Tramadol From A Toxicological Point of View

Essay
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By
Heba Abdo Abdel Razik
M.B., B.Ch.

ADMINISTRATOR OF FORENSIC MEDICINE AND CLINICAL TOXICOLOGY
Faculty of Medicine, Cairo University

Supervised by

Prof. Dr. Usama Mohamed El-Barrany
PROFESSOR AND HEAD OF FORENSIC MEDICINE AND CLINICAL TOXICOLOGY
Faculty of Medicine – Cairo University

Prof. Dr. Alaa Abdelhameed Mekdad
PROFESSOR OF FORENSIC MEDICINE AND CLINICAL TOXICOLOGY
Faculty of Medicine – Cairo University

Prof. Dr. Mervat Hamdy Abdelsalam
PROFESSOR OF FORENSIC MEDICINE AND CLINICAL TOXICOLOGY
Faculty of Medicine – Cairo University

Faculty of Medicine
Cairo University
٢٠١٢

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List of abbreviations

(٥-HIAA) : ٥-hydroxylindolacetic acid

(٥HT) : ٥-hydroxytryptamine

(٦-AM) : ٦-acetylmorphine

(ACTH) : pituitary adrenocorticotropic hormone

(ADH) : antidiuretic hormone

(AMP) : adenosine monophosphate

(AP-١) : activator protein-١

(APAP) : Acetaminophen

(ASAM) : American Society of Addiction Medicine

(ATP) : adenosine triphosphate

(AUC) : area under the concentration-time curve

(BDNF) : Brain-derived neurotrophic factor

(BRET) : bioluminescence resonance energy transfer

(cAMP-PKA): Cyclic AMP- protein kinase A

(CB١) : cannabinoid-type ١

(CB٢) : cannabinoid-type ٢

(cDNA) : deoxyribonucleic acid

(CeA) : central nucleus of the amygdala

(CK) : creatine kinase

(Cmax) : Peak plasma concentrations

(CPK) : creatine phosphokinase

(CPR) : cardiopulmonary resuscitation

(CRE) : Cyclic AMP response element

(CREB) : Cyclic AMP response element binding protein

(CRF) : Corticotropin releasing factor

(CSF) : cerebrospinal fluid

(CYP٢B٦) : cytochromeP٤٥٠ ٢B٦

(CYP٢D٦) : cytochromeP٤٥٠ ٢D٦

(CYP٣A٤) : cytochromeP٤٥٠ ٣A٤

(DA) : dopamine

(DBH) : dopamine beta hydroxylase

(DEA) : Drug Enforcement Administration

(DIC) : disseminated intravascular coagulation

(DNB) : dorsal noradrenergic bundle

(eCBs) : endocannabinoids

(ECG) : electrocardiogram

(ED) : emergency department

(EH) : extrahypothalamic

(EMs) : extensive metabolizers

(FDA) : Food and Drug Administration

(GABA) : gamma-aminobutyric acid

(GC) : gas chromatography

(GC) : glucocorticoids

(GC-MS) : gas chromatography-mass spectrometry

(GC-NPD) : Gas chromatography with nitrogen phosphorus detection

(GI) : gastrointestinal

(HPA) : hypothalamic–pituitary–adrenal

(HPLC) : high performance liquid chromatography

(ICU) : intensive care unite

(LAAM) : levo-acetylmethadol

(LC) : locus coeruleus

(LTP) : long-term potentiation

(M١) : O-desmethyltramadol

(M٢) : N-desmethyltramadol

(M٣) : N,Ndidesmethyltramadol

(M٣G) : morphine-٣-glucuronide

(M٤) : N,N,O-tridesmethyltramadol

(M٥) : N,O-desmethyltramadol

(M٦G) : morphine-٦-glucuronide

(MAO) : monoamine oxidase

(MMTPs) : maintenance treatment programs

(mRNA) :messenger ribonucleic acid

(MSN) : medium spiny neuron

(NAc) : nucleus accumbens

(NDT) : N-desmethyltramadol

(NE) : Norepinephrine

(NET) : NE transporter

(NMDA) : n-methyl-D-aspartate

(ODT) : O-desmethyltramadol

(PCP) : phencyclidine

(PEA) : pulseless electrical activity

(PET) : positron emission tomography

(PFC) : prefrontal cortex

(PMs) : poor metabolizers

(PTSD) : post-traumatic stress disorder

(PVNh) : paraventricular nucleus of the hypothalamus

(ROSC) : return of spontaneous circulation

(SCFs) : supercritical fluids

(SIM) : selected ion monitoring

(SNRI) : serotonin- norepinephrine reuptake inhibitor

