

## Opiates and Rigidity

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Potent synthetic opiates such as fentanyl, sufentanil, and alfentanil are used on a daily basis because they have little effect on hemodynamic stability in an aging population known for its cardiovascular comorbidity. However, this practice has complications linked to the adverse side effects of opiates in the perioperative period. In addition to the respiratory, cardiovascular, neurological, cutaneous, urinary, and gastrointestinal effects induced by opiates, there is another sign that is, at first glance, rather curious – rigidity. Described for the first time in the journal *Anesthesiology* in 1953,<sup>1</sup> this symptom is just one component of a more complex syndrome with potentially harmful physiological repercussions for a patient if it is unrecognized, ignored, or underestimated.

Clinically, this syndrome is more frequently described in general anesthesia practice when high doses of opiates are given to patients with heart failure. Its incidence is estimated to be > 50% with the synthetic opiates usually used in these patients. However, these patients represent only part of the population at high risk of developing this syndrome. When it does occur, usually more frequently during induction, it starts 1-2 minutes after a bolus injection of opiates and lasts from 10-20 minutes. The patient adopts a characteristic position that is produced by a simultaneous contraction of the main muscles, as confirmed by electromyographic studies.<sup>2</sup> Both pharmacokinetic and pharmacodynamic mechanisms responsible for this effect will be described in this issue. Preventive methods can be used to reduce the probability of the occurrence of this syndrome and to diminish its severity. The nature of the treatment, curative or symptomatic, will be selected depending on the moment the symptoms occur. These will be reviewed in detail.

### WHICH OPIATES ARE IMPLICATED?

Opiate-induced rigidity has been, for the most part, reported following the use of fentanyl, alfentanil, and sufentanil, as they are the molecules most frequently used to produce balanced general anesthesia (Table 1). In addition to these powerful molecules, morphine, meperidine and, more recently, remifentanil can be added as potential inducers. It appears that the most potent opiates are more likely to induce rigidity. The organ distribution of these molecules and their affinity for receptors are particularly important factors in this situation. Since it is believed that opiate-induced rigidity is due to a central agonist effect, it is likely that a rapid increase in concentration at the effector site and binding to the receptor are key elements in this phenomenon. Using the specific agonists  $\delta 1$  and  $\kappa 1$ , it was demonstrated that certain molecules may have potential modulating effects on muscle rigidity.<sup>3</sup> The observed variable response is probably due to the overall composition of the ensemble of opiate receptors in an individual and the combined  $\mu$ ,  $\delta$ , and  $\kappa$  effects of the different opiates used. Most opiates likely have the potency to induce muscle rigidity; however, the severity and frequency of this clinical phenomenon depend on the opiate dose received, the method of administration, and the administration of coanalgesic medications. It is equally important to note that the use of nitrous oxide potentiates opiate-induced rigidity.<sup>4</sup>

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**TABLE 1:** Opiates and the doses involved

• Fentanyl:	12-15	µg/kg
• Sufentanil:	2.6-3.5	µg/kg
• Alfentanil:	175	µg/kg

**HIGH-RISK POPULATIONS**

The risk of witnessing the opiate-induced rigidity syndrome is linked to the type of surgery and anesthesia on the one hand, and the comorbidity of the patients on the other. Patients undergoing major surgery under general anesthesia who may be susceptible to rigidity are those suffering from heart failure, myocardial ischemia, or any other source of hemodynamic instability. They will often receive a high-dose opiate bolus injection, accompanied by a short-acting dose of a benzodiazepine such as midazolam. This pharmacological combination is, in fact, an alternative to using a cardiodepressive hypnotic agent such as thiopental or propofol.

Certain patients may present with rigidity following the administration of doses that are lower than those that usually precipitate symptoms (Table 2). This population includes newborns (postoperative or in intensive care) presenting with an immature blood-brain barrier. The pediatric population is more vulnerable to this syndrome. In fact, the onset of rigidity in the pediatric population has been demonstrated on several occasions following the administration of fentanyl at doses lower (2.5-6.5 µg/kg) than those inducing the syndrome in the adult (12-15 µg/kg). It has also been observed that the geriatric population, adults in the ICU with severe metabolic conditions, patients with neurological deficits, and those being treated with neurotropic agents, are at increased risk of rigidity. A trend seems to emerge from this rather heterogeneous group. It appears that immaturity and neurochemical degeneration, as well as the administration of medication causing neurotransmitter disturbance, favour the onset of this syndrome. Sometimes, the only factor identified is the administration of a medication acting on the dopaminergic, noradrenergic, or serotonergic system.

