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REVIEW ARTICLE

Challenges Associated with Route of Administration in Neonatal Drug Delivery

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Abstract The administration of drugs to neonates poses significant challenges. The aim of this review was to provide insight into some of these challenges and resolutions that may be encountered with several of the most commonly used routes of administration and dosage forms in neonatal care, including oral, parenteral, transdermal, intrapulmonary, and rectal. Important considerations include fluctuations in stomach pH hours to years after birth, the logistics of setting up an intravenous infusion, the need for reduced particle size for aerosol delivery to the developing neonatal lung, and variation in perirectal venous drainage. Additionally, some of the recently developed technologies for use in neonatal care are described. While the understanding of neonatal drug delivery has advanced over the past several decades, there is still a deficiency of technologies and formulations developed specifically for this population.

Key Points

Intravenous drug administration to neonates may require extremely low flow rates (3–5 mL/h) and volumes, which can result in a large variability in the amount of drug reaching the neonate.

Due to the immaturity of the skin barrier function, topical and transdermal drugs tend to show greater systemic delivery in neonates compared to older age groups, suggesting that use of this route of administration should be carefully monitored to mitigate the risk of overdose.

Intrapulmonary delivery to neonates is optimized using particles with a size range of 1–2 μm, which is different to the 3–4 μm particles generated by many intrapulmonary delivery systems.

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1 Introduction

Dosing neonates requires particular care as a result of their physiologic differences from older pediatric patients and adults [1]. When discussing the dosage form and route of administration of a drug, absorption ducnis typically one of the most relevant pharmacokinetic parameters to consider. While absorption differences between most dosage forms are well-known and documented, rapid developmental changes that occur soon after birth can add more complicated variables to consider. Given that many dosage forms are used in neonatal care off-label, it is important to examine the benefits and downsides to each, and the interplay between administration and variations in neonatal

Table 1 Challenges associated with drug delivery via various routes of administration

Route of administration	Physiologic factor	Function in neonates compared with adults	Effect on bioavailability/deliverability of drug from selected dosage form	References
Oral	Stomach pH	At birth: more basic within 24 h Postnatal: approximately adult levels (1–3) 1 week postnatal: more basic	Weakly basic drugs will have increased bioavailability in basic stomach environment, while weakly acidic drugs will have decreased bioavailability	[8–11, 13, 14, 143]
	Gastric emptying	Reduced	Decreased absorption rate	[9, 15, 16]
	Intestinal surface area	Reduced	Decreased absorption	[9]
	Intestinal motility and peristalsis	Reduced	Increased absorption	[15, 26]
	Intestinal P-gp expression	Reduced	Increased absorption	[29]
	Intestinal CYP metabolism	Varied depending on CYP, but decreased in most cases	Depends on CYP, but often increased bioavailability due to decreased metabolism	[30–33, 35]
Intravenous	Blood volume	Reduced	Limitation to carrier flow rate for IV fluids	[15, 52, 54]
Intramuscular	Muscle mass	Reduced	Restricts options for IM delivery	[15, 69, 70]
	Muscle vascularization	Variable	Can result in reductions or fluctuations of IM drug reaching systemic circulation	[69]
Subcutaneous	Subcutaneous fat	Reduced	Can result in drug leaking from depot	[15, 80]
Topical and transdermal	Stratum corneum thickness	<35 weeks' gestation: reduced ≥35 weeks' gestation: approximately adult thickness	Increased systemic bioavailability for neonates <35 weeks' gestational age	[81]
	Stratum corneum hydration	Increased	Increased bioavailability for most hydrophilic drugs	[12, 82]
	Surface area to bodyweight ratio	Increased	Increased bioavailability	[12, 82]
Intrapulmonary	Lung branching and development	Immature	Unclear, potentially decreased lower lung deposition/bioavailability	[86, 87]
	Inspiratory flow and volume	Decreased	Reduced likelihood of upper airway impaction, potential for increased bioavailability	[87]
Rectal	Size of rectum	Reduced	Potential for reduced bioavailability due to inability to avoid portal absorption	[123]

IV intravenous, *IM* intramuscular, *P-gp* P-glycoprotein, *CYP* cytochrome P450

physiology. The objective of this review was to discuss the challenges associated with various routes of administration in neonates, defined by the World Health Organization as infants less than 28 days of age [1]. Routes of administration discussed include oral, intravenous, intramuscular, subcutaneous, topical and transdermal, intrapulmonary, intranasal, and rectal (Table 1).

