

## Alternative Routes of Drug Administration—Advantages and Disadvantages (Subject Review)

**ABSTRACT.** During the past 20 years, advances in drug formulations and innovative routes of administration have been made. Our understanding of drug transport across tissues has increased. These changes have often resulted in improved patient adherence to the therapeutic regimen and pharmacologic response. The administration of drugs by transdermal or transmucosal routes offers the advantage of being relatively painless.<sup>1,2</sup> Also, the potential for greater flexibility in a variety of clinical situations exists, often precluding the need to establish intravenous access, which is a particular benefit for children.

This statement focuses on the advantages and disadvantages of alternative routes of drug administration. Issues of particular importance in the care of pediatric patients, especially factors that could lead to drug-related toxicity or adverse responses, are emphasized.

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ABBREVIATIONS. FDA, Food and Drug Administration; TAC, tetracaine, adrenaline, and cocaine; EMLA, eutectic mixture of local anesthetics; CSF, cerebrospinal fluid.

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### GENERAL CONCEPTS

The development of alternative methods of drug administration has improved the ability of physicians to manage specific problems. Practitioners recognize the rapid onset, relative reliability, and the general lack of patient discomfort when drugs are administered by the transmucosal and transdermal routes. They have administered sedatives, narcotics, and a variety of other medications by transdermal, sublingual, nasal, rectal, and even tracheal-mucosal routes in a variety of practice settings.

The proliferation of reports describing "off-label" routes of administration, ie, routes currently not approved by the Food and Drug Administration (FDA), has resulted from attempts by practitioners to discover better, more reliable, and less painful methods of drug administration. Caution, however, is in order. Without appropriate controlled studies in children, these routes of administration will remain "off-label," and the potential dangers presented by such use may not be adequately recognized.<sup>3,4</sup> This issue is important because children are not often included in research sponsored by drug companies to obtain FDA approval of a drug. This exclusion often results in only partial discovery of information. An important nuance may be missed in a small series of pa-

tients studied at one institution, but it may later become evident with more widespread use. For approval of new drugs, the FDA regulations ask sponsors to identify potential uses in children, and approval may be withheld unless pediatric studies are done. However, this may not solve the problem for previously approved drugs or new routes of drug administration,<sup>5</sup> as demonstrated by the fatal toxicity associated with early formulations of tetracaine, adrenaline, and cocaine (TAC).

When new methods or routes of drug administration are introduced, it is vital that the practitioner understand the pharmacologic actions of the administered drug and the pharmacokinetic and pharmacodynamic implications that may be unique for pediatric patients.

### MECHANISMS OF DRUG ABSORPTION AND POTENTIAL PROBLEMS

#### Transdermal Drug Administration

A number of drugs may be administered transdermally.<sup>6-11</sup> Transdermal drug absorption can significantly alter drug kinetics and depends on a variety of factors including the following<sup>7,11-21</sup>:

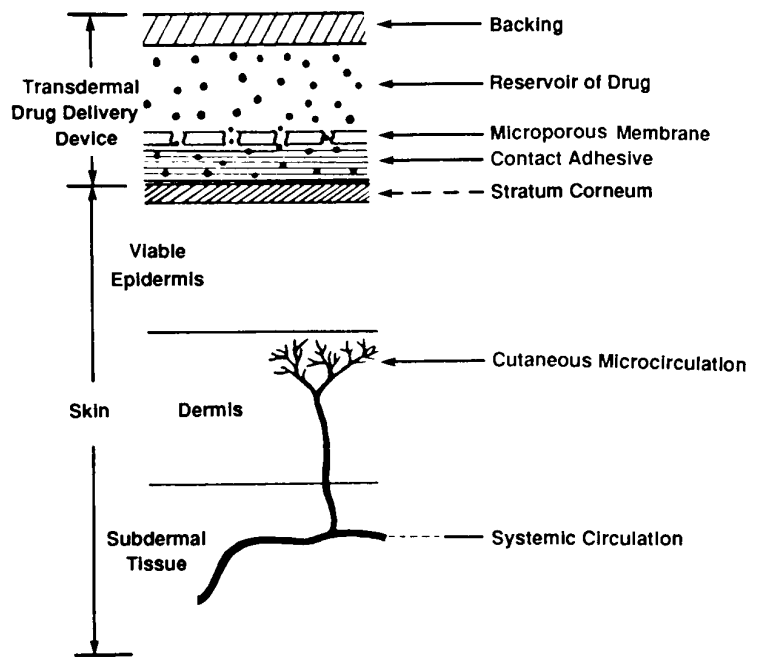
- Site of application
- Thickness and integrity of the stratum corneum epidermidis
- Size of the molecule
- Permeability of the membrane of the transdermal drug delivery system
- State of skin hydration
- pH of the drug
- Drug metabolism by skin flora
- Lipid solubility
- Depot of drug in skin
- Alteration of blood flow in the skin by additives and body temperature

