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" Cardiac Profile Assessment of Acute Opioid Intoxicated Addicted Patients Admitted to General Hospitals of Port Said and Damietta Governorates "

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ABSTRACT:

Substance abuse continues to be a significant global public health issue. With the availability of more potent medications and an increasing variety of drugs and their combinations, preventing and treating drug abuse disorders represents a formidable challenge. It necessitates a comprehensive strategy encompassing education, prevention, treatment, and recovery support. In addition to the rapidly rising fatality rate caused by drug overdose, non-fatal overdoses have also been linked to renal failure, aspiration pneumonia, cardiovascular and musculoskeletal disorders, and cognitive impairment. The nationwide mortality rate due to heroin overdose has risen by almost 15-fold since 1999. This phenomenon is mostly attributed to the common use of fentanyl in addition to heroin, an opioid that has a lethality 50-100 times greater than that of morphine. The increase in opioid misuse has led to the emergence of many often unnoticed symptoms of toxicity, especially among young victims. A plethora of clinical and experimental studies investigating the impact of opium on the cardiovascular system have consistently shown many adverse consequences. Principal results include QT interval elongation, bradycardia, torsade de pointes arrhythmia, and coronary artery abnormalities. Extension of the QT duration interval seems to be the most frequent adverse effect in the heart of synthetic opioids. Cardiovascular issues associated with opioids may elevate the mortality risk. Therefore, we investigate the cardiovascular characteristics of individuals experiencing acute opioid intoxication to identify further anomalies in their cardiac profile during acute addicted opioid poisoning. The objective of this research is to evaluate the cardiac characteristics of patients' admittance to general hospitals in the governorates of Port Said and Damietta who are acutely intoxicated with opioids in addicted patient.

Keywords: Opioids, Overdose, Acute Intoxication, Cardiovascular Profile.

INTRODUCTION

Substance abuse becomes a significant global public health issue. With more powerful pharmaceuticals are becoming available, and the range of drugs and their combinations is growing, preventing and treating drug abuse disorders represents a formidable challenge. It necessitates a comprehensive strategy encompassing education, prevention, treatment, and recovery support. [1]

Chemical poisoning may result in severe effects such as disability and bodily harm. Costs associated with treating drug addiction episodes have significantly risen as a result of higher numbers of emergency department visits, hospital hospitalizations, and ICU admissions. [1]

The drug overdose mortality rate in the United States surpasses all predictions. As to the Canters for Disease Control and Prevention (CDC), drug overdoses are the primary cause of fatalities associated to injuries in the United States, and have increased by more than three times in the last two decades. [2] [3]

Substance use disorders

Similar to many other chronic diseases, substance use disorders are amenable to successful treatment. Pharmaceutical interventions exist to address heroin use disorder by decreasing drug cravings and withdrawal symptoms, therefore enhancing the likelihood of attaining sobriety. Currently, there exists a diverse range of drugs that may be customized to meet an individual's specific requirements for rehabilitation, while also considering any concurrent health problems. [4]

Epidemiology of opioid abuse

Since the late 1990s and up to now, there has been a significant increase in public awareness of substance abuse disorders (SUDs) due to the opioid epidemic in the United States. This has also led to a rise in the availability of drugs to treat opioid addiction. In 2013, The International Narcotics Control Board performed a study in 32 countries and determined that tramadol usage is prevalent globally, with an estimated 69 cases per 1000 people annually.[5,6]

The rise in opioid misuse goes in tandem with the rise of prescribed opioids distributed from 2002 to 2012. Equally, the mortality rate resulting from opioid analgesic and heroin poisonings has increased fourfold throughout the same period. [7] Since 2016, the mortality rates for drug overdose-related fatalities involving opioids have been greatest for synthetic opioids other than methadone. From 1999 to 2020, the age-adjusted mortality rate for drug overdose fatalities caused by synthetic opioids other than methadone, such as fentanyl, fentanyl derivatives, and tramadol., rose at varying rates of temporal progression. There was a 56% rise in the rate from 2019 to 2020, rising from 11.4 to 17.8 per 100,000. [8]

Table (I) Controlled Substance Schedule [9]

Classification of drugs: Understanding drug schedule

Controlled Substance Schedule

Schedule	Classification	Examples
C-I	These drugs have a high potential for abuse. No medical uses for treatment	**Ecstasy, heroin, LSD, marijuana, PCP**
C-II	High potential for abuse. Has accepted medical use for treatment	**Morphine, oxycodone, methamphetamine**
C-III	Less abuse potential than C-II drugs. Accepted medical use.	**Anabolic Steroids, Hydrocodone**
C-IV	Less abuse potential than C-III drugs. Accepted medical use.	**Valium, Xanex, Darvon, Phentermine**
C-V	Less abuse potential than C-IV drugs. Accepted medical use.	**Cough medicines with Codeine**

