Novel routes of opioid administration

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In the early days of anaesthesia, opioids were traditionally given by the intramuscular and intravenous routes and other methods of administration were considered as novel. However, because of expanding interest in both acute and chronic pain over the past few decades, the anaesthetist routinely administers opioids via the oral, subcutaneous, rectal, intrathecal, extradural and transdermal routes. All these modes of delivery can now be considered as conventional, despite the vagaries of product licensing in some situations. In this short review, we shall consider three methods of opioid administration that can still be considered as novel: intranasal and inhalational administration and iontophoresis. Some may consider intra-articular administration as novel, but this has recently been reviewed in detail elsewhere.20

Intranasal administration

Intranasal administration is particularly familiar to the recreational abuser of opioids and central nervous system stimulants but it is less established in current clinical practice. Reliable absorption across the nasal mucosa depends on lipid solubility and has the advantage of avoiding first-pass metabolism. Table 1 shows the specific opioids and doses that have been administered intranasally and reported in the literature.

Intranasal opioids can be administered as either a dry powder or dissolved in water or saline. A specifically designed spray device has been shown to produce a wider distribution of drug compared with simple drops.13 Butorphanol has been formulated in an intranasal metered-dose spray (0.25 mg)26 and pethidine,34 oxycodone37 and fentanyl35 have been diluted with saline and given via a pre-metered spray bottle. Sufentanil has been given with a 1- or 3-ml syringe,16 nasal spray or nasal dropper,40 and diamorphine as a 3% mixture with lactose via a straw935 or in solution with a tuberculin syringe.45

Only a few investigators have reported the absorption pharmacokinetics of their preparations (table 1). Takala and colleagues37 found that the mean (95% CI) bioavailability of oxycodone after intranasal administration was 46(25–67)%, with a median (range) tmax of 25 (10–240) min. In contrast, tmax for diamorphine absorption was achieved within 5 min in two studies.831 Bioavailability was not measured in these studies but the relative potency of intranasal diamorphine compared with intramuscular was 50%. Haynes and colleagues15 found that, after intranasal sufentanil 2 μg kg⁻¹, the range for plasma tmax was 1–30 min and analgesic plasma concentrations were maintained for at least 2.5 h. Streibel and others35 did not measure the absorption pharmacokinetics of fentanyl 45 μg but found that intranasal fentanyl had a similar relative potency compared with i.v. administration (perhaps suggesting good bioavailability) and mean (SD) time to maximum post-operative analgesia was 26.3 (15.0) min compared with 20.2 (12.0) min after i.v. administration. Similarly, the same group34 did not report the pharmacokinetics of intranasal pethidine absorption but when compared with subcutaneous injection, there was no significant difference in requirement or duration of analgesia.

Proposals for the clinical use of intranasal opioids include pre-operative sedation and post-operative pain control. Its use in children has been investigated particularly. For example, intranasal sufentanil produced a somnolent child and smooth induction of anaesthesia.151648 Providing adequate analgesia in the accident and emergency department for children with moderate to severe pain is particularly difficult. Wilson and colleagues,46 in an open study, found that intranasal diamorphine provided analgesia as rapidly and efficiently as intramuscular morphine but with significantly better parent acceptability. All the parents whose children received intranasal medication described the episode as acceptable compared with 55% of those in the intramuscular group. Diamorphine 0.1 mg kg⁻¹ was given in a constant volume of 0.2 ml via a 1-ml syringe. The solution was allowed to drop gently into one nostril.

Others30 have reported that intranasal was as effective as i.v. fentanyl for the treatment of “severe” post-operative pain in more than 50 adult patients after a variety of general and orthopaedic procedures. When intranasal was compared with intermittent s.c. pethidine after orthopaedic surgery, pain scores and patient satisfaction were improved.34

There are few reported side-effects related specifically to the intranasal route of administration, presumably because, unlike midazolam, none of the opioids are particularly irritant. For example, 85% of children cried after intranasal midazolam compared with 28% of those receiving sufentanil as premedication for day-care anaesthesia.46 However, pethidine was associated with a bitter, burning taste in 20% of

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patients self-administering a nasal preparation after operation.\textsuperscript{34}

Intranasal administration of opioids for postoperative pain relief is not likely to supersede other techniques such as patient-controlled analgesia. However, it may have a role in patients with difficult i.v. access and in the management of acute pain in children. Further work is required in this area.

Inhalational opioids

Although inhalation is considered as a novel method of administration in medicine, opioids have been inhaled for centuries. Investigations into this technique have been encouraged by the suggestion that inhalation is not just another method of systemic administration of opioids, but also a method of targeting specifically opioid receptors in the lungs. Using immunoreactive techniques, opioid peptides have been detected in bronchial mucosal cells\textsuperscript{5} and doses as low as 5 mg of nebulized morphine have been reported to reduce significantly the sensation of breathlessness in patients with chronic lung disease.\textsuperscript{47} This has led some to speculate on the possibility of a true peripheral opioid action. However, a peripheral action is not accepted generally and any observed effects may be secondary to central actions, such as relief of anxiety or an effect on a central attenuation of the response to afferents from peripheral receptors.