The potential for toxic effects of the drug and difficulty in limiting drug uptake are major considerations for nearly all transdermal delivery systems, especially in children because skin thickness and blood flow in the skin vary with age. The relatively rich blood supply in the skin combined with thinner skin have significant effects on the pharmacokinetics of transdermal delivery systems for children (Fig 1). In some situations this may be an advantage, while in others systemic toxicity may result. Central nervous system toxicity occurred in neonates washed with hexachlorophene because their very thin skin and large body surface area allowed toxic levels to

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The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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**Fig 1.** Schema of a transdermal drug delivery system. Transdermal drug delivery systems involve a backing to protect the patch from the environment, a drug reservoir, a porous membrane that limits the rate of drug transfer, and an adhesive to secure the patch to the skin surface at the stratum corneum epidermidis. Drug uptake is then determined by additional factors such as skin thickness and blood flow in the skin (see text for details). Reproduced with permission from Varvel et al. *Anesthesiology*. 1989;70:933.

develop from systemic drug absorption.<sup>22-24</sup> The practitioner must understand the clinical implications of these factors when prescribing a drug to be administered by the transdermal route.

Examples of drugs currently administered by the transdermal route include scopolamine patches to prevent motion sickness;<sup>18,25-29</sup> a eutectic mixture of local anesthetics (EMLA) cream to reduce the pain of procedures;<sup>30-34</sup> corticosteroid cream administered for its local effect on skin maladies;<sup>35</sup> TAC for anesthesia when suturing small lacerations,<sup>36,37</sup> and fentanyl patches to treat cancer pain or chronic pain syndromes.<sup>38-41</sup> Episodes of systemic toxic effects, including some fatalities in children, have been documented with each of these, often secondary to accidental absorption through mucous membranes.

#### Toxic Effects

1. Scopolamine patches are used to treat motion sickness or to prevent nausea and vomiting. However, excessive uptake through the skin and rubbing of the patch on the eye have resulted in unilateral and bilateral mydriasis.<sup>18,25-28</sup> In some patients this has been mistaken for an intracranial catastrophe.<sup>29</sup>
2. Absorption of the prilocaine in EMLA cream through a mucous membrane (eg, should the child suck on the mixture or rub it in the eye) may cause toxic effects.<sup>42</sup> Methemoglobinemia requiring medical intervention after mucosal absorption and prolonged but low-level methemoglobin values have been reported after standard administration, particularly in infants.<sup>43-46</sup> The use of EMLA cream on the oral mucosa for dental procedures has been reported,<sup>47-49</sup> this application is contraindicated.

Published reports emphasize the importance of adherence to guidelines for administration of the drug and avoidance of excessive application to the

skin or application to damaged skin, particularly in neonates and infants.<sup>45,50,51</sup> Application to mucosal surfaces should be avoided. EMLA cream should be used with caution on patients taking medications that can contribute to the production of methemoglobin. These include sulfonamides, acetaminophen, phenobarbital, and phenytoin. Even after appropriate application, children must be carefully observed so ingestion by chewing through the dressing is avoided.<sup>42</sup> Optimal anesthesia is generally achieved 1 to 2 hours after application.<sup>44,52</sup>