Opioids and their sources

Opioids encompass a wide range of drugs that share structural similarities with the naturally occurring alkaloids found in opium. These substances are derived from the resin of the opium poppy, Papaver somniferum. Opioids may be obtained from natural sources (opium poppies), artificially produced (by laboratory methods), or partially artificial. Natural derived opioids are sometimes referred to as opiates. Included among the natural opioids are Morphine, opium, and codeine. The human body also synthesizes endogenous opioid peptides, which are a kind of opioids that may manifest effects comparable to those of other opioids. [10,11]

Naturally occurring opioids are derived from the opium poppy (Papaver somniferum). Most precisely, they are found in the latex, which is the milky sap extracted from the stem and leaves of the poppy. Naturally occurring opioids are also derived from the seeds of the poppy. Commonly, natural opioids are obtained using the poppy straw method, which entails the extraction of alkaloids, or organic chemicals, from the desiccated and pulverized poppy plant. [11]

Opioids are particularly powerful and efficient analgesics, including a collection of substances that exert their effects on the opioid receptors in the brain. These substances are classified as analgesics, which means they induce numbness and alleviate pain. Most, however, have a significant propensity for addiction and misuse. [10,11]

Opioids receptors

When opioids bind to and activate opioid receptors in various parts of the brain, spinal cord, and other organs, they can reduce pain signals and increase the release of dopamine. This can lead to a strong desire to continue using the drug due to the pleasurable effects. Therefore, inducing a desire in the user to repeat the experience. [4]

The mechanism of action of opioids involves the interaction with certain cell surface receptors known as ε [mu], κ [kappa], and δ [delta]. Various opioid receptor subtypes have a shared analgesic impact on brain circuits, however each subtype has distinct actions and specialized distribution in different brain areas. The distribution of these receptors is mostly in the central nervous system, brain, and spinal cord, it is present in peripheral blood mononuclear cells, the heart, lungs, and the gastrointestinal tract. [10]

The activation of opiate receptors triggers a cascade of intracellular signals, such as the suppression of adenylate cyclase, reduced calcium channel opening, heightened potassium currents, and stimulation of protein kinase C (PKC). The primary impact of these signalling pathways is a decrease in cellular excitability and neurotransmission. The endogenous opioid peptides, including enkephalins, endorphins, and endomorphins, are the known natural ligands for the opiate receptors. [10]

Classification of opioids

Based on their chemical makeup, the opioids can be divided into subclasses: semisynthetic derivatives of natural alkaloids (oxycodone, hydromorphone, codeine, and morphine), opium alkaloids (opiates: codeine, morphine), and several groups of synthetic opioids, such as the compounds of diphenyl propylamine and anililopiperidines (fentanyl, alfentanil, sufentanil, remifentanil).diphenyl propylamine derivatives (propoxyphene, dextropropoxyphene, methadone, diphenoxylate, loperamide), and others (pentazocine, butorphanol, nalbuphine, levorphanol, tramadol), and, the opioid antagonists (nalmefene, naloxone, and naltrexone). [10]

Based on their primary application, the various opioid types can be categorized as follows: anesthesia (fentanyl, alfentanil, remifentanil, sufentanil), intense pain (morphine, hydromorphone, levorphanol, meperidine), moderate-to-severe acute or chronic pain (fentanyl, codeine, oxycodone, hydrocodone, levorphanol, methadone in transdermal or trans buccal administration), diarrhea (loperamide, diphenoxylate), and cough (codeine, hydrocodone). Additionally, opioids can be categorized as complete agonists, partial agonists, mixed agonist/antagonists, or antagonists of opiate receptors based on how they work. [10]

Table (II): full and partial opioid agonist drugs arranged alphabetically. [10]

Full and partial agonists	
1-	Alfentanil
2-	Buprenorphine
3-	Butorphanol
4-	Codeine
5-	Diphenoxylate
6-	Fentanyl
7-	Heroin
8-	Hydrocodone
9-	Hydromorphone
10-	Levorphanol
11-	Loperamide
12-	Meperidine
13-	Methadone
14-	Morphine
15-	Opium
16-	Oxycodone
17-	Oxymorphone
18-	Pentazocine
19-	Remifentanil
20-	Sufentanil
21-	Tramadol

Table (III) A list of opiate antagonist drugs. [10]

Opiate antagonists	
1-	Naldemedine
2-	Nalmefene
3-	Naloxegol
4-	Naloxone
5-	Naltrexone

