Guidelines in analgesia: tolerance and dependence

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The desired level of analgo-sedation for the critically ill patient has undergone an important change. In the past the goal was meanly sedation in order to completely detach the patient from his environment. Nowadays, the goal is to keep patient comfortable by balanced analgesia and sedation. Continuous infusions are preferred on drug administration by intermittent bolus injections. Continuous infusions allow for greater controlled administration, minimize high blood concentrations and avoids subtherapeutic levels. However, it is very easy to start an infusion, but much more difficult to stop. Drugs can accumulate because of overdosing or elimination impairment. Consequences of the prolonged administration of sedative and analgesic agents to the intensive care unit (ICU) patients include tolerance, physical dependence, and withdrawal due to abrupt discontinuation of drug therapy[1].

Definitions

It is important for clinicians an appropriate understanding of terminology and mechanisms relative to these phenomena.
Tolerance is a pharmacological phenomenon that develops with the repeated use of a drug and is defined by a decrease in a drug's effect over time or the need for increasing doses to maintain similar pharmaceutical effects[1]. If tolerance appears over a short time frame, then it is termed acute tolerance or ***tachyphylaxis***. Tolerance has been divided into various subcategories. Innate tolerance refers to a genetically predetermined lack of sensitivity to a drug, whereas pharmacokinetic tolerance refers to changes in a drug's effect because of alterations in distribution or metabolism. Learned tolerance is the reduction in a drug's effect as a result of learned or compensatory mechanisms. Finally, pharmacodynamic tolerance or "True Tolerance" is related to changes at or distal to the receptor following prolonged drug exposure. Plasma concentration of the drug remains constant but results in a decreased effect.
Generally pharmacodynamic tolerance is caused by changes at the cellular level. Several molecular mechanisms are involved in the development of opioids tolerance, mediated by the protein kinase systems (protein kinase C and cyclic AMP-dependent protein kinase), by the cholecystokinin and by the N-metyl-D-aspartate (NMDA) receptors[2]. Finally, self-induced neuroadaptive change of neuronal sensitization may be responsible of tolerance following prolonged opioid exposure.

Physical dependence is defined by the occurrence of an abstinence syndrome (withdrawal) following an abrupt reduction of the drug or the administration of an antagonist.
Withdrawal syndrome includes the physical signs and symptoms that manifest when the administration of a sedative or analgesic agent is abruptly discontinued.
When a potent exogenous opioids is administrated over a long period of time, such as during ICU analgo-sedation, the endorphinergic system seems to be suppressed. Following abrupt discontinuation of opioids therapy, abstinence symptoms may be related to postinhibitory increased endorphin synthesis. Beta-endorphin and met-enkephalin levels seem to be inversely correlated with withdrawal symptom intensities in ICU patients[3].
Psychological dependence, which is the need for a substance because of its euphoric effects, should be shared from physical dependence.
Addiction is a chronic neurobiological disease caused by genetic, psychosocial and environmental factors. Addiction is a complex pattern of behaviours characterized by the repetitive, compulsive use of a substance despite harm, associated with antisocial or criminal behaviour to obtain the drug.
Psychological dependence and addiction are extremely rare after the appropriate use of sedative/analgesic agents in the ICU setting.

Tolerance and dependence in ICU

The potential for opioid, benzodiazepine, and propofol withdrawal should be considered after high doses or more than approximately seven days of continuous therapy[1].
The incidence of withdrawal in ICU is up to 60-80% of patients after long-term sedation. In a recent German survey, the frequency of withdrawal/transitional syndrome stated an

Table I. – Calculation of withdrawal intensity in patients following discontinuation of sedation in intensive care unit[3].

Parameters	0	1	2	3
Temperature*	<36	38-37	37-38	>38
HR**	<90	<100	100-120	>120
MAP***	<90	<100	>100	>120
Sweating	Absent	Mild	Moderate	Severe
Mydriasis	Absent	Mild	Moderate	Severe
Diarrhea	Absent	Mild	Moderate	Severe
Nausea/vomiting	Absent	Mild	Moderate	Severe
Restlessness	Absent	Mild	Moderate	Severe
Yawning	Absent	Mild	Moderate	Severe

* Temperature [°C]
** Heart Rate (HR) [beats/min]
*** Mean Arterial Pressure (MAP) [mmHg]

average rate of 20%, which is explained by the fact that all patients, even short-term patients, were included[5].

