mg/kg i.v for older children and adolescents. 3-4mg/kg i.m	-Muscle relaxation -Laryngospasm	-Bradycardia especially with the second dose -Tachycardia -Hypotension, hypertension -Hyperkalemia -Malignant hyperthermia
Vecuronium	1-10 years of age- 0.1mg/kg i.v Or 0.05-0.07mg/kg/hr continuous infusion Neonates- 0.1mg/kg i.v loading dose and 0.03-0.15mg/kg i.v maintenance dose 7 weeks-1 year old- 0.08-0.1mg/kg i.v loading dose and 0.05-0.1mg/kg i.v maintenance dose.	-To facilitate tracheal intubation and intraoperative muscle relaxation. -Mechanical ventilation	-Skeletal muscle paralysis -Apnoea -Hypersensitivity reactions
Rocuronium	0.45-0.6mg/kg i.v	-To facilitate tracheal intubation and muscle relaxation. -Mechanical ventilation.	-Hypotension, hypertension -Dose related tachycardia -Hypersensitivity reaction
Pancuronium	Contraindicated in neonates and preterms because it contains the preservative benzyl alcohol. For >1month old- 0.04 -0.1 mg/kg i.v loading dose and 0.015-0.1mg/kg i.v maintenance dose.	-To facilitate tracheal intubation and muscle relaxation. -Mechanical ventilation	-Tachycardia -Hypertension -Histamine release

Atracurium	Contraindicated in neonates. 1 month-2 years age- 0.3-0.4mg/kg i.v >2 years – 0.4-0.5mg/kg i.v loading dose followed by 0.08-0.1mg/kg maintenance dose.	Endotracheal intubation and mechanical ventilation.	 -Hypotension -Histamine release
Opioids			
Morphine	0.05-0.1mg/kg i.v over 3-5 minutes. May repeat every 5-10 minutes at half the dose till the desired effect is achieved or 0.1mg/kg i.m every 3-4 hours.	For sedation and analgesia.	-Respiratory depression -Bradycardia - Biliary spasm
Fentanyl	continous sedation and analgesia 0.5-2µg/kg/hr -Adjunct anesthesia <2years:contraindicated ≥2 years-2-3µg/kg i.v/ i.m -For premedication 1-12 years: 0.5-2µg/kg i.v given 3 minutes before the procedure. >12 years of age 0.5-2µg/kg maximum 50µg/dose to be given 3 minutes prior to procedure.	Premedication, sedation, analgesia and anesthesia.	-Anorexia, nausea, vomiting -hypoventilation -Influenza like symptoms
Benzodiazepines			
Midazolam	Sedation: 500-750µg/kg per oral (maximum 20 mg) 20-30 minutes prior to procedure or 100-150µg/kg i.m. For intravenous sedation: <6 months-50µg/kg i.v over 2-3 minutes and titrate. 6 months to 6 years- 50-100µg/kg i.v over 2-3 minutes, repeat every 2-3 minutes and titrate (maximum 6mg). 6-12 years- 25-50µg/kg i.v over 2-3 minutes, repeat every 2-3 minutes and titrate (maximum 10mg). -For anesthesia: avoided in neonates Loading dose 50-100µg/kg i.v over 2-3 minutes. Continuous infusion: 1-2µg/kg/min.	Sedation and anesthesia.	-Apnoea -Nausea/ vomiting -Paradoxical reaction
Diazepam	0.04-0.3mg/kg /dose i.v for sedation to perform diagnostic and therapeutic procedures.	Seizures, anxiety, tetanus and muscle spasm.	-Respiratory depression -Arrhythmias -Muscle weakness

NON-PHARMACOLOGICAL FACTORS AFFECTING DRUG DOSING IN CHILDREN

Besides pharmacological variables numerous non-pharmacological factors also influence drug administration in pediatric population. These include but are not limited to obesity, underlying disease pathology to be treated, gender, age, associated co-morbidities like myopathies, neuropathies, burns, interactions with concomitantly administered drugs. The risk and safety concerns in anaesthesia practice should always be the priority while administering anaesthetic drugs[61].