Clinical picture of acute opiate/opioid toxicity

As the number of patients admitted to hospitals for opioid overdoses—including those involving prescription drugs, synthetic opioids, and heroin—rises, the critical care unit will be responsible for handling the most challenging admissions. Furthermore, since this population may require more complex and expensive multiorgan support, these hospitalizations may also result in higher hospital and societal costs. [12]

Opioid poisoning is primarily manifested by pinpoint pupils, emesis, respiratory depression, somnolence, jerks in consciousness, and reduced awareness ranging from somnolence to stupor to coma. Although respiratory depression is typically considered the primary cause of death, hypothermia may occasionally have a mediating role. Respiratory problems, such as oedema and pneumonia, muscular illnesses, such as rhabdomyolysis from prolonged muscle strain while unconscious, and renal failure from muscle tissue breakdown are the most common signs and symptoms of overdose morbidity. [13]

Several European retrospective studies have endeavoured to identify predictive variables in individuals who need to be admitted to a medical intensive care unit (ICU) after an opioid overdose. The median duration of hospitalizations in the Intensive Care Unit (ICU) varied from 2 to 3.2 days, and mechanical breathing was necessary for 71% to 88% of patients. Mortality rates varied between 2% and 14%, resulting from specific reasons such as hypoxic brain damage, sepsis, and severe lung injury. [7]

In the majority of instances of opioid poisoning, distinct clinical symptoms known as opioid toxidrome are observed: pinpoint pupils (the absence of which does not rule out opioid poisoning), drowsiness, coma (depression of the central nervous system), and respiratory distress, involving a breathing pattern that is shallow, sluggish, and erratic, which can lead to apnea (reduction of the

respiratory center). Additional symptoms and indicators include vertigo, hypotension, bradycardia, paralytic ileus, urine retention, nausea, vomiting, and pallor.[14]

Where poisoning is severe, patients may have convulsions and acute lung damage. Both opioid overdose and treatment with methadone have the potential for serious arrhythmia and conduction abnormalities, such as torsades de pointes, extended QTc intervals, and enlarged QRS complexes. Additionally, take into account the potential danger of concurrent use of alcohol, benzodiazepines, and stimulants, since this might impact your clinical evaluation and approach to treatment. [14]

Management of acute opiate/opioid poisoning

Full history taking

All demographic data will be obtained including Age, sex, place of residence, job, degree of education, marital status, socioeconomic status, special habits of medical importance as smoking, and age of starting smoking. The delay time per hour (period between taking the substance and admission to the emergency department of the hospital). Opioid type, estimated amount, form, method, and mode of exposure. [15]

In conducting this study, ethical considerations were thoroughly addressed to ensure the safety, well-being, and rights of the participants. Given the vulnerability of participants in research settings, special attention was paid to obtaining informed consent from all the participants or the legal guardian (in cases of children), prior to enrolment in the study, outlining the purpose of the study as well as the procedures that were commenced. This process respects the patient's autonomy and ensures that their participation is voluntary.

Furthermore, the study protocol was reviewed and approved by an institutional ethics committee, ensuring that all procedures complied with ethical standards for research involving minors. The rights of the participants to leave the study at any moment without consequence were emphasized, and confidentiality of all patient data was strictly maintained.

Examination based on grading of Poison Severity Score PSS:

Data comparison is made easier and a qualitative evaluation of morbidity is made possible by a standardized and broadly applicable metric for determining the severity of poisoning. utilizing a simple grading scheme developed by the European Association of Clinical Toxicologists and Poisons Centres.

Based on the Poison Severity Score (PSS), patients were categorized into 5 groups:
Grade 0 (None): characterized by absence of symptoms or indications of any harmful effects.
Grade I (minor): modest symptoms and indications of poisoning.
Grade II (moderate): characterized by significant symptoms or indications of poisoning.

Grade III (severe): presents with life-threatening symptoms or indications of toxicity. Grade IV (Fatal): Lethal poisoning. [16]

Cardiac profile Assessment:

Examination of the cardiovascular system, using auscultation, percussion, palpation, and inspection. Cardiac imaging techniques including ECG that was done in all cases and Transthoracic echocardiography was done in some selected cases with severe symptoms or shocked patients. Cardiac enzyme measurement including Troponin I was done in selected cases (in severe cases or with ECG ischemic changes) and Creatine kinase – myocardial band (CK-MB).