**TABLE 2:** High-risk populations

• Newborns
• Elderly persons
• Patients with cardiac failure
• Patients in intensive care
• Neurological conditions
• Neurotropic medications

**TABLE 3:** Symptomatology

• Whole-body rigidity
• Upper airway (glottis) closure
• Tonic-clonic movements
• Athetotic movements
• Vertical nystagmus

**SYMPTOMATOLOGY**

Symptoms of rigidity can be divided into three groups representing the different periods during which the syndrome is manifest (Table 3). Induction, emergence, or the late postoperative period are all critical moments during which certain symptoms will be observed more frequently and their morbidity will be more significant.

When rigidity occurs during anesthesia induction, signs include flexing of the upper limbs, extension of the lower limbs, immobility of the head, rigidity of the chest and abdomen, and jaw closure. The critical period occurs rapidly after injection of the opiate, at about 70 seconds for alfentanil, and 180 seconds for fentanyl. Therefore, the symptoms theoretically appear before the maximum concentration at the target organ is reached, at the level of the central nervous system. The anesthesiologist may observe that the patient is difficult and sometimes impossible to ventilate. Contrary to what was once believed, the main reason for the difficulty in ventilating the patient is not the increase in thoraco-abdominal muscle tone, but upper airway (glottis) closure.<sup>5</sup> Indeed, the majority of studies on this phenomenon reveal that there is no significant change in the intubated patient's ventilatory compliance. On the other hand, patients being ventilated with a mask will show an increase in the resistance to ventilation. The mechanism was recently illustrated through fiberoptic vision, demonstrating closure of the glottis causing obstruction.<sup>6</sup> However, this new information does not imply that thoraco-abdominal rigidity does not contribute partially to ventilation difficulties.<sup>7</sup> This rigidity causes reduced thoracic compliance and hypoventilation with respiratory acidosis, which in turn provokes a drop in blood pressure and cardiac output following the decrease in venous return. The slight decrease in oxygen consumption in the brain caused by the opiate cannot compensate for the increase in central venous pressure, the decrease in cerebral blood flow, and the increase in intracranial pressure that puts the patient at risk of cerebral hypoxia.

While muscle rigidity is sometimes observed during the second critical period, ie, during emergence and the minutes following it, it is the appearance of tonic-clonic or athetotic movements and ver-

tical nystagmus that are the most predominant signs. Most of the available data suggest that these abnormal movements are not linked to cortical or subcortical convulsive brain activity,<sup>8</sup> but are the effects of a sudden increase in the concentration of opiates on the reticular formation. Indeed, during exposure to high doses inducing rigidity or abnormal movements, patients whose brain activity was recorded by electroencephalography (EEG), did not exhibit any convulsive activity.

It is difficult to precisely estimate the level of plasma concentration that is associated with the appearance of symptoms, since the syndrome occurs in a rather unpredictable fashion. However, there are reference values for clinicians practicing intravenous anesthesia.<sup>9,10,11</sup> It must be emphasized that episodes of rigidity or abnormal movements capable of causing acute respiratory failure were registered as late as 9 hours after exposure to an opiate.<sup>12,13</sup> Another disconcerting fact is that episodes can occur without any observed early symptoms. The delayed appearance of rigidity is probably the most worrisome manifestation and the most curious, since it implies that a third episode of clinically significant symptoms may appear when supervision of the patient has relaxed. The risks associated with this complication may be compounded by the simultaneous onset of other side effects of opiates such as inhibition of the sympathetic compensatory mechanisms, a vagomimetic effect, and direct respiratory depression of the medullary and pontine centers, with diminution of the carbon dioxide response. These considerations suggest that the physician should remain vigilant during the entire perioperative period to quickly identify a complex range of signs and symptoms.