2 Oral

Oral delivery is the preferred route of administration in pediatric patients because it is not invasive and carries a low risk of pain [2]. Parents will generally feel comfortable with this delivery method, leading to improved compliance for drugs administered via this route. However, the oral route has several drawbacks for drug delivery in neonates. Primarily, oral delivery is not an option when the newborn is seriously ill or otherwise cannot swallow or tolerate anything in his/her mouth [2]. Even when the neonate is in good health there are restrictions on which oral dosage forms are appropriate. While taste is an important consideration in oral dosage forms for neonates (Pein et al. have written an extensive review of current methods for assessing taste-masking properties [3], while Maniruzzaman and coworkers review hot-melt extrusion as a technique for achieving taste masking [4]), other measures of palatability (e.g. dose volume and texture) may be more important to adherence [2]. Liquid dosage forms are generally preferred in neonates due to their ease of administration, although flexible solid forms such as dispersible and soluble tablets can also be mixed into milk as a last resort if the formulation is appropriate [2]. It should be noted that not all drugs are suitable for administration with

milk as physical interactions with calcium may affect the absorption of some drugs. For example, ciprofloxacin absorption decreases when coadministered with milk, potentially reducing the bactericidal effect of the drug [5]. Furthermore, if the neonate does not drink the entirety of the milk that the drug has been mixed into, they may only receive a partial dose [6]. Nurses and physicians may also be concerned that an unpalatable medication mixed with milk may reduce the neonate's milk intake. In this population, pills, tablets, capsules, and other dosage forms meant to be swallowed whole are generally not considered appropriate, although one group is currently exploring the acceptability of minitablets for oral delivery to neonates [7].

In addition to the importance of dosage form and formulation, there are also physiological differences in neonates that must be taken into consideration in regard to oral drug delivery. Immediately after birth, the pH of the neonate's stomach will drop from approximately 7 to approximately 2, a value similar to adult levels [8–10]. However, shortly thereafter, the pH will rise above 4 and will then slowly decline back to adult levels over the course of the next 2 years [9, 11]. It should be noted that the initial changes in stomach pH are generally not seen in preterm infants who have little free acid during the first 2 weeks of life [12]. Due to reduced transfer of ionized drugs across a membrane, this time of relatively high pH gastric environment may increase absorption of weakly basic drugs and reduce absorption of weakly acidic drugs [10, 13, 14].

Gastric emptying in the neonate, another important factor in oral drug delivery, is reduced and generally linear compared with the biphasic emptying of adults. While gastric emptying is known to mature rapidly after birth, its early impairment leads to a diminished absorption rate by delaying the drug reaching the increased absorptive surface of the small intestine, particularly in neonates less than 1 week of postnatal age [9, 15, 16]. Gastroesophageal reflux, a condition experienced by many neonates, can further delay gastric emptying, and therefore the absorption of drug, by pumping the stomach contents back into the esophagus before expelling them into the duodenum [17, 18]. Absorption rate can also be influenced by age-associated changes in splanchnic blood flow, which can result in an altered concentration gradient across the intestinal mucosa, particularly in preterm neonates [19, 20]. Specifically, newborn intestinal circulation, due to a low resting vascular resistance, has a relatively high blood flow rate, and thus areas that are perfused will see an increased drug absorption [21–23]. However, overall absorption may be lessened as a result of decreased neonatal intestinal surface area [9].

Pancreatic and biliary functions also develop over the course of the neonatal period. Their initial reduced function can lead to decreases in bioavailability of certain oral compounds, as is the case with drugs requiring solubilization or intraluminal hydrolysis (i.e. prodrug esters such as clindamycin [24] or chloramphenicol palmitate [25]) for adequate absorption [10]. While it might be expected that the bioavailability of some drugs administered orally may actually be slightly increased as a result of prolonged intestinal transit time from reduced intestinal motility and peristalsis in newborns, data suggest that these factors are often negated by the previously mentioned influences, resulting in an overall delayed and incomplete absorption [15, 26]. As a result of the importance of peristalsis in proper neonatal nutrition and oral drug delivery, one group has developed a stethoscope for monitoring the infant's abdominal sounds [27]. In 2013, this same group demonstrated the ability of that stethoscope to record bowel sounds in real time, information which could be used in consideration of oral dosing regimens for neonates [28].