DRUG DISASTERS IN CHILDREN

- Literature is replete with evidence of tragedy with elixir of sulphanilamide in which diethylene alcohol was used as solvent resulted in death of 107 Americans mainly children in 1937[62].
- Benzyl alcohol was incriminated for neonatal gasping syndrome resulting in death in 16 premature babies way back in 1982, when it was used in flush to keep intravenous lines patent. It manifested as acidosis, respiratory and circulatory failure, seizures and death[63].

Cautions to be exercised in drug dosing

Clinical experience gathered over the years has taught that to avoid drug mishaps in children following considerations need to be pondered and highlighted:

- The instructions during pediatric dosing should be clear and comprehensible. A very common error which can result in mishaps in the form of morbidity and mortality is the wrong interpretation and implementation of the instructions especially by untrained staff. E.g., administration of pavulon (pancuronium) instead of perinorm (metaclopromide) in a child in our setup.
- Avoiding of abbreviations during documentation and prescribing.
- Indication regarding route of administration should be clear e.g., adrenaline for nebulization can be accidently administered intravenously if instructions are not clear.
- Prescribing the correct dose keeping in mind the physiology, pathology and associated co-morbidity apart from pharmacokinetic and pharmacodynamic profile.
- Counseling and caution regarding the expected side effects of the administered drug should be highlighted.
- All the medications should be kept away from the reach of children to prevent accidental intake as well as over dosage of the drug.
- While administering liquid formulations, plausible instructions regarding the dose must be given eg. There should not be any confusion regarding teaspoon and tablespoon.
- Apart from the trade name the chemical name of the drug to be administered should also be written in the prescription to avoid confusion if any.

CONCLUSION

Paediatric drug dosing undoubtedly remains most intimidating and challenging to the attending clinicians. Variations in the pharmacodynamic and pharmacokinetic variables make the pharmacology of the children quite unique from those of adults. Paediatric patients comprises of vast group including preterms, neonates, infants and adolescents and they are definitely not young adults, the inferences therefore drawn from the adult pharmacology cannot be extrapolated on them. Various pathological, physiological, pharmacogenetic factors as well as clinical experiences gathered over the years influence drug dosing which has to be always kept in mind by the attending clinicians[64].

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REFERENCES

1. Thomson AH. Introduction to clinical pharmacokinetics. Pediatric and Perinatal Drug Therapy. 2000; 4(1):3–11 Crossref
2. Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants. Age-related differences and therapeutic implications. Clin Pharmacokinet. 1980; 5(6):485–527. Crossref PMid:7002417
3. Javadzadeh M, Hashemieh M and Saneifard H. Intranasal midazolam compared with intravenous diazepam in patients suffering from acute seizure. A randomized clinical trial. Iran J Pediatr. Mar 2012; 22(1):1–8. PMid:23056852 PMCid:PMC3448208
4. Fritz G, Rockney R, Bernet W, Arnold V, Beitchman J, Benson RS, et al. Practice parameter for the assessment and treatment of children and adolescents with enuresis. J Am Acad Child Adolesc Psychiatry. 2004; 43(12):1540–50. Crossref PMid:15564822