3. The TAC combination may essentially eliminate pain and increase hemostasis during suturing of a laceration.<sup>36,37</sup> However, systemic levels of cocaine have been documented after simple application of TAC soaked-pledgets to an open wound, thus, emphasizing the need for calculating and limiting the dose of cocaine administered.<sup>53</sup> A "safe" dose is not calculated by using the length of a laceration or the age of a patient, but by using the patient's size and the site of administration. Strict limitation of the total dose of each component according to the patient's lean body weight is crucial. Because the components of TAC are formulated in different ratios, practitioners using TAC must know the composition of the formulation in their clinical setting. Patients with long lacerations or lacerations on mucosal surfaces may be treated more safely with some other form of analgesia or anesthesia.

Specific formulations of TAC influence its potential to cause toxic effects. The initial mixtures contained .5% tetracaine (5 mg/mL), adrenaline 1:2000 (500 µg/mL), and 11.8% cocaine (118 mg/mL).<sup>37,54</sup> The described safe upper limit in adults is approximately 6 mg/kg for cocaine and about 1.5 mg/kg for tetracaine. Studies of toxicity have not been performed in children. The initial TAC dose recommen-

dations for children (cocaine and tetracaine in mg/kg) exceeded the recommended upper limits of these drugs for adults.<sup>55</sup> One death has been attributed to the toxic effects of cocaine. An infant received an overdose through the oral and nasal mucosa and was found dead several hours after hospital discharge.<sup>56</sup> Seizures have also been reported after application of only 2.0 mL to the oral mucosa to provide anesthesia for suturing a laceration of the tongue.<sup>57</sup> Measurable cocaine levels have been found in 75% of children who received 3.0 mL of standard TAC on nonmucosal lacerations.<sup>53</sup> With the widespread use of this drug combination, physicians must be familiar with the potential toxic effects.<sup>57,58</sup> The vasoconstrictive action of this drug combination also suggests that it should not be applied to areas with limited collateral circulation, such as the penis, fingers, or toes.

Equivalent efficacy of TAC with less potential for toxicity has been found with lower adrenaline and cocaine concentrations (tetracaine 1.0% [10 mg/mL], adrenaline 1:4000 [250 µg/mL], and cocaine 4.0% [40 mg/mL]).<sup>59</sup> Although controlled studies have not been conducted, safety and efficacy can likely be preserved and toxicity minimized by the following.

- Avoiding application to mucous membranes
  - Avoiding application to areas with limited collateral circulation
  - Reducing drug concentrations, particularly of cocaine
  - Using the lower-dose formulations of cocaine
  - Calculating the total dose on the basis of milligrams per kilograms (or mL/kg) of body weight by using the recommended dose of 1.5 mL/10 kg (this equals 1.5 mg/kg tetracaine and 6.0 mg/kg cocaine).<sup>60</sup>
4. The transdermal fentanyl patch is a new drug delivery system developed to treat chronic pain (Fig 1). The transdermal patch was developed to mimic the delivery achieved by constant intravenous infusion.<sup>40</sup> The desired effect is achieved, but not immediately after the patch is applied. Although it is tempting to provide patients with the latest in technology, the fentanyl patch presents a potential threat to children. Fatal toxic effects have occurred after accidental ingestion of new or "used" patches, which have been inadequately stored or discarded, and secondary to inappropriate application, ie, applied to children who have not received narcotics chronically.<sup>61,62</sup>

The pharmacokinetics and pharmacodynamics of the fentanyl patch in children are not yet defined.<sup>63</sup> In adults, transdermal uptake of fentanyl begins within 1 hour of administration, generally achieves low therapeutic levels by 6 to 8 hours, peaks at 24 hours, and then slowly decreases.<sup>64,65</sup> The drug accumulates in the skin as transfer occurs from the administration device. Because of the slow onset of clinical effect and the skin depot effect,<sup>16,65,66</sup> the potential for drug-drug interaction with other sedatives or narcotics administered to provide analgesia during the period before therapeutic fentanyl blood levels are reached may result in catastrophic respiratory depression. When approved by the FDA, transdermal fentanyl was intended only for treat-

ment of adult patients with cancer or chronic pain syndromes.<sup>38-41,67-70</sup> It was not designed to treat patients experiencing other types of pain (eg, acute postoperative pain) or for patients who had not received long-term narcotic therapy.