Laboratory Investigations:

Diagnostic tests, point-of-care testing refers to the administration of urine drug tests as immunoassays. It offers prompt findings to medical professionals and might be valuable in pharmacological screening of patients. Nevertheless, urine testing for opioids may not provide reliable diagnosis of acute opioid toxicity. While a positive result may indicate the use of a drug, it does not definitively establish the presence of a toxidrome and may instead indicate a false-positive result. [14]

In instances of secondary overdose caused by synthetic opioids, the outcome may provide a false negative. For instance, substances such as fentanyl, hydromorphone, dextromethorphan, and tramadol typically need a specialized immunoassay. Chromatography offers confirmatory testing, yet it does not enable the practitioner to get real-time data to direct treatment. [14] Laboratory testing may include drug screening, although, there is a prevailing consensus that drug screening in this context lacks use in promptly diagnosing opioid toxicity. In contexts like pre-employment testing, drug screening proves to be very beneficial for detecting concealed opioid usage. Gas chromatography and mass spectroscopy (GCMS) may provide a conclusive response to a drug test result dispute between the patient and the provider, determining the specific components present in the patient sample. The standard laboratory analyses were a comprehensive blood count, arterial blood gases, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), blood urea nitrogen (BUN) and creatinine, serum electrolytes (Na and K), and random blood glucose. Urine analysis using a fast drug detection testing kit. [26]

Therapeutic Management

The diagnosis of acute opioid toxicity is mostly based on clinical evaluation. Under conditions of overdose, hypopnea might progress to apnea. Although Naloxone is an essential component of therapy, it is important for the practitioner to recognize that the primary focus should be on controlling the airway and providing rescue breathing. Optimal intravenous access is essential to provide sufficient administration of fluids and drugs. [17]

Administering an initial intravenous dosage of 0.4 to 0.8 mg of naloxone can rapidly alleviate both neurological and cardiorespiratory disturbances. In certain instances, significantly greater

dosages are required, with documented case reports indicating that as much as 100 mg of naloxone is needed to effectively revive a single overdose patient. The lead rescuer should promptly use bag-valve mask ventilation or a comparable intervention to reinstate oxygen delivery to essential organs, while additional rescuers assess the available techniques of naloxone administration. Adherence to Basic Life Support and Advanced Cardiac Life Support strategies is necessary when resuscitating a patient who has been poisoned with opioids. [17]

Management was conducted in accordance with the guidelines of the American College of Medical Toxicology, emergency procedures (ABCDEFG), airway, breathing, circulation, decontamination, medicine delivery, antidote search, and general supportive measures. [15]

The following are the essential procedures in the treatment of acute opioid toxicity:
1. Administer oxygen, establish internal venous (IV) access using two large-bore IV cannulas, and transfer the patient to a supervised environment. [14]

2. In the context of respiratory improvement, naloxone, an antidote, is a nonselective antagonist of all types of opioid receptors. It is administered either as an intravenous bolus or, in cases where venous access is not feasible, intramuscularly or intranasally. Furthermore, naloxone may be delivered by means of an endotracheal tube or a continuous infusion. [14]

Intravenous, intramuscular, subcutaneous administration: The recommended first dosage for individuals experiencing apnea is between 0.4 to 2 mg administered every 2 to 3 minutes until the breathing rate exceeds 12 breaths per minute. Ten milligrammes is the maximum cumulative dosage. It is advisable to provide a reduced first dosage (0.1-0.2 mg) to individuals who are at risk of concomitant stimulant overdose. [14]
- Intranasal administration of Naloxone does result in a somewhat delayed beginning of effect. A single dosage is normally 2 to 4 milligrammes delivered into one nostril. Readminister the dosage at intervals of 2 to 3 minutes while using alternate nostrils. [14]

- Endotracheal administration: Naloxone may be administered by the endotracheal route at a dosage ranging from 0.8 to 5 mg. [14]

- Continuous infusion: Naloxone may be administered in a continuous infusion form. This is often recommended only in the event of an inadequate response to the first bolus treatment. The dosage ranges from 0.25 to 6.25 mg/h, most often representing two-thirds of the original therapeutic dose. Maintain the patient in a closely observed environment, consistently monitor their vital signs, and evaluate for any indications of withdrawal. [14]

3. Referral: Consider scheduling social work and addiction medicine appointments upon admission, provided that the patient is willing and such services are accessible in the local area. [14]
4. Opioid agonist treatment (OAT): Patients exhibiting opioid intoxication or overdose should be evaluated for symptoms which are indicative of opioid use disorder (OUD). Individuals who test

positive should be provided with the chance to explore the possibility of Outpatient Antibiotic Therapy (OAT), which may include the possibility of receiving treatment either on-site or promptly via referrals after testing. [14]

5. Prevention of further harm: Before releasing a patient, make sure they have a naloxone kit and clear instructions on how to use it. [14]