## MECHANISMS

The rigidity observed during general anesthesia induction, upon emergence, or later, and the tonic-clonic movements and vertical nystagmus, are most likely caused by a common neurophysiological mechanism. This type of response possibly represents the final expression of the effects of the agonist on the different central opiate receptors, depending on how they are combined in each patient. Thus, immaturity, a neurological pathology, or treatment with neurotropic agents will induce effects that are as variable as they are unpredictable. This response may be evident at different levels: physiological, pharmacological, or cellular.

As mentioned previously, recent clinical studies in humans suggest that the principal mechanism responsible for difficult ventilation during an episode of rigidity is upper airway (glottis) closure<sup>6</sup> following the effect of the opiate. While it has been visually demonstrated that the decrease in total ventilatory compliance is associated with mechanical closure of the glottis, certain studies also note a small

decrease in total pulmonary compliance in certain intubated patients.<sup>4,10</sup> The problem is different in the younger population, as in the case with newborns placed in the ICU who require ventilatory support. Following a dose of 4 µg/kg of fentanyl in this particular population, an increase in the peak ventilatory pressure is necessary to oxygenate these patients. This phenomenon may be due to the fact that the newborn ribcage is much more compliant and the pulmonary parenchyma more rigid. Muscle contractions in the thoracic and abdominal muscles during an episode of rigidity are therefore able to produce a more significant decrease in total respiratory compliance. That being said, a formal study in infants < 6 months that measured total respiratory compliance in intubated patients who received 4 µg/kg of fentanyl, showed no decrease in total respiratory compliance.<sup>14</sup> Hence, the question remains unresolved in young infants. The use of powerful, synthetic opiates in these patients must take into account the associated risks and benefits.

Tonic-clonic and athetotic movements or vertical nystagmus that occur during the perioperative period are not accompanied by EEG changes.<sup>8</sup> They more likely correspond to activation of spinal and subcortical centers. Indeed, in a retrospective study,<sup>8</sup> the only high-amplitude signs seen on EEG following the administration of opiates were related to contamination due to the movements of the patients during the recording procedure.

The first hypothesis about the neurochemical nature of abnormal movements implicated the dopaminergic system, a logical explanation since similar abnormal movements are observed in patients with Parkinson's disease. Upon further review, it was concluded that the complication likely originates in the gabaergic, adrenergic, and serotonergic systems that together form the substratum. It appears that the reticular formation is the site involved since it contains opiate receptors; however, they are also found in the limbic system, the hypothalamus, the caudate nucleus, the periventricular gray substance, the periaqueductal gray matter, and the frontal cortex. In stimulation studies with opiates at high doses,<sup>16</sup> metabolic activity in the limbic system appears to be significantly disturbed. In fact, involvement of both sites (reticular formation and limbic system) is logical in that the reticular formation and, more precisely the nucleus raphe magnus, projects towards the limbic structures and most likely represents the cornerstone of the clinical scenario.

The dorsal portion of the raphe nucleus projects upwards toward the basal nuclei, the medial portion projects toward the limbic system, and the medullary portion of the same nucleus forms a descending medullary pathway. Therefore, it seems that the reticular formation, the basal nuclei, and the limbic system form the substratum needed to generate

the observed symptoms. It might then be legitimately asked if the reticular formation acts as an ascending activator or whether it represents a final descending pathway. The current experimental data suggest that the reticular formation is where the effects of opiates are expressed. This medullary structure situated in the pons includes two functionally distinct nuclei:

- The nucleus raphe magnus is an important descending inhibitory pathway. Low doses of opiates applied locally to this nucleus produce an increase in the number of action potentials generated by the serotonergic neurons. This leads to inhibition of spinal activity in the posterior horn, hence a decrease in nociceptive afferents. This pathway may be modulated via the disinhibition of serotonergic neurons under the influence of a group of gabaergic inhibitor interneurons located in the same nucleus.

- The locus coeruleus, the second nucleus in the reticular formation, also projects into the spine, more precisely towards the anterior horn. This nucleus is involved in the motor response observed during an episode of opiate-induced rigidity. Experimental data suggest there is activation of the noradrenergic neurons with stimulation of the motor neurons of the anterior horn. What remains uncertain, however, is the effect of opiates at this level. It is acknowledged that opiates have an inhibiting effect on the genesis of action potentials; it appears then that opiates inhibit the gabaergic interneurons of this nucleus to produce an increase in motor activity and activation of the EMG in experimental animals.