The role of the fentanyl patch in pediatric patients remains to be defined; it is likely that the pharmacokinetics and pharmacodynamics will be quite different in children. Safe use awaits the completion of controlled studies to define the differences in pharmacokinetics and pharmacodynamics as they relate to age (primarily blood flow in the skin and skin thickness),<sup>20</sup> disease entity,<sup>71</sup> and the previous long-term use of narcotics and the definition of children who are suitable candidates for this form of narcotic administration.<sup>11,63,72</sup>

### Transmucosal Routes

Drug absorption through a mucosal surface is generally efficient because the stratum corneum epidermidis, the major barrier to absorption across the skin, is absent. Mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism.

The amount of drug absorbed depends on the following factors<sup>13,14,73-78</sup>:

- Drug concentration
- Vehicle of drug delivery
- Mucosal contact time
- Venous drainage of the mucosal tissues
- Degree of the drug's ionization and the pH of the absorption site
- Size of the drug molecule
- Relative lipid solubility

### Respiratory Tract Mucosal Administration

The respiratory tract, which includes the nasal mucosa, hypopharynx, and large and small airway structures, provides a large mucosal surface for drug absorption. This route of administration is useful for treatment of pulmonary conditions and for delivery of drugs to distant target organs via the circulatory system.

One of the oldest examples of respiratory administration for systemic drug delivery is inhalation anesthesia. An increasing variety of drugs are being administered by this route to obtain a direct effect on the target tissues of the respiratory system, including β-agonists, corticosteroids, mast cell stabilizers, antibiotics, and antifungal and antiviral agents. Surfactant is an example of a drug given to replace deficient factors. This route of drug administration is being used increasingly for other medications, such as vasoactive drugs for resuscitation, sedatives, and hormones.

Distribution of the drug depends on the following factors:

- Formulation
- Dilution
- Particle size
- Lipid solubility
- Method of administration
- Site of administration

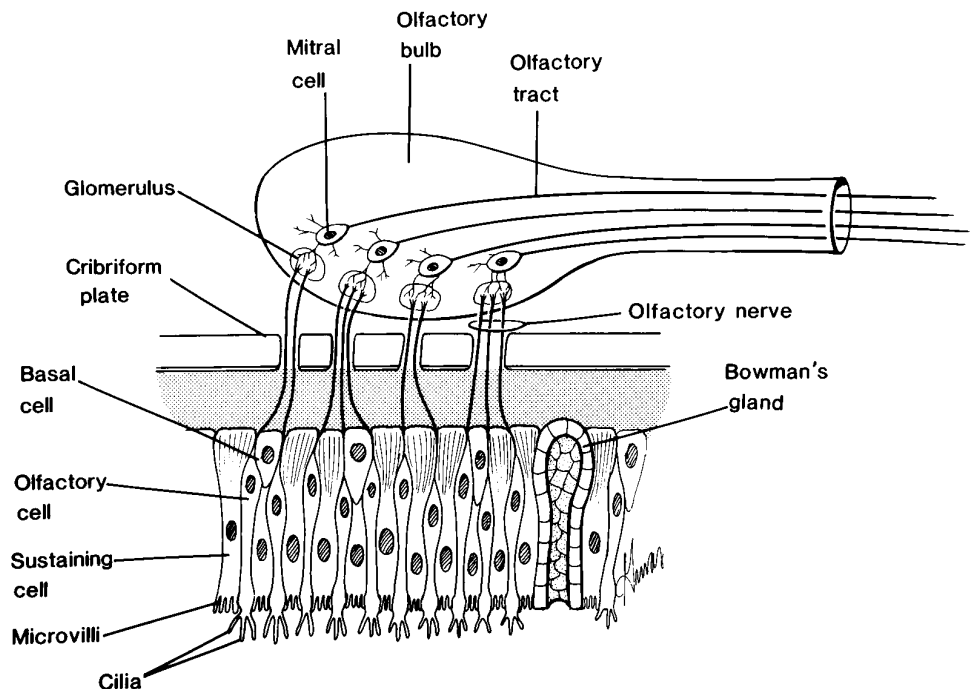
Administration may be accomplished by inhalation of vaporized, nebulized, powdered, or aerosolized drug, as well as by direct instillation. Metered-dose inhalers and nebulizers are often used for the administration of  $\beta_2$ -agonists, corticosteroids, antivirals, antibiotics, and cromolyn for the treatment of asthma. To achieve sufficient systemic blood levels, drugs used for resuscitation, such as epinephrine, lidocaine, and atropine, must be delivered past the tip of the endotracheal tube or diluted in a volume sufficient to allow propulsion to distal airways during positive pressure ventilation.