Neonates also have an altered expression of transporters and drug metabolizing enzymes right after birth compared with older children and adults. A relative lack of intestinal P-glycoprotein expression in neonates, particularly those born before 28 weeks' gestation, can lead to reduced drug efflux and may result in an increase in the bioavailability of drugs that typically undergo significant efflux [10, 29]. The development of cytochrome P450 (CYP) enzymes responsible for metabolizing many different drugs also has an effect on the bioavailability of several oral agents. First-pass metabolism of high extraction drugs may be notably different due to altered expression of the intestinal CYPs and transporters, as well as hepatic drug metabolizing enzymes (including CYPs, UGTs, and other enzyme systems) and transporters. It has been shown that first-pass metabolism of oral zidovudine was decreased in the first 14 days of life, resulting in an increase in bioavailability (89 %) relative to neonates aged >15 days (61 %) [30, 31]. Several studies in adults have demonstrated that CYP3A metabolism in the small intestine plays a large role in the metabolism of several drugs, including cyclosporine and midazolam [32–34]. Taking this into consideration with the limited expression of CYP3A4 and 3A5 in neonates, it follows that presystemic clearance of these drugs will be decreased, and therefore bioavailability may be increased in neonates [35, 36].

In a similar vein, the microbiome and its development can also play a role in the exposure of neonates to orally delivered drugs. Recent studies have demonstrated the presence of a microbiome within the placenta and the fetal meconium, contradicting the previously held belief that the in utero environment was largely sterile [37–39]. After birth, the microbiome then undergoes rapid maturation during the first year of life [37]. However, several factors can influence the speed, pattern, and extent of colonization.

For example, breastfed infants will demonstrate gut colonization dominated primarily by *Bifidobacteria*, while infants who are formula fed will develop a much more diverse bacterial gut profile [37]. In addition, preterm neonates are known to have reduced microbial diversity and increased pathogenic organism colonization compared with term neonates [40, 41]. Research has shown that the gut microbial profile can be an integral part in the activation [42] or degradation [43, 44] of certain xenobiotic compounds, and therefore an important part of oral drug delivery in neonates. Carmody and Turnbaugh have recently published a review that more explicitly details the interactions between gut microbes and xenobiotics [45]. Currently, the factors that contribute to the development of various gut microbe profiles, and future research elucidating those factors, could augment physicians' understanding of which antimicrobial agents may be safe to use in certain neonatal drug regimens.

Another element to consider in oral delivery to neonates is the risk of inconsistent dosing resulting from the need to calculate doses explicitly for small patients. Most medications used in neonates have been formulated for adults, with very few being packaged specifically for neonates [46]. Indeed, while this is an issue that can lead to medication errors in all pediatric patients, a particular concern for neonates is the fact that the volume required for appropriate oral dosing of solutions and suspensions is often too small to reproducibly deliver the same dose [47]. Ultimately, the dosage form, as well as many different ontological aspects, can profoundly affect the absorption and bioavailability of an orally delivered drug in neonates.

Finally, the incorporation of excipients into neonatal medications for oral delivery should be monitored as many excipients are potentially, or are known to be, harmful to neonates. While excipients are generally thought of as being 'inactive ingredients', it has become evident that many excipients considered to be pharmacologically inert in adults may be toxic in neonates. For example, the use of small quantities of ethanol as a solvent in formulations such as diazepam oral solution is not an issue for adults but can lead to CNS depression in neonates, therefore making it inappropriate for use in that population [48]. For some excipients, the apparent toxicity is not so straightforward. The inclusion of propylene glycol in formulations used in neonates (such as cetirizine oral solution) has historically raised concerns for ototoxicity and CNS toxicity [48]. However, Allegaert et al. performed a prospective study of propylene glycol exposure in neonates and determined that a median unintended exposure of 34 mg/kg/day for 2 days was well tolerated in both term and preterm neonates, thereby providing a short-term safety limit for exposure [49]. Based on the sometimes unpredictable activity/toxicity of excipients in the developing neonate, additional studies such as Allegaert's are required to bolster understanding of excipient effects in the neonatal population. To that end, there are ongoing efforts in both the US and Europe (Safety and Toxicity of Excipients for Paediatrics [STEP] and European Study of Neonatal Exposure to Excipients [ESNEE]) to test and document potential toxicity of commonly used excipients in children [50, 51].