The delivery by inhalation of several opioids has been investigated (table 2). In each case the drug has been administered by wet nebulization in a wide range of doses, concentrations and volumes (2–6 ml). Only a few authors have measured and reported absorption pharmacokinetics (table 2). On inhalation of morphine and diamorphine, morphine has been detected in the plasma after 1 min\textsuperscript{25} with a plasma $t_{\text{max}}$ for morphine after morphine and diamorphine inhalation of approximately 10 and 6 min, respectively. A similar $t_{\text{max}}$ after morphine inhalation was found by Massood and colleagues.\textsuperscript{24} Fentanyl is also absorbed rapidly ($t_{\text{max}}$ approx 2 min).\textsuperscript{46} Several factors can affect the bioavailability of inhaled opioids. These include nebulizer design,\textsuperscript{8} amount of drug swallowed\textsuperscript{7} and the inspiratory/expiratory ratio of the respiratory cycle.\textsuperscript{12} Mean bioavailability of morphine has been reported as 17 and 5.5% with a wide variability (table 2).\textsuperscript{7, 24} The larger value was measured during morphine administration to patients receiving positive pressure ventilation.

Inhaled opioids have been investigated for several indications: dyspnoea at rest associated with severe heart or lung disease; exercise tolerance; pain after surgery; and the provision of analgesia in general practice. Effect on breathlessness and exercise tolerance in patients with severe dyspnoea has been studied widely but results are inconsistent. Young and colleagues\textsuperscript{47} reported a marked improvement in exercise

<p>| Table 1 | Opioids administered by the nasal route, with bioavailability and $t_{\text{max}}$ where reported |
|---------|--------------------------------------------------|-----------------|-----------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Bioavailability</th>
<th>$t_{\text{max}}$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>0.1 mg kg$^{-1}$</td>
<td>46%</td>
<td>Median (range) 25 (10–240) min</td>
<td>37</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>0.1 mg kg$^{-1}$</td>
<td>45</td>
<td>6, 12 mg</td>
<td>35</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.027 mg</td>
<td>16</td>
<td>Within 5 min</td>
<td>15, 48</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>1.5, 3, 4.5 µg kg$^{-1}$</td>
<td>15–30 min</td>
<td>2 µg kg$^{-1}$</td>
<td>35</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>0.54 mg</td>
<td>29</td>
<td>27 mg as required</td>
<td>34</td>
</tr>
<tr>
<td>Pethidine</td>
<td>0.25, 0.5, 1, 2 mg</td>
<td>26, 19</td>
<td>27 mg as required</td>
<td>34</td>
</tr>
</tbody>
</table>

<p>| Table 2 | Opioids delivered by inhalation, with bioavailability and $t_{\text{max}}$ where reported; *during mechanical ventilation |
|---------|--------------------------------------------------|-----------------|-----------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Bioavailability</th>
<th>$t_{\text{max}}$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10, 20 mg</td>
<td>Mean (range) 17 (9–35) %*</td>
<td>22, 23</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>Mean (95% CI) 5.5 (3.2–7.8) %</td>
<td>25, 26</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>2 mg</td>
<td>5 mg</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
<td>5 mg</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>10, 25 mg</td>
<td>2.5, 5 mg</td>
<td>10, 25 mg</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>80 mg</td>
<td>Approx. 10 min</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>Approx. 6 min (morphine)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100, 300 µg</td>
<td>Approx. 2 min</td>
<td>46</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>192, 477, 954 µg</td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>50 mg</td>
<td>Approx. 6 min (morphine)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1–20 mg</td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Codeine</td>
<td>15–60 mg</td>
<td></td>
<td></td>
<td>11</td>
</tr>
</tbody>
</table>
endurance in patients with severe lung disease (FEV₁ 0.4–1.4 litre) after inhalation of nebulized morphine 5 mg. However, several authors have reported no effect. For example, Beauford and colleagues found no effect of morphine (maximum 10 mg) in a similar group of patients. In a comparison of inhaled morphine 10 mg and 25 mg with smaller doses of i.v. morphine, no difference could be detected. Furthermore, two other groups found no effect after the same doses used by Young and colleagues. In the latter study, only exercise tolerance was measured and not the subjective symptom of breathlessness. The potential for nebulized morphine to deliver easily administered analgesia in general practice has been investigated in a few subjects. The authors concluded that the technique was suited for use in general practice but expressed concern regarding the inefficiency of the apparatus and unpredictable absorption.