Inhaled drugs are primarily deposited in the tissues of the upper airway.<sup>79</sup> Access to distal airways is a function of particle size.<sup>80</sup> In humans, large particles ( $>4 \mu\text{m}$ ) and small particles ( $0.5$  to  $1.0 \mu\text{m}$ ) tend to deposit in the nasopharyngeal structures, whereas intermediate particles ( $1$  to  $4 \mu\text{m}$ ) reach distal airways.<sup>80,81</sup> Water-soluble drugs tend to remain on the tissues of the upper airway and fat-soluble drugs are more likely to reach distal airways.<sup>82</sup> Fat-soluble drugs are usually absorbed more rapidly than are water-soluble drugs.<sup>82</sup> Respiratory patterns and delivery systems also have important effects on drug delivery.<sup>79-81</sup>

The practitioner must consider multiple issues when contemplating the administration of drugs through any portion of the respiratory tract. Potential problems or concerns include the following:

- Drug metabolism in the respiratory tract and reduction of systemic effect<sup>82</sup>
- Possible conversion to carcinogens<sup>83</sup>
- Protein binding
- Mucociliary transport causing increased or decreased drug residence time
- Local toxic effects of the drug (eg, edema, cell injury, or altered tissue defenses)<sup>84</sup>
- Local or systemic toxic effects of propellants, preservatives, or carriers such as sulfites<sup>84</sup>

**Fig 2.** Anatomy of the nasal mucosa-cribriform plate interface. The nasal mucosa is the only location in the body that provides a direct connection between the central nervous system and the atmosphere. Drugs administered to the nasal mucosa rapidly traverse through the cribriform plate into the central nervous system by three routes: (1) directly by the olfactory neurons, (2) through supporting cells and the surrounding capillary bed, and (3) directly into the cerebrospinal fluid. Reproduced with permission from Hilger PA. *Fundamentals of Otolaryngology, A Textbook of Ear, Nose and Throat Diseases*. 6th ed. Philadelphia, PA: WB Saunders Co; 1989:184.



### Nasal Mucosal Administration

Drug addicts know that the nasal mucosal surface provides a site for rapid and relatively painless drug absorption resulting in rapid central nervous system effects. Drugs sprayed onto the olfactory mucosa are rapidly absorbed by three routes (Fig 2): (1) by the olfactory neurons, (2) by the supporting cells and the surrounding capillary bed, and (3) into the cerebrospinal fluid (CSF). Transneuronal absorption is generally slow, whereas absorption by the supporting cells and the capillary bed is rapid.<sup>85</sup> A rapid rise in systemic blood levels has been demonstrated following the nasal administration of corticosteroids.<sup>86</sup> For some drugs, administration by nasal spray results in a greater ratio of CSF to plasma concentration than does intravenous or duodenal administration,<sup>87-91</sup> giving evidence for diffusion of these compounds through the perineural space around the olfactory nerves, a compartment known to be continuous with the subarachnoid space.<sup>85,87,92-96</sup>

Vasopressin and corticosteroids were among the first drugs to be administered by this route.<sup>97-101</sup> However, the nasal mucosa also has been used for the administration of sedatives<sup>102-107</sup> and potent narcotics, which generally results in a rapid systemic response.<sup>105,108,109</sup> It is not known if this response to sedatives and narcotics is due to systemic absorption followed by transport to the central nervous system, direct transport into the CSF, or transneuronal transport. In general, children object to this mode of drug administration (75% cry when midazolam is given)<sup>105,106</sup> because of the discomfort and, if the drug is unpalatable, its unpleasant taste in the posterior pharynx.