3 Intravenous

Intravenous administration is the preferred route of administration in severely ill neonates [2]. Care must be taken to avoid administering too much fluid to neonates at once as blood volumes range from approximately 250 mL (approximately 78 mL/kg) for a standard term neonate to less than 60 mL for a 600 g preterm neonate, and less for even smaller newborns who are surviving today [52, 53]. Therefore, typical intravenous fluid infusion rates of 10–20 mL/h are used for full-term neonates, and 3–5 mL/h for neonates weighing less than 1000 g (compared with approximately 100 mL/h in adults) [15]. Inconsistency of flow rate and drug passage through the intravenous line can present a challenge, with dead space in the line and components such as inline filters adding to the variability seen in intravenous delivery [54]. Sherwin et al. demonstrated that gentamicin delivery may only reach 80 % of the expected delivery to normal-weight newborns after 60 min, while the reduced flow rates used for extremely-low-birthweight (0.5 kg) neonates may result in delivery of only 60 % of the expected drug dose in that time period [55]. Medlicott et al. described other issues in intravenous delivery to neonates, including the potential for retrograde flow of the drug solution and poor mixing at the connection between the primary fluid and the drug solution resulting in delayed and/or incomplete gentamicin delivery [56]. Accounting for all of these factors is extremely difficult and empiric data may be required for a given drug in order to optimize the intravenous dosing regimen for that specific drug and to ensure that the full dose is being delivered. For a more in-depth review of the variability associated with the mechanical aspects of intravenous delivery in neonates, refer to Sherwin et al. [54].

Placement of a line, such as a peripherally inserted central catheter (PICC), can also be a very challenging aspect of delivery via the intravenous route. Common complications of line placement include infiltration, phlebitis, occlusion, infection, leakage, effusion, and edema [57]. Katheria et al. explored the use of ultrasound to guide placement of the line, and demonstrated that neonatal PICC lines placed using that technique were associated with a reduced duration of insertion of approximately 30 min and required fewer manipulations than traditional radiographic placement [58]. Panagiotounakou et al. also examined

differences in insertion site of the PICC line in preterm neonates and reported that infants with axillary PICC lines were 12 times less likely to have line-related complications than any other site of insertion, and seven times more likely to have the PICC line removed resulting from completed enteral nutrition rather than other (negative) causes [59].

Similarly, coadministration of drugs via the intravenous route can lead to serious complications in neonatal drug administration. A fairly recent example of this was coadministration of ceftriaxone and calcium-containing drugs, which can lead to life-threatening complications in neonates. As a result of this finding, the label for ceftriaxone was updated in 2007 to reflect that administration of the drug with calcium-containing drugs was contraindicated [60]. Interactions between drugs and intravenous fluids can also occur, leading to incompatibility in the intravenous line if they are mixed [61]. For example, Robinson and Sawyer have documented several incompatibilities of total parenteral nutrition with various drugs, including acyclovir and phenytoin, where mixing results in immediate precipitation of a white precipitate [62]. The potential for issues arising from these incompatibilities can be mitigated through the use of dedicated intravenous lines and/or access ports for each incompatible drug, although this course of action is not always feasible due to the number of drugs being administered to some neonatal patients [61].

Even in cases of single drug intravenous administration, it is important that the drug solution being administered intravenously to the neonate has the proper osmolality. Solutions should typically have an osmolality similar to that of serum (275–295 mOsm/kg) to avoid pain and tissue irritation [63]. Of more concern, infiltration of a hypo- or hypertonic solution can result in trauma and necrosis of the injection site [64].

Similar to oral drug delivery, the excipient profile of a given drug formulation must be noted when administering intravenous drugs to neonates in order to prevent any adverse events stemming from harmful chemicals. As mentioned previously, several excipients known to be safe for adult intravenous administration are not for neonates. For example, polysorbate 80, a commonly used excipient generally recognized as safe (GRAS) by the US FDA, was demonstrated to be responsible for the deaths of several preterm neonates treated with a formulation of vitamin E that contained this surfactant [65]. In addition, treatment with formulations containing the preservative benzyl alcohol led to CNS toxicity, respiratory distress, and lethal metabolic acidosis known as ‘gasping syndrome’ [66, 67].

