

# Treatment of Tetralogy of Fallot Hypoxic Spell With Intranasal Fentanyl

## abstract

We present the case of a 3-month-old girl who had unrepaired Tetralogy of Fallot who presented to the emergency department with an acute hypoxic episode. The patient was hyperpneic and cyanotic, with an initial oxygen saturation of 56%. She did not respond to knee-to-chest positioning. A single dose of intranasal fentanyl was administered with subsequent resolution of her symptoms and improvement of her oxygen saturation to 78% within 10 minutes. To our knowledge, this is the first report of the successful treatment of a hypoxic episode of Tetralogy of Fallot using intranasal fentanyl. *Pediatrics* 2014;134:e266–e269

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### KEY WORDS

Tetralogy of Fallot, congenital heart disease, tet spell, hypoxic spell, hypercyanotic spell, intranasal, fentanyl

### ABBREVIATIONS

BP—blood pressure  
bpm—beats per minute  
ED—emergency department  
HR—heart rate  
IM—intramuscular  
IN—intranasal  
IV—intravenous  
O<sub>2</sub> sat—oxygen saturation  
RR—respiratory rate  
SC—subcutaneous  
TOF—Tetralogy of Fallot  
VSD—ventricular septal defect

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Tetralogy of Fallot (TOF) is one of the most common forms of cyanotic congenital heart disease, and consists of a ventricular septal defect (VSD), pulmonary valve stenosis, an overriding aorta, and right ventricular hypertrophy.<sup>1</sup> The leading cause of morbidity and mortality in patients who have uncorrected TOF are acute episodes of hypoxia and cyanosis known as hypoxic, hypercyanotic, or “tet” spells. These spells are characterized by a paroxysm of hyperpnea, irritability or agitation, and prolonged crying, leading to worsening cyanosis. The underlying pathophysiology involves a shunting of deoxygenated blood from the right to left ventricle through the VSD, which results from increased pulmonary outflow tract obstruction, decreased systemic vascular resistance, and obstruction of the right ventricular outflow tract. A cycle is established as the subsequent decrease in the partial pressure of oxygen and increase in carbon dioxide in the blood continue to stimulate and perpetuate hyperpnea. This results in increased systemic venous return, and in turn increases the shunting through the VSD.<sup>2</sup> If left untreated and the cycle persists, the patient will become progressively more hypoxic and acidotic, which will lead to eventual cardiac arrest.

The treatment of TOF hypoxic spells is aimed at breaking this cycle by abolishing the hyperpnea and/or increasing the systemic vascular resistance. The easiest and most readily available maneuvers are to place the patient in a knee-to-chest position, which will increase systemic vascular resistance, and to administer oxygen. If these maneuvers are unsuccessful, the most common subsequent treatment is to administer morphine, which calms the patient, resolves the hyperpnea, normalizes the systemic venous return, and increases the partial pressure of oxygen in the blood.<sup>2</sup>

Morphine may be administered by the intramuscular (IM), subcutaneous (SC),

or intravenous (IV) route, all of which can be painful and distressing to the child, and may exacerbate the existing hypoxia. There is also the concern that morphine may exacerbate a hypoxic spell because of its potential to decrease systemic vascular resistance.<sup>3,4</sup> Intranasal (IN) fentanyl is an alternative strategy, combining a painless and effective route of administration with the use of an opioid less likely to cause hemodynamic instability than morphine.<sup>3–6</sup> We describe the first case, to our knowledge, of administering IN fentanyl to successfully treat a child experiencing a TOF hypoxic spell.

### CASE REPORT

A 3-month-old girl with standard TOF physiology, consisting of a large outlet VSD and infundibular and pulmonary valve stenosis, was initially being evaluated in the cardiology clinic for a pre-operative appointment. She began crying vigorously when an EKG was being obtained, and her oxygen saturation ( $O_2$  sat) dropped from “the 80’s into the 50’s.” She did not improve with knee-to-chest positioning and was emergently transported to the pediatric emergency department (ED).

On arrival to the pediatric ED, the patient was grunting and centrally cyanotic, but awake, alert, and crying vigorously. Her initial ED vital signs were a temperature of  $36.7^\circ\text{C}$ , a heart rate (HR) of 176 beats per minute (bpm), respiratory rate (RR) of 63 breaths/minute, blood pressure (BP) of 107/78 mm Hg, and an  $O_2$  sat of 56% in room air. Her extremities were warm and well perfused. A calming environment was immediately optimized, including parental presence and involvement of a child-life specialist; knee-to-chest positioning was performed; and 100% oxygen was administered by using a non-rebreather mask. Eight minutes later, the patient remained awake, alert, and well perfused, but was still crying and cyanotic. Her HR

was 175 bpm, RR 44 breaths/minute, BP 99/74 mm Hg, and the  $O_2$  sat had dropped to 37%. At this time, we administered 10  $\mu\text{g}$  (2  $\mu\text{g}/\text{kg}$ ) of IN fentanyl using a mucosal atomization device. Ten minutes after IN fentanyl administration, the patient had calmed down, was no longer grunting, and remained awake and well perfused. The vital signs had stabilized, with a HR of 163 bpm, RR 34 breaths/minute, BP of 92/48 mm Hg, and an  $O_2$  sat of 78% on a 100% oxygen non-rebreather. At this point, an IV line was placed without complication, so that IV access would be available during the hospital admission. A 20-mL/kg bolus of normal saline was administered. The patient remained in the ED for ~2 hours before admission to the hospital, during which time her clinical condition and vital signs remained stable with  $O_2$  sat  $>80\%$ . She did not receive any additional medications and did not experience any more hypoxic episodes during her ED course.