When sedatives and opioids are administered nasally, there is little danger of delayed absorption. However, continued absorption of medication swallowed after nasal administration or delayed transfer of substances of different sizes or solubility through

neuronal or CSF transport could theoretically produce sustained, delayed, or neurotoxic effects. Neurotoxic effects have been demonstrated when ketamine or midazolam is applied directly to neural tissues.<sup>110</sup> For ketamine, the preservative chlorobutanol was believed to be the source of neurotoxic effects, but this preservative is not used for all formulations of ketamine.<sup>111</sup> Furthermore, the preservative for midazolam has not been examined. Also, potentially any drug or its carrier may be converted into a carcinogen by nasal cytochrome P-450 enzymes.<sup>82</sup>

Until appropriate studies of the neurotoxicity of drugs and their carriers are completed, it would seem prudent not to administer drugs unapproved for use by this route, particularly when additional doses are contemplated.

#### *Oral Transmucosal (Sublingual, Buccal) Administration*

Oral transmucosal absorption is generally rapid because of the rich vascular supply to the mucosa and the lack of a stratum corneum epidermidis. This minimal barrier to drug transport results in a rapid rise in blood concentrations. The oral transmucosal route has been used for many years to provide rapid blood nitrate levels for the treatment of angina pectoris. The drug appears in blood within 1 minute, and peak blood levels of most medications are achieved generally within 10 to 15 minutes, which is substantially faster than when the same drugs are administered by the orogastric route.<sup>76</sup> The fentanyl Oralet™ was developed to take advantage of oral transmucosal absorption for the painless administration of an opioid in a formulation acceptable to children.<sup>112-117</sup> The administration of other medications by this route and with similar delivery systems is being investigated.<sup>76,77,118,119</sup>

Most pediatric patients will swallow medications administered orally, potentially leading to drug degradation in the gastrointestinal system. Oral transmucosal administration has the advantage of avoiding the enterohepatic circulation and immediate destruction by gastric acid or partial first-pass effects of hepatic metabolism. For significant drug absorption to occur across the oral mucosa, the drug must have a prolonged exposure to the mucosal surface. Taste is one of the major determinants of contact time with the buccal or oral mucosa.<sup>120</sup> Drug ionization also affects drug uptake. Because the pH of saliva is usually 6.5 to 6.9, absorption is favored for drugs with a high  $pK_a$ .<sup>121</sup> Prolonged exposure to the oral sublingual mucosal surface may be accomplished by repeated placement of small aliquots of drug directly beneath the tongue of a cooperative child or incorporation of the drug into a sustained-release lozenge.<sup>75,106,122,123</sup> Drug absorption is generally greater from the buccal or oral mucosa<sup>77,119,120</sup> than from the tongue and gingiva.

The fentanyl Oralet™ is the first FDA-approved formulation of this type for children.<sup>62</sup> Current approval is for preoperative sedation and for painful procedures in a hospital setting.<sup>117,124-128</sup> Because the  $pK_a$  of fentanyl is 8.4, absorption through the oral mucosa is favored. The fentanyl Oralet™ has been used successfully in oncology patients undergoing

painful procedures such as bone marrow aspiration or lumbar punctures.<sup>127,128</sup> Oral transmucosal administration of morphine (by a buccal tablet) has been considerably less reliable than administration of fentanyl; this is not surprising given the relatively low lipid solubility of this drug.<sup>75</sup> Absorption of buprenorphine is better than that of morphine, but the utility of this drug is limited by the slow onset of effect.