Also like oral administration, intravenous administration often requires a small volume of drug, making it difficult to ensure reproducible delivery. A retrospective study performed by Uppal and colleagues examined medications that had commercially available parenteral formulations listed in the Hospital for Sick Children formulary, and it was found that 22 % of medications used in neonates had one or more indications that required less than 0.1 mL of stock solution [68]. In an additional clinical observational study, these investigators found that over 7 % of the doses administered to patients admitted to their pediatric intensive care unit over a 1-year period were prepared from less than 0.1 mL of stock solution [68]. While concentration data were not available for patients treated with these drugs, it is likely that there would have been a large variability resulting from the imprecise dosing often seen with doses prepared from less than 0.1 mL of stock solution. Indeed, because of the difficulty in measuring such small volumes, physicians will often dilute the dose with isotonic saline in order to work with a larger volume. However, one of the concerns in doing this is that the infant will receive more than the intended dose, resulting in so-called ‘dilution intoxication’ [15]. This then highlights the importance of developing either better methods and technologies for measuring small volumes, or neonatal-specific drug formulations. Overall, these studies demonstrate the importance of considering a conglomerate of both physical and developmental factors for neonatal intravenous delivery.

4 Intramuscular

Intramuscular injections are difficult to deliver to neonates because of their limited muscle mass and variable muscular vascularization and blood flow in the first 2–3 weeks of life [15, 69]. When intramuscular injections are used, the target injection site is typically the anterolateral thigh [70]. One common intramuscular injection for neonates is a vitamin K formulation for prophylaxis against vitamin K deficiency bleeding [71, 72]. In this case, the intramuscular injection is preferred and used because of superior efficacy to the oral formulation [71, 72]. Vaccines are also largely administered by this route [70]; however, this intramuscular injection can cause pain and sterile abscesses in the neonate. Efforts are ongoing to either reduce pain during the injection or to determine the best way to produce analgesia following the injection via both pharmacological and nonpharmacological means [73–78].

5 Subcutaneous

Similarly, concern has been raised over the utility of subcutaneous injections in neonates. Recombinant erythropoietin (rhEPO) is an example of a drug commonly administered subcutaneously; however, subcutaneous administration of rhEPO requires injection three times a week, a likely cause of discomfort for the neonate [79, 80].

Additionally, it has been observed that the drug can sometimes leak from the depot formed at the injection site [80]. This issue may be compounded by the relatively smaller proportion of subcutaneous fat in neonates compared with adults [15]. Based on these concerns, Costa et al. examined the use of intravenous fluids for erythropoietin delivery and concluded that 24-h intravenous infusion of erythropoietin was not inferior to subcutaneous injection and therefore provides a potentially easier alternative in neonates who already have central line access [80]. It is important to note that this study had some limitations, including the use of subcutaneous treatment after the central line was removed from a neonate. In reality, virtually all forms of parenteral administration can result in pain for the neonate, which can subsequently lead to discomfort for parents and/or caregivers. Therefore, it would be beneficial to use other dosage forms when available and appropriate.

6 Topical and Transdermal

The extent of percutaneous drug absorption is inversely related to the thickness of the stratum corneum and directly related to the degree of skin hydration and relative surface area [9]. The stratum corneum is fully developed by 35 weeks' gestational age, and full-term neonates possess intact skin barrier function [81]; however, the skin thickness and keratinization of preterm neonates is reduced [12]. Additionally, neonates have a more hydrated stratum corneum and a higher surface area to bodyweight ratio compared with adults, factors that can all lead to greater topical drug exposure and absorption in a neonate [12, 82]. While enhanced percutaneous absorption in neonates could theoretically be useful in certain situations, it also carries an increased risk of overexposure, resulting in unintentional systemic delivery of drugs and potential toxic effects [83, 84]. Possibly the most potent example of accidental percutaneous delivery is demonstrated by hexachlorophene, a topical antibiotic that was widely used in newborns to prevent staphylococcal infections until it was shown that doses were being delivered to systemic circulation and causing neurotoxicity in preterm infants [82, 85]. To mitigate the risk of toxicity, Bartelink et al. suggested that percutaneous administration of drugs in both preterm and term infants should be avoided in the first 2 weeks of life, particularly if systemic effects are not desired [12].