Individuals with opioid use disorder are increasingly accepting of the frequent use of methadone, a complete mu receptor agonist, buprenorphine, a partial mu receptor agonist and Kappa antagonist, and naltrexone, an opioid receptor antagonist. A growing body of research has emerged in the literature that compares different approaches to recovery and relapse prevention methodologies. Simultaneously, the administration of depot naltrexone injection to maximize total avoidance of opioids became accessible. An average duration of each naltrexone injection is about 30 days. Under such circumstances, the efficacy of opioids is compromised due to the impact of naltrexone on the receptors that they target. [17]

Heroin

Diacetylmorphine, often known as heroin, is a semisynthetic narcotic that is produced from the opium plant Papaver somniferum. First synthesised in 1874, it was first promoted as a safer and nonaddictive alternative to morphine. Quickly after its introduction, heroin was recognized to possess the same addictive properties as morphine, leading the US government to implement steps to regulate its use. The Harrison Narcotics Act of 1914 banned the self-administration of heroin without a prescription. The Dangerous Drugs Act of 1920 completely banned the use of heroin, therefore essentially relegating it to underground status. [18]

The natural substance morphine, which is isolated from the seed pod of several opium poppy plants grown in Southeast and Southwest Asia, Mexico, and Colombia, is the source of heroin, an opioid drug. Morphine, a naturally occurring substance extracted from the seed pod of some varieties of poppies, is the source of heroin, an illegal and extremely addictive drug. [4]

Heroin is sometimes marketed as a white or brownish powder that has been diluted with sweets, flour, powdered milk, or quinine. Black tar heroin may manifest as either a white or brown powder or as a black adhesive material. The street names often used to refer to heroin include Big H, Black Tar, Chiva, Hell Dust, Horse, Negra, Smack, and Thunder. [4,8]

Given its fast onset in the brain, heroin is highly addictive, both in terms of psychological and physical effects. Reports from heroin users include experiencing an initial period of intense excitement or "rush" followed by a transitional condition of both sleep and consciousness. An indisputable consequence of heroin use is the development of addiction. Prolonged heroin usage leads to the development of tolerance to the opioid. Once this has occurred, the individual needs consume a

greater quantity of heroin in order to get the same level of intensity. Prolonged usage of larger dosages of the medication leads to the development of physical dependency and addiction. Adverse effects of heroin use include somnolence, respiratory depression, narrowing of the pupils, nausea, a sensation of warmth flooding the skin, and xerostomia. [8]

Due to their lack of knowledge about the real potency and composition of heroin, users face a significant danger of overdose or mortality. Indications of a heroin overdose include sluggish and superficial respiration, cyanotic lips and fingernails, oedema, seizures, unconsciousness, and maybe fatality. Heroin is classified as a Schedule I drug according to the Controlled Substances Act, indicating its significant addictive potential and lack of presently recognized medical use in treatment inside the United States. The most prevalent cause of heroin poisoning is accidental overdose of the substance. Poisoning may also manifest in an individual who engages in "body packing," "body pushing," or "body stuffing." Body packers, often known as "mules," are individuals who ingest and strategically fill their gastrointestinal systems with bags of heroin in order to illicitly transport the prohibited substance across borders. [18]

Body stuffers are individuals who deliberately consume all the narcotics they have in their hands in order to hide the evidence from law enforcement. These packets, being generally not intended for safe gastrointestinal transportation, often break and often result in poisoning. [18]

Tramadol

Tramadol is an unconventional synthetic opioid analgesic developed in 1977 for its strong efficacy in treating acute pain (for instance, trauma or postoperative) and chronic pain (such as cancer). Furthermore, it elicits reinforcing and rewarding effects via activating the β-opioid and monoamine receptor systems. [6]

The recommended therapeutic range for moderate to severe pain is from 25 to 400 mg per day when taken orally either as dissolving tablets. Furthermore, the recommended oral dose form for chronic pain is extended-release capsules, with a recommended range of 100 to 300 mg per day. An overdose of tramadol may result in abrupt renal failure, increased levels of creatinine phosphokinase, hepatic failure, electrodermographic abnormalities, and acute malfunction of the right heart.
Furthermore, there are rarely fatalities attributed to the misuse of tramadol. [6]

The analgesic characteristics of O-desmethyl tramadol, the active metabolite of tramadol, establish it as a prodrug. The compound acts via two distinct mechanisms: as an agonist of the m-opioid receptor and as an inhibitor of the reuptake of serotonin and norepinephrine. Recent studies have shown that tramadol has a more prominent propensity for misuse, leading to its reclassification as a prohibited drug in many nations. [18]

Based on the examination of 9,851 urine samples, the estimated prevalence of tramadol usage in sports competition is 1.4%, indicating its widespread use by athletes. Cycling had the highest level of consumption at 65%, followed by triathlons at 8% and rowing at 6%. The given statistics align with

those obtained from other labs authorized by the World Anti-Doping Agency (WADA), therefore validating a prevalence of tramadol usage ranging from 49.5% to 61%. [18]