The oral transmucosal route of administration may offer some protection from the adverse effects of intravenous fentanyl. Peak respiratory depression and the development of glottic and chest wall rigidity are related to the dose and rate of administration; this effect may be attenuated by pretreatment with thiopental or benzodiazepine.<sup>129-132</sup> Glottic rigidity has been demonstrated to be an important cause of ventilatory difficulty due to fentanyl-induced muscle rigidity.<sup>133</sup> Chest wall or glottic rigidity has occurred in adults with an intravenous fentanyl dose as small as 75  $\mu\text{g}$ ; however, no dose response studies have systematically addressed this issue in adults or children. One pediatric study<sup>134</sup> found no change in chest wall compliance after the rapid administration of 4  $\mu\text{g}/\text{kg}$ , but these children were intubated, thus bypassing the glottis and eliminating the possibility of assessing glottic rigidity. One study<sup>135</sup> found a 50% incidence of chest wall rigidity in adult volunteers who received 150  $\mu\text{g}/\text{min}$  intravenously until 15  $\mu\text{g}/\text{kg}$  had been administered; all six patients in whom rigidity developed were apneic and amnesic. The patients who did not experience rigidity remained awake and responsive. Fentanyl administered by oral transmucosal route results in relatively rapid elevation of the drug concentration in the blood, but this rate of increase is less likely to result in glottic or chest wall rigidity than when fentanyl is given intravenously. However, one possible case of glottic or chest wall rigidity has been reported during the induction of anesthesia.<sup>136</sup> An additional possible safety factor is that a large proportion of swallowed drug is destroyed by gastric acid, which reduces the potential for later drug uptake.

Another possible advantage of oral transmucosal administration of fentanyl is that the sustained therapeutic blood levels achieved may offer analgesia for painful procedures that last an hour or more. This contrasts with the extremely short duration of analgesia (minutes) with single low doses of intravenous fentanyl.

As with any narcotic, the potential exists for respiratory depression and oxygen desaturation with the moderately rapid absorption through the oral mucosa. Pharmacodynamic studies have demonstrated a small but clinically important incidence of oxygen desaturation with the fentanyl Oralet™.<sup>62,137</sup> In response to these findings, the recommended dosage was lowered from 15 to 20  $\mu\text{g}/\text{kg}$  to the currently approved dose of 5 to 15  $\mu\text{g}/\text{kg}$ . The importance of pulse oximetry and careful vigilance must be emphasized.

The advantages of relatively rapid absorption offered by this drug delivery system make it a reasonable alternative to intravenous therapy. Some have

argued that narcotics administered to children should have a disagreeable taste, precluding the use of this oral transmucosal drug delivery system. This tenet is illogical. No evidence exists to suggest that appropriate narcotic therapy in children increases the risk of addiction in later life. Furthermore, this rationale has never been used to prevent the palatable delivery of other potentially harmful drugs, such as children's vitamins. Because the relief of pain and anxiety is such an important part of the daily practice of many pediatric care givers, it is appropriate to encourage the development of these innovative, nonpainful, and nonthreatening techniques of drug administration. Each drug must pass rigorous scientific evaluation to ensure safe usage and to define the precise role of the drug in pediatric health care. It would be wrong to reject this route of drug administration simply because of the concern that children would think that it is pleasurable to take narcotics or sedatives via this route or modality of drug delivery.<sup>62</sup>

### Rectal Transmucosal Administration

Medications may be administered by the rectal mucosal route for systemic effects if other more preferable routes are not available for the treatment of nausea and vomiting, sedation, control of seizures, analgesia, or antipyresis.<sup>2,122,138-153</sup> Rectal administration provides rapid absorption of many drugs and may be an easy alternative to the intravenous route, having the advantage of being relatively painless, and usually no more threatening to children than taking a temperature. However, rectal administration of drugs should be avoided in immunosuppressed patients in whom even minimal trauma could lead to formation of an abscess.