7 Intrapulmonary

Like many other aspects, the lungs of neonates continually develop prior to and after birth. Most full-term neonates have entered the final, alveolar stage of lung development in which secondary septation occurs and the number and size of capillaries and alveoli increase [86]. However, late preterm neonates born at 28–34 weeks' gestation may only be in the saccular stage of lung development when alveolar ducts and air sacs form, while even more preterm infants may still be in the process of developing bronchioles and alveolar epithelium [86]. It is currently unclear how drug delivery to the lungs is affected by their development, although it is likely that their reduced size results in greater deposition in the upper and central airways, and therefore reduced delivery to the lower airways [87]. This may be partially offset by lower inspiratory volume and flow, which reduces the likelihood of impaction in the upper airways [87]. Interestingly, while the absolute dose delivered is often low (<1 % of the nominal dose), when corrected for bodyweight it is typically comparable to that seen in adults [87]. Inhaled delivery platforms often generate particles in the size range of 3–4 μm for delivery to adults, but it has been suggested that the optimal size is <2.4 μm for delivery in neonates [88–91]. Additionally, data from Fok et al., using radiolabeled salbutamol in intubated neonates and infants, suggested that particle size <1 μm at the aerosol generator actually decreases pulmonary deposition, indicating that an optimal particle size for delivery to the lower respiratory tract of a neonate is likely in the range of 1–2 μm, a range that can be difficult to target without the proper equipment [92, 93]. Because of this size restriction, aerosol delivery in neonates is generally limited to nebulizers (jet, vibrating mesh, and ultrasonic) and metered dose inhalers (MDIs) with spacers [94, 95]. Lugo et al. used a working neonatal ventilated lung model to show that MDIs with spacers provided more efficient delivery of albuterol than jet nebulizers [96]. Fok et al. demonstrated a similar trend in vivo wherein an MDI was equally as effective as an ultrasonic nebulizer, and more effective than a jet nebulizer, at delivering salbutamol to the lower respiratory tract of ventilated preterm neonates [97]. Therefore, it is important to consider the method of aerosol generation when employing the intrapulmonary route for delivery to neonates.

Another developmental concern is the surfactant deficiency often experienced by neonates born at <28 weeks' gestational age that frequently results in respiratory distress syndrome [98, 99]. These patients typically receive prophylactic and/or rescue surfactant replacement therapy, which may complicate further drug delivery to the lungs, although some drugs such as antibiotics, anti-inflammatory agents, and bronchodilators may potentially be deliverable using surfactant as a vehicle [100–103]. The effectiveness of this technique was investigated in a pilot study that demonstrated a reduction in death and bronchopulmonary dysplasia in very-low-birthweight infants treated with the surfactant combined with the steroid budesonide compared with infants treated with surfactant alone [104]. Indeed, delivery of the surfactant itself can be difficult. The

procedure often requires intubation, and atelectasis with collapsed alveoli is a frequent comorbidity which may lead to uneven distribution in the lung. Despite this, there have been several recent (non-invasive) procedures developed for surfactant delivery which have been well-described in a review by El-Gendy et al. [99].

An additional barrier to the use of inhaled agents in neonates is their inability to adhere to adequate technique to ensure proper pulmonary delivery of the drug. In 2012, the American Association for Respiratory Care provided guidelines suggesting the use of a small-volume nebulizer with a mask or hood when delivering aerosols in neonates and infants [105]. While it is possible to have some measure of reproducibility of drug delivery in calm neonates who are breathing tidally, this delivery route becomes much more challenging when the neonate is crying or otherwise has abnormal breathing patterns. It has been shown that the dose absorbed is reduced in crying neonates, largely due to deposition primarily in the upper airway [106, 107]. As a result, it is essential to promote tidal breathing by minimizing distress when delivering inhaled drugs to neonates [87]. Furthermore, neonates are obligate nose breathers, meaning a facemask is necessary and high nasal deposition of inhaled drug is likely [87, 108]. In turn, this can result in absorption of drug from the nasal cavity and increased systemic availability of a drug that may be intended to have a local pulmonary effect [87]. Additionally, nose breathing is known to be less effective in delivering aerosol to the lungs than mouth breathing, likely due to relatively high resistance, airflow, and turbulence experienced in the nose and nasopharynx [109].