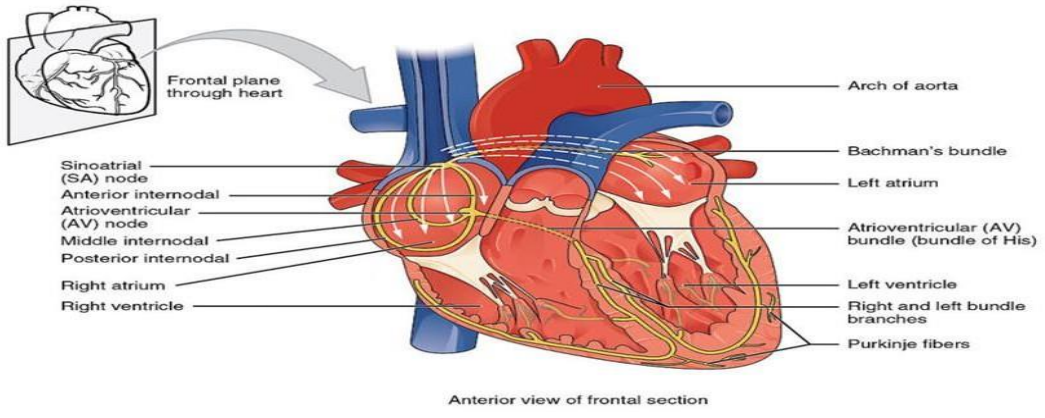
The preferential binding of tramadol's metabolite, O-desmethyl tramadol, to β opioid receptors is responsible for its analgesic effects. Moreover, it prevents serotonin and norepinephrine from being reabsorbed, raising the risk of adverse effects in the event of an overdose (opioid syndrome,
serotonin syndrome, and/or seizure risk), and high doses may have cardiotoxic consequences. [19]

Cardiac profile assessment

Overview of the cardiovascular system

An thorough evaluation of the heart yields vital data on the physiological operation of a patient's circulatory system. Proficiency in evaluating the cardiovascular system and distinguishing between normal and abnormal assessment results will enable us to provide high-quality and safe treatment to the patient. [20]

Prior to evaluating a patient's cardiovascular system, it is crucial to comprehend the many operations of the cardiovascular system. The primary cardiac anatomical components consist of the atria, ventricles, and heart valves. During the diastole of a heart contraction, blood that has lost oxygen is transferred from the posterior and superior vena cava into the right atria and ventricle. The pulmonary artery (PA) carries deoxygenated blood to the lungs as the right ventricle contracts during systole. Meanwhile, oxygen-rich blood from the pulmonary veins return the lungs to the left ventricle and atria during diastole, and subsequently expelled from the body through the aorta during systole. Schematic of the cardiac conduction system (Figure-I). The provided graphic illustrates the conduction route by which electrical stimulation is received by the cardiac tissue. [20]



(Figure-I) Shows the conduction system of the heart. [20]

Effect of opioids toxicity on blood pressure

A common side effect of all opioids, including heroin, hydromorphone, morphine, and hydrocodone, is hypotension. These opioids aid in the release of histamine, which significantly lowers blood pressure and systemic vascular resistance. The way this phenomena is handled could be

accomplished by the use of H 1 and H 2 antagonists; vasopressors and intravenous liquids. According to recent research, opioids barely affect the vasomotor tone of coronary vessels. [21]