The symptomatology of withdrawal syndrome varies from patient to patient and may be affected by several factors, including the agent involved, the patient's age, cognitive state, and associated medical conditions.

It is sometimes difficult to assess whether confusion and agitation in the ICU patients are due to withdrawal of benzodiazepines and opioids or to other factors more related to the ICU environment, or rather to another drug or disease state.

Based on Himmelsbach's scale[6], signs of opioid withdrawal syndrome are pupillary dilation, sweating, lacrimation, rhinorrhea, piloerection, tachycardia, vomiting, diarrhea, hypertension, yawning, fever, and tachypnea. Symptoms of opioids withdrawal include drug craving, restlessness, irritability, increased sensitivity to pain, nausea, cramps, muscle aches, dysphoria, insomnia, and anxiety. Signs and symptoms of acute benzodiazepine withdrawal syndrome include dysphoria, tremor, headache, nausea, sweating, fatigue, anxiety, agitation, increased sensitivity to light and sound, paresthesia, strange sensations, muscle cramps, myoclonus, sleep disturbance, dizziness, delirium, and seizures.

A composite set of opioid and/or benzodiazepine withdrawal criteria was created by Cammarano *et al.*[7] in 1998 to identify patients with a diagnosis of "acute withdrawal syndrome". Korak-Leiter *et al.*[3] used a scoring system (Tab. I) to evaluate the intensity of withdrawal symptoms in patients after long-term administration of an opioid/hypnotic-based sedation.

In a retrospective analysis of medical records in an adult trauma/surgical ICU, Cammarano *et al.*[7] observed a high (32.1%) frequency of acute withdrawal syndrome potentially related to the administration of analgesic or sedative medications. The group of patients experiencing withdrawal were of younger age and there was a significant association between withdrawal syndrome and a diagnosis of ARDS. In addition, they were significantly more likely to have received neuromuscular blocking agents or propofol for >1 day while in the ICU. Duration of mechanical ventilation, and duration of benzodiazepine, or propofol therapy were significantly greater in the withdrawal group, which received a significantly higher mean daily doses of fentanyl and lorazepam equivalents. These differences suggest that prolonged administration of higher daily doses of opioids and benzodiazepines and prolonged mechanical ventilation, combined with the use of neuromuscular blocking agents and propofol, may exacerbate development of withdrawal syndrome after discontinuation of analgo-sedation in ICU. Patients with ARDS, who often require prolonged mechanical ventilation, and administration of neuromuscular blocking agents may be at increased risk for withdrawal syndrome related to these drugs.

In addiction, relative overdosing of patients could have contributed to development of withdrawal symptoms. The daily doses received by patients who experienced withdrawal were several fold higher than those recommended.

Finally, patients experiencing withdrawal received a significantly lower mean daily dose of haloperidol, that could act to attenuate the signs or symptoms of acute withdrawal syndrome. Haloperidol is the preferred agent for the treatment of delirium in critically ill patients[4]. Haloperidol has been studied in the treatment of alcohol withdrawal syndrome (AWS) occurring in adult ICU patients. Haloperidol was shown to be effective in reducing the severity of AWS in patients with productive psychotic symptoms[8]. Olanzapine, a second-generation antipsychotic, may be a safe alternative to haloperidol in delirious ICU patients, especially when haloperidol is contraindicated[9]. Patients should be monitored for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol[4].

Combination therapy of opioids and benzodiazepines may increase the risk of opioids tolerance. The combination of sufentanil with a benzodiazepine (Midazolam) results in significant increase in opioid requirement within 72 h, and a longer duration of abstinence symptoms in the period following sedation[3]. The cause of such an increase could be a benzodiazepine-related inactivation of the descending inhibitory serotininergic and noradrenergic system, as well as a benzodiazepine-induced down-regulation of opioid receptors in the CNS.