5. Mahmoudian T, Najafian M. Comparing the effect of intravenous midazolam with rectal sodium valproate in controlling of children with refractory status epilepticus. J Res Med Sci . 2006; 11(1):1–5.
6. O'Dell C, Shinnar S, Ballaban-Gil KR, Hornick M, Sigalova M, Kang H, et al. Rectal diazepam gel in the home management of seizures in children. Pediatr Neurol. 2005; 33(3):166–72. Crossref PMid:16139730
7. Strolin Benedetti M, Baltes EL. Drug metabolism and disposition in children. Fundam. Clin. Pharmacol. 2003; 17:281–99 Crossref PMid:12803568
8. Kearns GL: Impact of developmental pharmacology on pediatric study design: Overcoming the challenges. J Allergy Clin Immunol. 2000; 106(3 suppl):S128–38. Crossref PMid:10984393
9. Cartwright RG, Cartlidge PH, Rutter N, Melia CD, Davis SS. Transdermal delivery of theophylline to premature infants using a hydrogel disc system. Br J Clin Pharmacol. 1990; 29(5):533–9. Crossref PMid:2350529 PMCid:PMC1380152
10. Benedetti MS, Whomsley R, Baltes EL. Differences in absorption, distribution, metabolism and excretion of xenobiotics between the pediatric and adult populations. Expert Opin Drug Metab Toxicol. 2005; 1:447–71. Crossref PMid:16863455
11. Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part I). Clin Pharmacokinet. 1988; 14(4):189–216. Crossref PMid:3292100
12. Anderson GD, Lynn AM. Optimizing pediatric dosing: A developmental pharmacologic approach. Pharmacotherapy. 2009; 29:680–90. Crossref PMid:19476420
13. Adams MM, Hahn JS, Benitz WE. A series of neonatal patients with paradoxical seizure like reactions to bolus intravenous injections of midazolam. Pediatric Research. 1997; 41:134. Crossref1 Crossref2
14. Thornton SR, Compton DR, Smith FL. Ontogeny of mu opioid agonist anti-nociception in postnatal rats. Brain Res Dev Brain Res. 1998; 105:269–76. Crossref
15. Bhaskar SB, Bajwa SS. Pharmaco genomics and anaesthesia: Mysteries, correlations and facts. Indian J Anaesth. 2013; 57:336–7. Crossref PMid:24163445 PMCid:PMC3800323
16. Meeker ND, Yang JJ, Sciffman JD. Pharmacogenomics of pediatric acute lymphoblastic leukemia. Expert Opin Pharmacother. 2010; 11(10):1621–32. Crossref PMid:20429672
17. Kondo N, Matsui E, Nishimura A and Kaneko H. Pharmacogenetics of asthma in children. Allergy Asthma Immunol Res. 2010; 2(1):14–9. Crossref PMid:20224673 PMCid:PMC2831608
18. Izquierdo M, Lanao JM, Jiminez NV, Dominguez-Gid A. Population pharmacokinetics of gentamycin in premature infants. Therapeutic Drug Monitoring. 1992; 14:177–83. Crossref PMid:1412601
19. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: Part I. Clini Pharmacokinet. 2002; 41: 959–98. Crossref PMid:12222995
20. Kirkby S, Novak K, McCoy K. Update on antibiotics for infection control in cystic fibrosis. Expert Rev Anti Infect Ther. 2009; 7(8):967–80. Crossref PMid:19803706
21. Sehgal V, Bajwa SS, Sehgal R, Bajaj A, Khaira U, Kresse V. Polypharmacy and potentially inappropriate medication use as the precipitating factor in readmissions to the hospital. J Fam Med Primary Care. 2013; 2:194–9. Crossref PMid:24479078 PMCid:PMC3894035
22. Grill MF, Maganti R. Cephalosporin induced neurotoxicity: Clinical manifestations, potential pathogenic mechanisms, and the roleofelecto encephalogram monitoring. Ann Pharmacother. 2008; 42(12): 1843–50. Crossref PMid:19033476
23. Johnson MC, Wood M, Vaughn V, Cowan L, Sharkey AM. Interaction of antibiotics and warfarin in pediatric cardiology patients. Pediatr Cardiol. 2005; 26(5):589–92. Crossref PMid:16235009
24. Reed MD, Besunder JB. Developmental pharmacology: Ontogenic basis of drug disposition. Pediatr Clin North Am. 1989; 36:1053–74. Crossref
25. Blouin RA, Bauer LA, Miller DD, Record KE, Griffin WO. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents. Chemother. 1982; 21:575–80. Crossref PMid:7081978 PMCid:PMC181944
26. Schwartz SN, Pazin GJ, Lyon JA, Ho M, Pascille AW. A controlled investigation of the pharmacokinetics of gentamicin and tobramycin in obese subjects. J Infect Dis. 1978; 138:499–505. Crossref PMid:712111