It is assumed that the heterogeneous distribution of opiate receptors from one individual to another is responsible for the unpredictable aspect of opiate-induced rigidity. The use of specific agonists of  $\delta 1$  and  $\kappa 1$  receptors clearly demonstrates that these two subtype receptors play a modulating role in the response to opiates. More precisely, these two receptors attenuate the rigidity induced by activation of the  $\mu$  receptors. To this modulating mechanism, one must add the role of  $\alpha 1$  adrenergic receptors<sup>17</sup> that, when blocked, produce a decrease in rigidity.

The cell membrane mechanism at the root of rigidity is generated by opiates at high doses<sup>18</sup> and involves inhibition of calcium conductance and activation of potassium conductance in the projection neurons of the reticular formation.

At the pharmacological level, one may conclude that any change that increases the concentration of the opiate in the central nervous system will cause an increase in symptoms of rigidity. Thus, any increase in the permeability of the blood-brain barrier (usual in a newborn), or pathologically in an adult with a traumatic,

inflammatory, neoplastic, or degenerative condition, will be conducive to the onset of this clinical scenario. Furthermore, any change in the metabolism or excretion of the opiate may exacerbate symptoms. The mechanisms most likely responsible for delayed episodes of rigidity include:

- a gastrointestinal cycle<sup>19</sup> that lengthens the time the opiate is present in the circulation
- the time it takes for the narcotic to penetrate the central nervous system
- the presence of a second target with a slower equilibrium constant that is affected by the opiate several minutes or hours after administration of the initial bolus.

#### PREVENTION OF RIGIDITY

It is essential to be on the lookout for this syndrome, recognize its precipitating factors, and identify populations at risk. In the case of potent, synthetic opiates used in the operating room (ie, fentanyl, sufentanil and alfentanil), the physician must be aware of the respective doses causing rigidity (Table 1) and, as much as possible, stay below these doses. Obviously, the opiate dose must be chosen to suit the particular clinical situation, but it is possible to administer it in fractional amounts, thus limiting the peak in plasma levels achieved with a single bolus. Limiting the speed of administration of the bolus will also decrease the incidence of rigidity. As mentioned above, one must be more vigilant when dealing with populations at risk or, if need be, limit the total dose of the opiate when the use of an adjuvant is possible. Avoid any metabolic disturbance that induces significant acidosis as it could potentially delay gastric emptying and lengthen the gastrointestinal cycle of the opiate; this situation is conducive to the onset of the delayed rigidity. It is noteworthy that the severity of muscle rigidity<sup>4</sup> is reduced if nitrous oxide is not used during anesthesia.

Many pharmacological agents used to limit the incidence and severity of this syndrome have produced mitigated results. The benzodiazepines and droperidol used in premedication have not succeeded in preventing the syndrome, and current induction agents have no preventive effect. Etomidate is potent enough to activate epileptic foci. The nondepolarizing neuromuscular blocking agents used in defasciculating doses do not prevent muscle rigidity. In fact, a complete dose of the chosen nondepolarizing neuromuscular blocking agent must be administered at the moment of induction to prevent complications linked to opiate-induced rigidity (Table 4).

There are, however, some encouraging experimental data on the subject of preventive

**TABLE 4:** Prevention

<ul style="list-style-type: none"> <li>• Recognize the high-risk patient</li> <li>• Decrease the bolus</li> <li>• Slow injection of bolus</li> <li>• Avoid nitrous oxide</li> <li>• Treat slow gastric emptying</li> </ul>
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pharmacological treatment. Ketanserin, a 5HT-2 and  $\alpha$ -1 type antagonist reduces symptoms, indicating the probable involvement of the serotonergic pathways and more specifically, the raphe nucleus, a constituent of the reticular formation. The use of the  $\alpha$ 1 antagonist, prazosin<sup>17</sup> reduces the intensity of the phenomenon, an indirect indicator that an adrenergic pathway is involved. While these two molecules attenuate the syndrome, they are not used in practice because they cause hemodynamic instability.

A more promising option is to use dexmedetomidine (30  $\mu$ g/kg), which through a central  $\alpha$ 2 agonist effect, reduces the severity of muscle rigidity. The pharmacological development of type  $\delta$ 1 and  $\kappa$ 1 specific agonists have also demonstrated their ability to diminish the rigidity produced by potent opiates and should also reduce the incidence and severity of the syndrome.