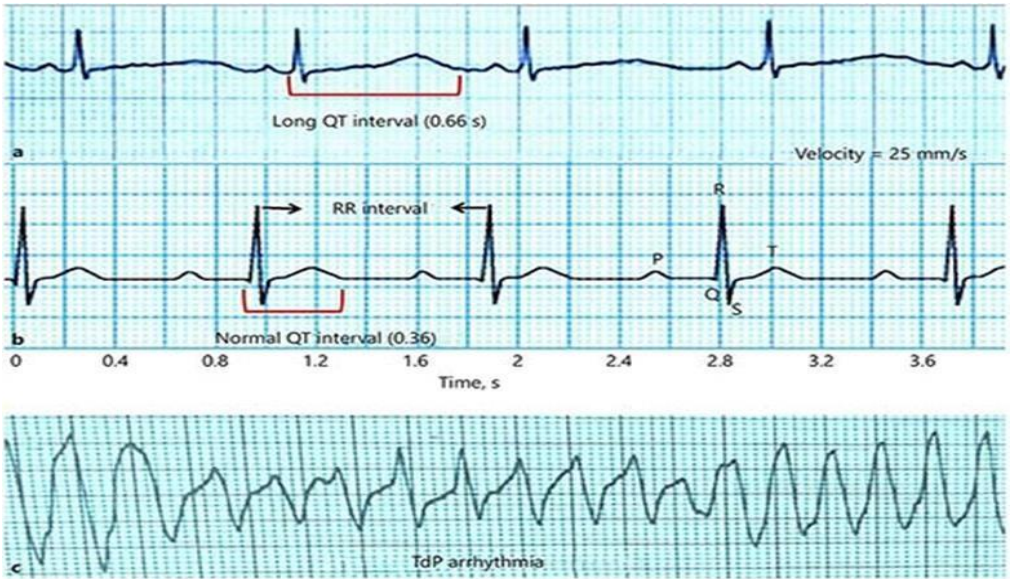
Effects of opioids toxicity on ECG

Extensive research has examined the detrimental effects of opioids on the organs of the body, particularly the cardiovascular system. The primary adverse effects of opioids include nausea, vomiting, constipation, headache, respiratory depression, reduced cardiac output, bradycardia, histamine release, cardiac electrical impairment, and other related symptoms. [21]

The following conditions are associated with acute opioid intoxication: cerebral and spinal ischemia or nerve compression syndromes, rapid heartbeat, low blood pressure, congestive heart failure, muscle injury leading to sequential crush syndrome or rhabdomyolysis after being immobilized while under the influence. [23]

The most common adverse effect of opioids on the heart is the prolongation of the QT interval, which can lead to torsades de pointes (TdP), a ventricular tachyarrhythmia that can be fatal. Because of the severity of this adverse reaction, most drugs have had their distribution restricted or taken off the market in recent years. Furthermore, prior to receiving regulatory clearance, all new drugs having systemic bioavailability are required by FDA guidelines to be assessed for their impact on QT interval prolongation. The time interval between the start of the Q wave and the end of the T wave, which is an electrical representation of ventricular depolarisation and repolarisation, is known as the QT interval in an electrocardiogram (ECG) (Figure II). Increased duration of the QT interval suggests that the electrical conduction in the ventricles is unusually sluggish (Figure II). Given that the QT interval fluctuates with heart rate, there exist numerous formulae, such as Bazette's, Fridericia's, and Framingham's formulas, to adjust the QT interval for heart rate. [21]

The most often used formula is Bazette's formula ($QTc = QT/\sqrt{RR}$), where RR represents the distance between the highest points of two successive R waves (Figure II). An interval of QTc (heart rate-corrected QT) over 450 ms in men, and 470 ms in females (or QTc exceeding 0.44 s), along with ΔQTc above 30 ms, is seen to be protracted irrespective of the correction formula used. An elevated QTc value above 500 ms is a significant risk factor for TdP, a ventricular tachyarrhythmia characterized by palpitations, which may result in syncope and severe seizures. Trigeminal arrhythmia (TdP) is often self-limiting but may sometimes progress to ventricular fibrillation, a potentially fatal arrhythmia that can result in abrupt death. [21]



(Figure-II) QT interval which is the electrical presentation of ventricular depolarization and repolarization in ECG. [21]

(a) A lead II ECG trace with an extended QT interval (66 ms). **(b)** A typical ECG tracing, where the QT interval is within the normal range (0.36 s) and the ECG waves (P, QRS, and T) are visible. The electrical depolarisation and repolarisation phases of the ventricles are included in the QT interval, which is a measurement of the duration between the start of the Q wave and the conclusion of the T wave in the ECG. R is the spot on the ECG that represents the peak of the QRS complex, while RR is the space between consecutive Rs. **(c)** A sign of TdP arrhythmia, a particular type of polymorphic ventricular tachycardia in individuals with extended QT intervals that is defined by fast, erratic heartbeats -which appear to be twisting around the ECG baseline. This arrhythmia may cease spontaneously or lead to ventricular fibrillation. (TdP) torsades de pointes. [21]

Although experimental studies have shown cardioprotective properties of morphine, it is mostly employed as a mu receptor agonist for the treatment of acute, cancer-related, and chronic pain. As a derivative of morphine, hydromorphone is another mu receptor agonist. Morphine and hydromorphone are associated with a range of cardiac-related adverse effects, including the release of histamine, resulting in bradycardia, vasodilation, and hypotension. These effects reduce cardiac output, particularly when combined with benzodiazepines. [21]

Several studies have examined the impact of morphine on QT interval, and TdP did not discover any correlation between QT duration and morphine exposure (average dosage 120 mg, within the dosage range of 30–300 mg). A more recent research examined the impact of methadone and morphine on heart rate, mean arterial pressure, and QT interval. The study revealed nocorrelation between morphine and QT interval, however methadone substantially raised QT interval. Furthermore, they showed that the QT interval exhibits a response to methadone that is depending on the dosage. [21]