27. De Boer AG, Moolenaar F, de Leede J, Breimer DD. Rectal drug administration: Clinical pharmacokinetic considerations. Clinical Pharmacokinetics. 1982; 7:285–311. Crossref PMid:6126289
28. Allegaert K, De Hoon J, Naulaers G, Van De Velde M. Neonatal clinical pharmacology: Recent observations of relevance for anesthesiologists. Acta Anaesthesiol Belg. 2008; 59:283–8. PMid:19235528
29. Vaslie B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med. 2003; 29(9):1417–25. Crossref PMid:12904852
30. Rusy L. Pediatric Anesthesia Review. 1998; 8(2):1-8.
31. Burcart GJ, White TJ III, Siegle RL, Jabbour JT, Ramney DR. Rectal thiopental versus an intramuscular cocktail for sedating children before CT. Am J Hosp Pharm. 1980; 37:222–4.
32. Cook DR, Davis PJ. Pediatric anesthesia pharmacology. In: Lake CL, editor. Pediatric cardiac anesth. 3rd ed. Stanford, Conn: Appleton and Lange; 1998. p. 123–64.
33. Lockhar CH, Nelson WL. The relationship of ketamine requirement to age in pediatric patients. Anesthesiology. 1974; 40:507–8. Crossref
34. Grant IS, Nimmo WS, McNiol LR, Clements JA. Ketamine disposition in children and adults. Br J Anaesth. 1983; 55:1107–11. Crossref PMid:6639827
35. Schnabel A, Poepping DM, Kranke P, Zahn PK, Pogatzki-Zahn EM. Efficacy and adverse effects of ketamine with lidocaine as an additive for pediatric caudal anesth: A quantative systemic view of randomized control trials. Br J Anaesth. 2011; 107:601–11. Crossref PMid:21846679
36. Malinovsky JM, Lepage JY, Cozian A, et al. Is ketamine or its preservative responsible for neurotoxicity in rabbit? Anesthesiology. 1993; 78:109–15. Crossref PMid:8424543
37. Reich DL,Silvary G. Ketamine: An update on first 25 years of clinical experience. Can J Anaesth. 1989; 36:186–97. Crossref PMid:2650898
38. Lin C, Duricux ME. Ketamine and kids an update. Pediatr Anaesth. 2005; 15:91–7. Crossref PMid:15675923
39. Bajwa SJ, Bajwa SK, Kaur J. Comparison of two drug combinations in total intravenous anesthesia: Propofol-ketamine and propofol-fentanyl. Saudi J Anaesth. 2010; 4:72–9. Crossref PMid:20927266 PMCid:PMC2945518
40. Goudsouzian NG, Liu LM, Cole CS. Comparison of equipotent doses of non-depolarizing muscle relaxants in children. Anesth Analg. 1981; 60:862–6. Crossref PMid:6274233
41. Fisher DM, Miller RD. Neuromuscular effects of vecuronium (ORGNC45) in infants and children during Nitrous oxide halothane anesthesia. Anesthesiology. 1984; 58:519–23. Crossref
42. Wierda JM, Meretoza OA, Taivaren T, Proost JH. Pharmacokinetics and pharmacodynamic modeling of rocuronium in infants and children. Br J Anaesth. 1997; 78:690–5. Crossref PMid:9215021
43. Cook DR, Wingard LB, Taylor FM. Pharmacokinetics of succinylcholine in infants, children and adults. Clin Pharmacol Ther. 1976; 20:493–8. Crossref PMid:975721
44. Goudsouzian NG, Liu M. The neuromuscular response of infants to a continuous infusion of succinylcholine. Anaesthesiology. 1984; 60:97–101. Crossref
45. Martyn JA, Richtsfeld M. Succinylcholine induced hyperkalemia in acquired pathological states: Etiological factors and molecular mechanisms. Anaesthesiology. 2006; 104:158–69. Crossref
46. Hopkins PM. Malignant hyperthermia pharmacology of triggering. Br J Anaesth. 2011 Jul; 107(1):48–56. Crossref PMid:21624965
47. Mereloja DA, Writavuorik, Neuvonen PJ. Age dependence of dose response curve of vecuronium in pediatric patients during balanced anaesthesia. Anesth Analg. 1988; 67:21–6.
48. Kupferberg HJ, Way HJ. Pharmacologic basis for the increased sensitivity of the newborn to morphine. J Phamacol Exp Ther. 1960; 130:285–93.
49. Hullett BJ, Chambers NA, Pascol EM, Johnson C. Tramadol versus morphine during adenotonsillectomy for obstructive sleep apnoea in children. Pediatr Anaesth. 2006; 16:648–53. Crossref PMid:16719881
50. Alderson PJ, Lerman J. Oral premedication for pediatric ambulatory anaesthesia: A comparision of midazolam and ketamine. Can J Anaesth. 1994; 41:221–6. Crossref PMid:8187256