Another consideration for inhaled drug delivery in neonates, particularly in the neonatal intensive care unit (NICU), is the potential for the newborn to be mechanically ventilated. In fact, aerosolized medications are administered to intubated neonates as part of routine therapy [95]. Several ventilator-related factors can also affect lung deposition after aerosol inhalation [110]. For example, it was demonstrated that albuterol delivery to an in vitro lung model was reduced with controlled mechanical ventilation, assist control, and pressure support of 10 and 20 cm H_2O compared with continuous positive airway pressure, and that pressure-controlled ventilation delivers significantly less nebulized albuterol in vitro than constant flow, volume-controlled ventilation [111, 112]. Positioning of the aerosol relative to the intubation setup has also been shown to be important, with most aerosol generators being placed within the inspiratory arm of the ventilator circuit or between the 'Y' connector and endotracheal tube, although more in-depth studies are required to determine the exact optimal placement of each given aerosol type [113]. The humidity of the ventilator circuit is also important as the formation of water condensate on aerosol particles may augment their mass, thereby increasing aerosol impaction and rainout in the circuit and decreasing the amount delivered to the lungs [114, 115]. Finally, Sood et al. compared three neonatal ventilator circuits and concluded that delivery of aerosolized gadopentetate dimeglumine was highest with conventional mechanical ventilation, followed by high frequency jet ventilation, and lowest with high frequency oscillatory ventilation [116]. This highlights the importance of ventilator-associated factors when delivering aerosols to neonates.

8 Intranasal

Another option for drug delivery to newborns is the intranasal route. While this route is less commonly utilized, there are some cases of intranasal drugs being used in the neonatal population. In particular, the use of intranasal midazolam has been explored for sedation of neonates in preparation for intubation [117]. The intranasal route is convenient for this scenario as it allows rapid delivery with high bioavailability, and without the time and difficulty of accessing peripheral veins. Baleine et al. demonstrated that monotherapy with intranasal midazolam was able to provide adequate sedation during intubation in 15 of 22 newborns, although this was an observational trial without controls, therefore the true impact of treatment is yet to be determined [117]. Midazolam has also been delivered intranasally in neonates for seizure control. Once again, the rapid onset of effect inherent in the intranasal administration of midazolam is a major advantage. In a study by Sharma and Harish, intranasal midazolam had an onset of action as fast as intravenous midazolam but was administered an average of more than two times faster, resulting in a significant decrease in overall time from physician contact to cessation of seizure activity using intranasal midazolam [118]. An additional benefit of intranasal midazolam is that it allows for acute seizure control in an outpatient setting, whereas intravenous midazolam typically does not. A notable downside to intranasal delivery is the potential for nasal mucosal irritation, which would likely be more poorly tolerated in neonates than in adults. It has been suggested that lidocaine could be coadministered with any intranasal drugs in neonates and children to help mitigate this issue [119].

9 Rectal

Rectal administration is a less invasive alternative to parenteral delivery and can be useful when neonates are vomiting or suffering from diarrhea or ileus. In addition, the rectal route is a good alternative in emergency

situations when venous access is not immediately accessible. Although rectal administration can result in some initial discomfort to the neonate, quick administration followed by soothing of the infant usually results in successful treatment [120]. It is important to consider that bioavailability is altered by drug placement in the rectum. Drugs administered deeply to the proximal rectum may undergo first-pass metabolism, but drugs in the distal rectum will be absorbed by the rectal veins and bypass the portal blood system [121, 122]. Because the rectum is so small in neonates, it is common for drug to be unintentionally administered in the proximal rectum, which decreases bioavailability for high extraction medications [123]. In addition, rectal temperature and formulation can affect absorption, with warmer rectums and lipophilic suppositories decreasing absorption time [124, 125]. Of note, certain rectal dosage forms, such as liquid-filled suppositories, cannot be modified to provide a dose small enough for a neonate, and thus are generally not appropriate for use in this population unless a specific neonatal formulation is available. Some examples of drugs commonly administered rectally in neonates include antiepileptic drugs and acetaminophen. There is often limited access to a venous route of administration during a seizure. Like intranasal drugs, rectal antiepileptics can easily be administered during an active seizure [120]. Additionally, acetaminophen can be administered to neonates rectally for analgesia to avoid undue stress from parenteral administration and increase the ease of administration [126]. However, studies have shown lower bioavailability of rectal acetaminophen when compared with orally administered drug (approximately 61 % of oral bioavailability) in preterm and term newborns [122, 127]. Despite this, rectal administration as a whole offers a viable, less invasive alternative to other routes of administration, if appropriate for the specific drug and the neonate.