### DISCUSSION

We have presented the first report of the successful treatment of a TOF hypoxic spell using IN fentanyl. The clinical response that we observed in our patient is consistent with the known pharmacologic and clinical CNS effects of IN fentanyl, and illustrates the successful application of a novel technique in resolving a life-threatening cardiac event. The potential benefits of IN fentanyl rather than SC or IM morphine result from being able to avoid needle sticks, the rapid CNS action achievable by IN administration, and the specific properties of fentanyl.

Both the IM and SC routes have relatively slow onset of action, and require a needle stick that is painful and can aggravate the distress and hyperpnea that perpetuate the cycle of hypoxia and worsening cyanosis. Obtaining IV access to administer morphine can be similarly distressing, is dependent on

the skill of the individual performing the cannulation, and may cause a delay in care. The IN route, on the other hand, is a needleless technique that eliminates the need for a painful injection, thereby providing a less distressing experience of medication administration to a child, and potentially less chance of aggravating the hypoxic spell. The ease of use and needleless technique of IN administration are consistent with the principles of optimizing patient comfort during a hypoxic spell.

The IN route of administration is generally an effective means of delivering medications to the brain, with onset of clinical effects approaching that of IV therapy.<sup>5–8</sup> The nasal mucosa is highly vascularized and allows for rapid absorption through the nasal respiratory epithelium into the systemic circulation, resulting in plasma concentrations comparable to those achieved by IV administration.<sup>9</sup> Additionally, the nasal route delivers medications directly to the brain through the olfactory and trigeminal nerves that are exposed in the nasal cavity (also known as the “nose-brain pathway”). This route circumvents the blood-brain barrier and produces both rapid central nervous system (CNS) effects, as well as resulting in potentially higher concentrations in the CNS than those achieved after systemic administration alone.<sup>6,10–12</sup>

Intranasal fentanyl, in particular, has been well studied and shown to be an

effective and rapid means of producing CNS effects, such as analgesia. Fentanyl has high lipophilicity, which allows it to pass the nasal respiratory epithelium by the transcellular route and rapidly achieve maximum plasma concentrations within 7 to 15 minutes, as well as readily cross from the plasma to the CNS through the blood-brain barrier.<sup>12–14</sup> The time to onset of clinically meaningful analgesia with IN fentanyl administration has been reported to be between 5 and 15 minutes, the rapidity of which could be attributed in part to the direct absorption of medication through the nose-brain pathway.<sup>9,15–18</sup>

The use of fentanyl instead of morphine could also address the possibility that morphine might lower the systemic vascular resistance, and potentially worsen the shunting of deoxygenated blood from the right to left heart. Fentanyl is less likely to cause hemodynamic instability and a decrease in systemic vascular resistance, which would help alleviate the concerns of potentially exacerbating the hypoxic spell.<sup>3,4</sup> There are reports, however, of rigid chest associated with the rapid administration of IV fentanyl, which decreases chest wall compliance and interferes with spontaneous ventilation.<sup>19–22</sup> To date, there have been no reports of rigid chest associated with IN fentanyl administration in children or adults.<sup>23–27</sup>

The implementation of a novel treatment with the benefits of IN administration may

be another means of preventing the progression to more intensive medical, and potentially emergent surgical, interventions. TOF hypoxic spells that do not respond to initial maneuvers will require, if not already obtained, IV access so that additional parenteral therapies can be administered. These include IV fluids, which can improve right ventricular filling and pulmonary flow;  $\beta$ -blockers (eg, propranolol or esmolol), which may relieve pulmonary outflow tract obstruction and increase systemic vascular resistance; phenylephrine, which would increase systemic vascular resistance; or ketamine, which both increases systemic vascular resistance and has a sedative effect. Patients refractory to these treatments may need general anesthesia to abort the hypoxic spell, or may require an emergency cardiac surgery.<sup>2,28</sup>

## CONCLUSIONS

We describe the case of a 3-month-old girl who had unrepaired TOF who presented with a hypoxic episode that was successfully treated with a single dose of IN fentanyl. The unique and specific characteristics of both the IN route and fentanyl suggest that IN fentanyl may be a potentially preferable first-line treatment of TOF hypoxic spells that are refractory to knee-to-chest positioning and oxygen.

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