The future will probably see the development of molecules with all the preponderant  $\delta$ 1 and  $\kappa$ 1 effects, in addition to their  $\mu$  analgesic effect, enabling the safe use of opiates at high doses when required in a clinical situation.

## TREATMENT

Little emphasis is placed on the treatment of this syndrome since, once the diagnosis is made, it is a relatively simple matter to treat. If rigidity occurs during induction, the most common approach is to paralyze the patient as quickly as possible in order to relax the periglottic contraction. When rigidity occurs during emergence or the immediate or late postoperative period, paralysis is no longer indicated; instead, treatment with naloxone (1-10  $\mu$ g/kg) is used to control the symptoms and prevent respiratory depression (Table 5).

The onset of tonic-clonic movements during the immediate or late postoperative period must be treated in the same way as an episode of rigidity, that is quickly, to avoid complications due to abnormal movements such as injuries or an increase in total oxygen consumption. The pharmacological treatment is the same as for an episode of rigidity; indeed, the tonic-clonic movements will subside after a dose of naloxone

**TABLE 5:** Treatment

<ul style="list-style-type: none"> <li>• Cardiopulmonary support</li> <li>• Rapid neuromuscular blocking at induction</li> <li>• Naloxone (1-10 <math>\mu</math>g/kg) after arousal</li> <li>• Hospitalization</li> <li>• Close surveillance</li> </ul>
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(1-10  $\mu$ g/kg). Patients must be supervised in case of recurrence. There are no randomized studies on the probable presentation of a second episode of rigidity following emergence after an episode during induction. Nonetheless, it is strongly recommended that these patients be kept under observation for 24 hours, regardless of the dose or opiate involved, given the unpredictability and gravity of delayed complications (up to 9 hours postoperatively). This decision will have an impact, particularly in cases of day surgery. Since all the delayed episodes cited in the literature are one-time events, observation after the event may be limited to simple measures, such as more frequent visits to the patient or oximetry every 2 hours. It is obviously recommended to consult a neurologist in the case of an epileptic patient whose medication is not well-adjusted (blood serum level below therapeutic level). If the rigidity is accompanied by myocardial or cerebral distress, aggressive intensive cardio-respiratory support should be started.

## CONCLUSION

It is vital that an episode of opiate-induced rigidity be recognized quickly and the appropriate treatment started immediately. Particular care should be taken when treating young children, elderly persons, and patients with severe metabolic or cerebral conditions, as these populations present a higher incidence of this syndrome.

The initial symptoms may be sudden, but they are easily treated. Upper airway (glottis) closure, which occurs simultaneously with the onset of muscle rigidity, leads to difficult ventilation during the preintubation period. Tonic-clonic movements and vertical nystagmus are not signs of an epileptic seizure. The reticular formation seems to be the seat of this complication and the dopaminergic, serotonergic, and adrenergic pathways play a role in the development of the response to opiates.

The acute difficulty with ventilation encountered during anesthesia induction will cause little morbidity when it is detected and treated promptly with a nondepolarizing neuromuscular

blocking agent. The problem is more complex if the syndrome occurs after emergence. Then the patient may present with muscle rigidity and tonic-clonic movements. In both cases, the potential for morbidity is greater because supervision of the patient may be relaxed at that time. Both symptoms may be controlled by a dose of naloxone (1-10 µg/kg), which can be repeated if necessary. It is wise to hospitalize day surgery patients presenting with an unexpected episode of opiate-induced rigidity. Other measures include extending the period during which vital signs are taken frequently and oximetry measurement for these patients once they return to their ward. Muscle rigidity and tonic-clonic movements may be observed during the postoperative period, that is, on arousal and up to 9 hours later. Avoiding bolus injections of opiates and reducing the speed of injection may limit the onset of these symptoms.

Certain pharmacological solutions look promising in terms of preventing this syndrome. Dexmedetomidine may help diminish its severity and specific agonists,  $\delta 1$  and  $\kappa 1$ , that are now under development should potentially be able to do so as well. The low morbidity related to this problem does little to promote research on the subject. Thus, the onus is largely on the physician to reduce the incidence and morbidity linked to this phenomenon.

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