10 Recent Developments and Future Directions in Neonatal Drug Delivery

Continued development of systems to improve the flexibility (the ability to easily and accurately deliver an appropriate dose according to a patient's individual needs) and/or dispersibility (the extent to which agglomerated particles can be separated to generate a new interface between those particles and a dispersion medium) of drugs for delivery to neonates should be a high priority moving forward [128, 129]. It has become evident that it is less than ideal to modify dosage forms or produce doses by extemporaneous dispensing without sufficient research to demonstrate the safety and efficacy of the practice. Errors are increased by attempts to administer very small volumes of concentrated medications to small premature newborns and when doses have to be diluted before administration. Therefore, efforts to develop novel dosage forms that prioritize ease of administration to neonates, or techniques to reproducibly modify a current dosage form so as to allow delivery of an appropriate dose, are required.

A handful of technologies have been developed specifically for use in neonates and young infants. One of these drug delivery devices is an aerosol mask that fits over the pacifier of an infant. Amirav et al. demonstrated the effectiveness of this device on sleeping infants, specifically noting an improved tolerance and reduced rejection over older devices [130]. Another device utilizes the pacifier as a drug reservoir for oral delivery of a given drug moiety. This technology has been in use since the early 1990s and is now widely available and continually being modified, although very little information is available on the pharmacokinetics of drugs delivered by this method [131–135]. A similar technology, the Medibottle®, utilizes an oral syringe that can dispense medicine into the baby's mouth through the bottle nipple [136]. This modified bottle can increase acetaminophen and prednisolone compliance in infants less than 2 years of age [137, 138].

An additional technology that has been developed in adults, but may be able to improve intravenous delivery in neonates, is a multi-lumen device that reduces disturbances in an infusion when carrier flow is disrupted [139]. Given the wide variations and large delays that can occur at the low flow rates used in neonatal intravenous delivery, presence of a device that could reduce these factors could potentially help minimize dosing errors resulting from a disturbance in flow. For that reason, it may be worth examining the effectiveness of this device at lower flow rates than those tested in adults.

One set of dosage forms that could potentially benefit neonates the greatest are the flexible solid dosage forms. In particular, development of powders or dispersible minitablets that could be dissolved into breast milk or formula without affecting the taste or texture of the milk, or the effectiveness of the drug, would be extremely convenient for use in neonates [140]. A fixed-dose combination tablet of zidovudine and lamivudine was developed with this general principle. The formulated tablet comprised eight separable subunits each of which could be dispersed into food or liquid [141].

Transdermal patches have the potential to be another convenient dosage form for use in neonates as they are noninvasive and can provide controlled drug delivery over an extended time period. However, due to difficulties stemming from the development and fragile nature of the skin, particularly in preterm infants, this dosage form has been largely unused in the neonatal population. Studies to

demonstrate the safety and effectiveness of resizing transdermal patches could remove one barrier to the use of patch technology in neonates. Another important step forward would be the development of an adhesive that is non-irritating and safe to use on the neonates' sensitive skin. Several groups have examined various types of adhesives for tapes used in neonatal care that may be adaptable for use in transdermal drug delivery. One intriguing example is the tape developed by Laulicht et al., which features a removable backing layer that separates from the adhesive in order to reduce the sheer forces on the infant's skin [142]. Investigation of these two factors could markedly improve the utility of transdermal patches in the neonatal population.

11 Conclusions

Neonates are a challenging population to administer drugs to due to their rapid development and the lack of approved formulations for many drugs used for treatment. Overall, there has been an improved awareness of some of the challenges facing neonatal drug delivery but there is still a need for technologies specifically designed for neonates. However, given the recent improvement and initiatives seen in pediatric formulations, there will hopefully be a subsequent interest in developing better neonatal drug delivery platforms.

Compliance with Ethical Standards

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