Management of narcotic toxicity in ICU

An essay submitted for partial fulfillment of master degree in intensive care

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بسم الله الرحمن الرحيم
وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ
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List Of Abbreviations

Abbr	Full term
NCCN	NATIONAL Comprehensive cancer network
GABA	gama-aminobutyric acid
NMDA	N-methyl-D-aspartate
NSAID	Non-Steroidal Anti-Inflammatory Drug
5-HT_{2A}	5-hydroxytryptamine 2A
ACTH	adrenocorticotropic hormone
BFI	Bowel Function Index
BPM	breaths per minute
cAMP	cyclic adenosine monophosphate
CINV	chemotherapy-induced nausea/vomiting
CNS	central nervous system
CTZ	chemoreceptor trigger zone
CYP450	cytocrome P450
D2	Dopamine
DHEAS	dehydroepiandrosterone sulfate
DSM-5	Diagnostic and Statistical Manual of Mental Disorders

ECG	Electrocardiogram
EMS	Emergency medical services
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GnRH	gonadotropin releasing hormone
H1	histamine
IBD	Inflammatory bowel disease
IVP	intravenous push
LES	lower esophageal sphincter
LH	lutenizing hormone
M_1	muscarinic
MNTX	Methylnaltrexone
NBS	narcotic bowel syndrome
OIC	Opioid induced constipation
OIH	Opioid Induced Hyperalgesia
OINV	opioid-induced nausea and vomiting
OIRD	**Opioid-induced respiratory depression**
OPIAD	opioid induced androgen deficiency
OxyNal	oxycodone/naloxone

PAMORAs	peripheral acting mu-opioid receptor antagonists
PCA	patient-controlled analgesia
PEG	Polyethylene glycol
PKA	protein kinase A
PONV	postoperative nausea/vomiting
PR	prolonged release
RCTs	randomized controlled trials
RIE	radiation-induced emesis
SBMs	spontaneous bowel movements
SHBG	sex hormone binding globulin
UDP	uridine diphosphate
UGTs	uridine glucuronosyl transferase
ICU	Intensive care unit

INTRODUCTION

Virtually every patient admitted into ICU is administered narcotic therapy. One may encounter a variety of pathologies of different grades of severity, in addition, the associated morbidity, the circulatory instability, and the pharmacodynamic alterations in critically ill patients can make treatment guidelines difficult to establish and implement ***(Costa et al., 2006).***

The provision of narcosis for patients in ICU is important in controlling pain, dyspnea, and delirium; relieving agitation and anxiety; decreasing oxygen consumption; providing amnesia; preventing seizure; maintaining brain function; applying neuromuscular blockage; aiding compliance with mechanical ventilation; thereby maintaining patient comfort ***(Muellejans et al., 2004).***

Fentanyl is a lipophilic, short-acting, synthetic opioid with a piperidine chemical structure ***(Prommer, 2009).*** It is used for the induction of anesthesia as well as for the management of severe pain ***(Palmer, 2010).*** Fentanyl family

include sufentanil, alfentanil and remifentanil ***(Vardanyan and Hruby, 2014).***

In one study, ***Cevik et al., (2011)*** compared the effect of fentanyl and remifentanil on ICU patients. Remifentanil provided significantly more potent and rapid effect and a statistically nonsignificantly shorter time to discharge. On the other hand, remifentanil also caused a significantly sharper fall in heart rate within the first six hours of treatment.

Morphine can be administered subcutaneously or as intravenous infusion. This opioid forms an active metabolite and presents unpredictable kinetics in patients with organ dysfunction In liver failure, there is a decrease in the metabolism of morphine, whereas in kidney failure there is an accumulation of its metabolites ***(Sakata, 2010).***

For patients in shock, the elimination is slower ***(Kumar and Brennan, 2009).*** The risk of respiratory depression is higher in newborns, in patients with cognitive alteration, those who are hemodynamically unstable, with history of apnea and respiratory disease. Morphine can cause arterial hypotension ***(Ahlers et al., 2010).***

Hydromorphone is a potent semisynthetic opioid agonist which is available in several forms including injection immediately release or retard tablets. Its analgesic efficacy surpasses morphine ***(Telekes, 2008).*** Side-effects include nausea, vomiting and itching ***(Felden et al., 2011).***

Tramadol hydrochloride is a widely prescribed, centrally acting analgesic. Tramadol has dual mechanisms of action by which analgesia may be achieved: micro-opioid receptor activation and enhancement of serotonin and norepinephrine transmission ***(Reeves and Burke, 2008).*** The most commonly reported adverse events include dizziness, followed by vomiting, nausea, somnolence and constipation, often in sequence ***(Vazzana et al., 2015)..***

AIM OF THE WORK

The present essay aims at discussing management of narcotic toxicity in ICU patients.