The most important concern for the practitioner is irregular uptake; clinically important patient-to-patient variability exists. The absorption of the drug may be delayed or prolonged, or uptake may be almost as rapid as if an intravenous bolus were administered, which may cause adverse cardiovascular or central nervous system effects. One reported death after rectal administration of multiple doses of morphine underscores the importance of being aware of this factor.<sup>154</sup>

The rate of rectal transmucosal absorption is affected by the following factors:

- Formulation (time to liquefaction of suppositories)
- Volume of liquid
- Concentration of drug
- Length of rectal catheter (site of drug delivery)
- Presence of stool in the rectal vault
- pH of the rectal contents
- Rectal retention of drug(s) administered
- Differences in venous drainage within the rectosigmoid region

Anatomical differences in hemorrhoidal venous drainage of the rectum may substantially influence the systemic drug level achieved. Drugs administered high in the rectum (drained by the superior rectal veins) are usually carried directly to the liver

and, thus, are subject to metabolism. Drugs administered low in the rectum are delivered systemically by the inferior and middle rectal veins before passing through the liver.<sup>155-157</sup> Problems may occur with drugs that normally have a high hepatic extraction ratio. The clinical implications of rectal venous drainage for absorption and metabolism of most drugs are not well-defined.

Diluent volume is also an important determinant of rectal drug uptake, as demonstrated with methohexital administered rectally for preprocedure sedation. Equivalent deep sedation was achieved with 25 mg/kg of a 10% solution (0.25 mL/kg) and with 15 mg/kg of a 2% solution (0.75 mL/kg). Peak blood levels of the drug, however, were significantly higher for a longer time in the children treated with the 2% solution.<sup>158</sup> This finding could have important clinical implications for the depth and duration of sedation.

Rectal pH may also influence drug uptake by altering the amount of drug that is ionized. The greater lipid solubility of nonionized drugs enhances their movement across biological membranes.<sup>74</sup> The pH of the rectal vault in children ranges from 7.2 to 12.2.<sup>159</sup> This pH range favors absorption of the barbiturates that will remain in a nonionized state because their  $pK_a$  is near the physiologic range (~7.6).

Despite the limitations associated with drug absorption in the rectum, many drugs usually administered by the intravenous and orogastric routes have also been administered rectally. Sedatives commonly administered by this route include midazolam, diazepam, and ketamine.<sup>138,140,141</sup> In children, the rectal route is convenient for the administration of benzodiazepines to treat status epilepticus because an intravenous line is not required.<sup>146,147</sup> The rectal dose generally must be higher than the dose administered intravenously or orally. The extent of the increase depends on the factors that affect absorption (listed earlier). The most important considerations are the slow onset of effect (minutes) and the prolonged duration of effect (hours). The peak blood levels vary considerably from patient to patient. The potential for rapid and almost complete absorption has serious implications when drugs with cardiac or pulmonary depressant effects are administered. Practitioners must be prepared to monitor the patient after drug administration and to manage an emergency should it occur; equipment suited to the size of the patient is required.<sup>160</sup> The patient also may expel an unmeasurable amount of the drug, which makes it difficult for the practitioner to decide how much more of the drug to administer.

### CONCLUSION

New routes of drug administration offer many advantages for the care of pediatric patients. Controlled laboratory and clinical trials are vital to determine the safe use of medications originally formulated to be administered by other routes.

COMMITTEE ON DRUGS, 1995 TO 1997  
Cheston M. Berlin, Jr, MD, Chairperson  
D. Gail May-McCarver, MD

Daniel A. Notterman, MD  
Robert M. Ward, MD  
Douglas N. Weismann, MD  
Geraldine S. Wilson, MD  
John T. Wilson, MD

LIAISON REPRESENTATIVES  
Donald R. Bennett MD, PhD  
American Medical  
Association/United States  
Pharmacopeia

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American College of Obstetricians  
and Gynecologists

Paul Kaufman, MD  
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Manufacturers Association of  
America

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Health Protection Branch, Canada

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Centers for Disease Control and  
Prevention

Gloria Troendle, MD  
Food and Drug Administration

John March, MD  
American Academy of Child and  
Adolescent Psychiatry

Sumner J. Yaffe, MD  
National Institutes of Health

AAP SECTION LIAISON  
Stanley J. Szeffler, MD  
Section on Allergy & Immunology  
Charles J. Coté, MD  
Section on Anesthesiology

CONSULTANT  
Helen W. Karl, MD

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