Short-acting drugs should be considered agents of choice, when the goal of analgo-sedation is to allow rapid awakening and neurologic evaluation on a daily basis. However, acute tolerance has been observed after short-acting drug administration. In addition, withdrawal symptoms may be more severe after cessation of shorter-acting rather than longer-acting drugs. Between benzodiazepines, Midazolam offers multiple advantages for sedation in the ICU. The usually short elimination half-life of midazolam accounts for less drug accumulation and rapid recovery after prolonged administration. In general, sedation levels are easily controlled with titration of midazolam infusion However, tolerance to midazolam has been described in ICU patients after continuous intravenous infusion for >7 days[10]. Benzodiazepine withdrawal symptoms have been reported when midazolam infusion is ceased. Withdrawal phenomena have been reported more commonly when large doses of midazolam have been administered over long periods of time (>3 to 5 days), both in adult and paediatric patients. Reduction of the infusion rate by 50% decrements is preferred to abrupt discontinuation. Alternatively, a transition to long-acting benzodiazepines may be of benefit. Oral lorazepam has been advocated to prevent withdrawal from prolonged midazolam infusions in paediatric ICU patients. The subcutaneous route has been used as an effective alternative to intravenous administration, for gradual weaning from sedative/analgesic agents after prolonged sedation in the pediatric ICU[11].

Similarly to Midazolam, withdrawal syndrome after cessation of short-acting opioid-based sedation has been seen in the ICU setting. Three case reports of severe and fast-onset withdrawal syndrome, with signs of acute tolerance, have been

described after remifentanil-based sedation[12]. Authors reported the incidence of withdrawal syndrome, between patients receiving a similar sedation, was about 10%. Symptoms occurred approximately 10 min after discontinuation of the short-acting remifentanil over a short (2 hours) period of time. Current guidelines recommend to prevent opioid withdrawal syndrome by gradually tapering the infusion rate[4]. Opioids should be weaned in daily dose decrements of no greater than 5% to 10% to avoid acute withdrawal syndrome in critically ill patients exposed to high doses of opioids[13]. Authors recommended tapering a remifentanil-based sedation over 24-48 h, in conjunction with a concurrently running morphine infusion[12].

Treatment of withdrawal syndrome

The first rule is to prevent drug withdrawal by avoiding abrupt discontinuation of therapy and by gradual tapering doses systematically[4].

Once withdrawal syndrome is diagnosed, pharmacological treatment include the use of alpha-2 agonists, such as Clonidine and Dexmedetomidine, for sedative withdrawal, and Methadone for patients with opioid withdrawal symptoms[14].

Withdrawal from narcotics is characterized by a hypernoradrenergic state. Opiates and alpha-2 agonists act synergistically on central sympathetic outflow. The use of alpha-2 agonists for the amelioration of opioids withdrawal symptoms has been described. Their effects are largely mediated by the postsynaptic alpha-2-A-receptor subtype in the locus caeruleus. By decreasing sympathetic outflow and noradrenergic activity, and increasing parasympathetic tone, alpha-2 agonists reduce metabolism, heart rate, myocardial contractility and oxygen requirements, and vascular resistance. Clonidine has been used to attenuate the symptoms of withdrawal from narcotics for more than 20 years. Clonidine infusion may be started at a dose of 1 mcg/kg/h and titrated according to need and to haemodynamic parameters (HR and MAP)[3]. Dexmedetomidine is an alpha-2-adrenergic agonist with an affinity for the alpha-2 receptor 8 times more than that of clonidine, resulting in more selective alpha-2-A activation and less of the deleterious alpha-1 stimulation. Dexmedetomidine has been used to facilitate acute benzodiazepine and opioid withdrawal both in adults[15] and in infants[16]. The advantage of dexmedetomidine is that it provides sedation, analgesia, and blunted sympathetic activity without significant respiratory depression. Dexmedetomidine relieve anxiety, reduce opioid needs, and facilitate conscious sedation.

In conclusion, tolerance, physical dependency, and withdrawal syndrome should be familiar to an intensivist and should be considered when discontinuing analgo-sedation therapy. However, concerns regarding these phenomena should not limit the use of analgesic/sedative agents in the ICU population.

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