There are fewer published data on the use of inhaled opioids for post-operative analgesia and the problems associated with absorption pharmacokinetics led Chrubasik and colleagues to reject it as a method for future study. Worsley and colleagues investigated the effect of fentanyl inhalation (100 and 300 μg) on pain scores in patients in the recovery room immediately after surgery. The study was not double-blind and involved a wide range of surgical procedures (from varicose veins to vagotomy). They reported an improvement in post-operative pain scores after inhaled fentanyl associated with plasma concentrations 95% lower than those regarded as analgesic. The authors speculated that the mechanism of analgesia during inhalation may differ from that associated with other methods of administration. The same group subsequently reported a double-blind study and concluded that there was no evidence that this mode of delivery was more effective than other parenteral methods.

Problems related specifically to the method of drug delivery reported in the literature include the sensation of a bitter taste with morphine and half-life after removal of the patch is extended because of the formation of a deposit of fentanyl in the skin and surrounding tissue. Rapid and reliable changes to the delivery rate are not possible with this technique—a problem of little consequence in chronic pain but of vital importance in the acute situation.

Iontophoresis is a method of transdermal administration of drugs in an ionized state by electric current. The theory is simple. If a drug is applied to the skin in an electrode of the same charge as the drug (for example, lignocaine/anode) and an electric current is applied, the drug will pass with the current and be deposited not only superficially but in the deeper subcutaneous tissues. The circuit is completed by a drug-free electrode of opposite charge placed close to the active electrode. The efficiency and safety of this technique depend on several factors, such as current wave form and electrode design.

Although interest in iontophoresis has waxed recently, it was originally described by Veratti in 1747 and again by Leduc at the beginning of the 20th century. Leduc showed that iontophoretic application of strychnine to rabbits rapidly produced convulsions. When the polarization of the electrodes was reversed, no effect was observed.

To date, most of the interest in iontophoresis has concerned the administration of local anaesthetics, although other drugs have been investigated—for example, gonadotrophin–releasing hormone, diclofenac, acyclovir, and nicotine. It has been used for the administration of pilocarpine in infants as a diagnostic test for cystic fibrosis. Evidence of deep penetration of lignocaine when given by iontophoresis was demonstrated by Isrsfiel and colleagues, who compared the effect of EMLA cream applied for 60 min under an occlusive dressing with iontophotopically-applied lignocaine (5% lignocaine 0.5 ml; 0.1–0.2 mA cm⁻² for 10 min) on the pain on injection of hypertonic saline into an antecubital vein. They showed that both methods produced skin analgesia but only the iontophoretic technique abolished pain in injection. Recent work has shown the efficacy of the method in preventing pain on injection of propofol.

There is some interest in the administration of opioids by this technique. The potential advantages of the method are illustrated by a study of fentanyl and sufentanil administration in rats. Sufentanil and fentanyl (dissolved in an acetate buffer pH 5) were placed with the anode electrode on the skin of hairless rats and a direct current applied (0.17 mA cm⁻²) between it and a nearby cathode electrode. There was a rapid achievement of sufentanil and fentanyl plasma tₘₐₓ (1.5 h), with pharmaco logically significant plasma concentrations as measured by plasma assay and changes in the tail flick test. The factors affecting the delivery of fentanyl by this technique have been investigated extensively and it is recognized that delivery is affected by the physicochemical nature of the drug and solution and the voltage, duration and nature (for example, exponentially decaying pulses vs² square wave) of the current.

The pharmacokinetics and pharmacodynamics of iontophoretically delivered fentanyl have been reported in five adult volunteers. Current was applied
were 0.76 (0.2) and 1.59 (0.2) ng ml⁻¹ for fentanyl and pethidine delivered by iontophoresis but morphine has not been detectable after 5 min with a tₘₐₓ of approximately 1 h.

A pH of 4.5. Mean (SD) tₘₐₓ after 1 and 2 mA were 122 (14.4) min and 119 (7.4) min respectively. Cₘₐₓ values were 0.76 (0.2) and 1.59 (0.2) ng ml⁻¹. Morphine is the classical water-soluble opioid that is not absorbed transdermally. However, it can be administered by iontophoresis and plasma concentrations after the application of 2 mA of pulsed direct current (2.5 kHz) have been reported in volunteers. Morphine was detectable after 5 min with a tₘₐₓ of approximately 1 h. Maximum concentration ranged from 11.4 ng ml⁻¹ to 19.8 ng ml⁻¹.

There are few published data on the clinical use of opioids delivered by iontophoresis but morphine has been used for postoperative analgesia after total hip or knee replacement surgery. Patients were stabilized on pethidine patient-controlled analgesia and, on the morning after surgery, devices delivering morphine hydrochloride or lactate solution were applied for 6 h. During this time, and up to 12 h after completion of iontophoresis, the active group used significantly less pethidine.

The delivery of fentanyl by iontophoresis has been investigated more extensively than that of other opioids. These data suggest that iontophoresis may enable transdermal administration with a rapid achievement of steady state and the ability to vary delivery rate. This would be potentially beneficial not only in patients suffering chronic pain with breakthrough symptoms but also for the treatment of acute pain — an indication where the simple transdermal patch was found wanting because of its prolonged tₘₐₓ and the inability to vary the rate of administration.

References