Another comparative study found that methadone was more often linked to QT interval extension than slow-releasing morphine and buprenorphine. In a case report, a patient with a documented medical history of depression was discovered in a state of unconsciousness due to the simultaneous overdose of morphine, diazepam, citalopram, oxycodone, and zopiclone. The patient's first electrocardiogram (ECG) revealed a corrected QT interval of 650 ms. [21]

Nevertheless, a separate study has shown that none of these medications had an impact on the QT interval. No relevant research was identified that assessed the impact of hydromorphone on QT interval. Therefore, while there is little data on morphine, most of the evidence supports its safety in relation to cardiac electrical activity, particularly at standard therapeutic dosages. [21]

The drug tramadol is extensively used for pain management and is classified as a mild synthetic mu receptor agonist. An excessive dosage of tramadol might result in symptoms such as nausea, vomiting, high blood pressure, rapid heart rate, severe depression of the central nervous system and respiratory system, restlessness, and seizures. Cardiovascular side effects are not significant at analgesic levels; nonetheless, the activity of tramadol as a serotonin and norepinephrine reuptake inhibitor may result in serotonin syndrome, which may cause cardiac arrhythmia. [21]

Initial assessment of tramadol's impact on QT interval was conducted on 479 individuals. Among them, one-fourth had QTc prolongation, indicating a likely blockage of potassium channels. This study suggests that tramadol may increase the likelihood of QT interval prolongation. Furthermore, a recent research demonstrated a significant augmentation in QT interval after tramadol use. [21]

Codeine or 3-methylmorphine is a mu receptor agonist opioid medication used for the treatment of mild to severe pain, diarrhea, and cough. Typical adverse effects include somnolence and gastrointestinal disturbances similar to those of other opioids. No in vivo investigation has been conducted to assess the impact of codeine on QT interval. However, two in vitro studies have convergently shown that codeine lacks the ability to inhibit the hERG K+ channel, which is the primary mechanism responsible for prolonging QT. A recent case study revealed that an excessive dosage (400 mg daily) of loperamide, a β-opioid-receptor agonist, might cause arrhythmia by prolonging QTc and causing ventricular tachycardia in individuals with opioid addiction. [21]

Effects of acute opioid toxicity on cardiac enzymes

The clinical predictors of mortality associated with drug overdose rely on many parameters associated with each exposure. However, a prevalent route of in-hospital drug-induced cardiac arrest is likely to include myocardial toxicity, while respiratory arrests may be easily prevented in the hospital environment. [24]

Opioid overdose results in respiratory depression, which has the potential for severe hypoxemia and cardiac arrest. However, direct cardiotoxicity is not often seen as a secondary effect.

Empirical data from many animal models has shown a correlation between long-term use of tramadol and severe cardiac inflammatory disease. [19]

While the American College of Cardiology (ACC's) list of troponin elevations does not explicitly include opioid toxicity and overdose, it is worth noting that acute respiratory distress syndrome may still lead to increased troponin levels. Massive respiratory depression and acute respiratory distress syndrome (ARDS) may result from opioid overdose, perhaps leading to artificially increased levels of cardiac biomarkers. [13]

Effects of acute opioid toxicity on echocardiography

Echocardiographic changes in acute opioid-intoxicated patients include diastolic dysfunction and segmental wall motion abnormalities. A significant risk factor for ischemic heart disease, which is associated with various illicit substance consumption, including the abuse of tramadol, is segmental wall motion abnormalities. [25]

Conclusion

Overdoses of opioids are on the rise; opioids will soon overtake all other drugs as the leading cause of overdose deaths. The number of heroin and tramadol overdose deaths is increasing on a national level. This study concluded that opioid abuse and acute opioid intoxication were more prominent among males, not working and smokers. The findings highlight that most common ECG changes among cases with confirmed opioid toxicity were sinus bradycardia followed by hyper acute T wave, the most prominent echocardiography abnormalities were abnormal regional wall motion and tricuspid regurge, cases had more elevated levels of CK-MB and Troponin I compared to the control group, The most common morbidities among cases were coma followed by shock and non-cardiogenic pulmonary edema, cardiovascular changes were more prominent in cases than control group, ECG, Echocardiographic and cardiac enzymes abnormalities have significant association with acute opioid intoxication. Looking forward, ongoing research is needed to refine the effects of opioid abuse especially heroin and tramadol which are more commonly used in Egypt on cardiac functions. Additionally, preventive measures, including public education on the risks and complications of substance abuse including opioids should be considered. Ultimately, this study contributes to the broader goal of decreasing complications, morbidity, and mortality of drug abuse.

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