PHARMACOLOGY OF NARCOTICS

Pharmacodynamics

The term opioid narcotics refers to a broad class of drugs including (1) alkaloids extracted from poppy seeds (morphine, codeine) and their semisynthetic derivatives (oxycodone, hydromorphone, oxymorphone) and (2) synthetic phenylpiperidines (meperidine, fentanyl) and synthetic pseudopiperidines such as methadone ***(Chang et al., 2007).***

- **Mechanism of action:**

Opioids act on 3 major classes of receptors: μ, δ, and κ receptors. Each of these classes of receptors has its representative endogenous ligand (eg, endorphin for the μ receptor and dynorphin for the κ receptor). These classes of opioid receptors are widely distributed throughout the central and peripheral nervous system as well as other systems such as the gastrointestinal tract. On the basis of their pharmacodynamic profiles, opioid analgesics can also be classified as a full agonist at opioid receptors (eg, morphine,

fentanyl) or an agonist-antagonist such as buprenorphine ***(Chen et al., 2014).***

Activation of opioid receptors produces profound analgesia mediated through a combined presynaptic and postsynaptic effect. Presynaptically, opioid analgesics act on primary nociceptive afferents (inhibition of calcium channels), resulting in the reduced release of neurotransmitters such as substance P and glutamate implicated in nociceptive transmission. Postsynaptically, opioid analgesics directly inhibit postsynaptic neuronal activity by hyperpolarizing cell membranes via opening potassium channels. Other effects of opioids (eg, antitussive, reducing gastrointestinal tract motility) also have practical therapeutic use ***(Johnston, 2010).***

Because of a widespread distribution of opioid receptors both within and outside the nervous system, opioid analgesics also produce a broad spectrum of adverse effects including euphoria, dysphoria, sedation, respiratory depression, constipation, suppression of endocrine systems, cardiovascular disorders (eg, bradycardia), convulsion, nausea, vomiting, pruritus, and miosis. Although the extent of these adverse effects may differ among individual opioids

depending on dose regimen, these effects substantially narrow the clinical therapeutic window for effective opioid therapy ***(Ballantyne and Mao, 2003).***

Pharmacokinetics

- **Metabolism:**

The majority of opioids undergoes extensive first pass metabolism in the liver before entering the systemic circulation. Hepatic metabolism is generally intended to facilitate renal excretion through a transformation to hydrophilic substances that are easy to eliminate. All opioids are metabolized through two major enzyme systems, CYP450 and, to a lesser extent, the UDP-glucuronosyl transferases (UGTs) ***(Mercadante, 2015).***

Opioid metabolism results in the production of both inactive and active metabolites. In some cases opioids are pro-drugs which become active after metabolism. In other circumstances, after an initial metabolism they are further transformed in more potent drugs. Two principal forms of metabolism are typically available for opioids. Phase I metabolism usually precedes phase II metabolism, but this is not always the case ***(Zhou, 2009).***

(a) Phase I metabolism:

Phase I metabolism is characterized by reactions of oxidation or hydrolysis, and accounts for approximately 75% of the total metabolism of all drugs. A large number of cytocrome P450 (CYP) enzymes facilitates chemical reactions, and include dealkilation, hydroxylation, oxidation, sulfoxydation, deamination and dehalogenation ***(Gudin, 2012).***

These enzymes are localized primarily in the liver, but also in the enterocytes of the small intestine, where there is a relevant source of first-pass metabolism of drugs. These reactions reduce the systemic availability of opioids ***(Wilkinson, 2005).***

Cytocrome P450 enzymes are identified by the root symbol CYP followed by Arabic number (family), a capital letter (subfamily), and an Arabic number (individual enzyme). For example, CYP2D6 corresponds to Cytocrome P450, family 2, subfamily D, polypeptide 6. CYP1, CYP2, and CYP3 families are responsible for the majority of biotransformation reactions ***(Virani et al., 1997).***