51. Reimche LD, Sankarank K, Hindmarsh KW, et al. Chloral hydrate sedation in neonates and infants-clinical and pharmacological considerations. Dev Pharmacol Ther. 1989; 12:57–64. PMid:2714158
52. Panda A, Bajwa S, Sen S, Parmar SS. Penile block for paediatric urological surgery: A comparative evaluation with general anaesthesia. Indian J Urol. 2011; 27:457–64. Crossref PMid:22279309 PMCid:PMC3263211
53. Bajwa SJ, Kaur J, Bajwa SK, Bakshi G, Singh K, Panda A. Caudal ropivacaine-clonidine: A better post-operative analgesic approach. Indian J Anaesth. 2010; 54:226–30. Crossref PMid:20885869 PMCid:PMC2933481
54. Gunter JB. Benefits and risks of local anesthetics in infants and children. Pediatr Drugs. 2002, 4(10):649–72. Crossref
55. Bajwa SS, Kaur J. Clinical profile of levobupivacaine in regional anesthesia: A systematic review. J Anaesthesiol Clin Pharmacol. 2013; 29:530–9. Crossref PMid:24249993 PMCid:PMC3819850
56. Bajwa SS, Jindal R. Use of Articaine in loco-regional anesthesia for day care surgical procedures. J Anaesthesiol Clin Pharmacol. 2012; 28:444–50. Crossref PMid:23225921 PMCid:PMC3511938
57. Bajwa SJ, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, Kulshrestha A, Singh A, Parmar S S, Singh A, Goraya S. Dexmedetomidine and clonidine in epidural anaesthesia: A comparative evaluation. Indian J Anaesth. 2011; 55:116–21. Crossref PMid:21712865 PMCid:PMC3106381
58. Bajwa SJ, Kulshrestha A. Dexmedetomidine: An adjuvant making large inroads into clinical practice. Ann Med Health Sci Res. 2013; 3:475–83. Crossref PMid:24379995 PMCid:PMC3868110
59. Bajwa SJ, Gupta S, Kaur J, Singh A, Parmar SS. Reduction in the incidence of shivering with perioperative dexmedetomidine: A randomized prospective study. J Anaesthesiol Clin Pharmacol. 2012; 28:86–91. Crossref PMid:22345953 PMCid:PMC3275980
60. Bajwa SS, Kaur J, Singh A, Parmar S S, Singh G, Kulshrestha A, Gupta S, Sharma V, Panda A. Attenuation of pressor response and dose sparing of opioids and anaesthetics with pre-operative dexmedetomidine. Indian J Anaesth. 2012; 56:123–8. Crossref PMid:22701201 PMCid:PMC3371485
61. Bajwa SJ, Kaur J. Risk and safety concerns in anesthesiology practice: The present perspective. Anesth Essays Res. 2012; 6:14–20. Crossref PMid:25885495 PMCid:PMC4173431
62. Ballentine C. Taste of raspberries, taste of death the 1937 elixir sulfanilamide incident. FDA consumer magazine; 1991.
63. Centres for Disease Control and Prevention. Neonatal deaths associated with the use of benzyl alcohol-United States MMWR. Morb Mortal Wkly Rep. 1982; 31(22):290–1. PMid:6810084
64. Bajwa SS, Kalra S. Logical empiricism in anesthesia: A step forward in modern day clinical practice. J Anaesthesiol Clin Pharmacol. 2013; 29:160–1. PMid:23878433 PMCid:PMC3713659