(SPE) : solid phase extraction

(SS) : Serotonin syndrome

(SSRIs) : selective serotonin reuptake inhibitors

(TCAs) : tricyclic antidepressants
(TrkB) : tyrosine kinase B
(UMs) : ultrarrapid metabolizers
(UROD) : ultrarapid opioid detoxification
(UV) : ultraviolet
(VNB) : ventral noradrenergic bundle
(VTA) :ventral tegmentum area

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Abstract

Tramadol is a centrally acting synthetic opioid analgesic commonly prescribed for moderate to severe pain. Its increasing use may be related to the fact that it has fewer side effects than other opiates, in particular, less addictive potential and less respiratory depression.It possesses weak agonist actions at the mu -opioid receptor, and inhibits the reuptake of norepinephrine. It was the second most frequent opioid reported**.** Numerous clinical trials have proven its efficacy and safety over a broad range of painful conditions, both acute and chronic; however, in severe pain, morphine may be superior to tramadol.

Opioid users recognized tramadol as an opioid only when given in an amount that was ٦ times the therapeutic dose, but at this dose, the users did not develop opioid like clinical effects such as miosis. The most common reported side effects are dizziness, nausea, constipation, and headache.

However, tramadol toxicity may be underestimated. Some non-lethal cases of respiratory depression, seizures, and serotonin syndrome have been reported with tramadol. Several deaths have also been reported when tramadol was ingested alone in overdose, or when it was ingested with others drugs, particularly with central nervous system (CNS) depressants like benzodiazepine.

***Key words*:**
(tramadol toxicity, μ-opioid, norepinephrine, respiratory depression, seizures, serotonin syndrome)

INTRODUCTION

Tramadol is a synthetic analog of codeine with both opioid and monoamine reuptake inhibitory effects. It is a pure opioid agonist, but its affinity for the μ receptor is weak, being tenfold less than that of codeine. Analgesia results also from its inhibition of the reuptake of norepinephrine and serotonin, endogenous neurotransmitters that modulate pain **(Kleinschmidt et al., ٢٠٠١).**

Tramadol is composed of a racemate of the two enantiomers (+)-tramadol and (-)-tramadol and is converted to N- and O-demethylated metabolites by cytochrome P٤٥٠٢B٦ (CYP٢B٦)/CYP٣A٤ and CYP٢D٦, respectively. The pain relief is mediated by weak opioid receptor agonism and inhibition of serotonin and noradrenaline reuptake, mechanisms that are attributable to tramadol and the active metabolite, O-desmethyltramadol. The (+)-enantiomer of O-desmethyltramadol has higher affinity for the opioid μ receptor than the

(-)-enantiomer and both enantiomers of tramadol. Furthermore, the (+)-enantiomer of tramadol preferentially inhibits serotonin reuptake and the (-)-enantiomer is the most potent inhibitor of noradrenaline reuptake **(Tjaderborn et al., ٢٠٠٧).**

The main symptoms of intoxication which are similar in all species are independent of the mode of administration and are characterized by restlessness, unsteady gait, reduced spontaneous activity, exophthalmus, mydriasis, salivation, vomiting, tremor, convulsions, slight cyanosis and dyspnoea. Death may occur due to respiratory arrest in combination with severe convulsions **(Matthiesen et al., ١٩٩٨).**

Tramadol abuse has been reported but its extent is undefined. In a review of physician drug abuse in several states, tramadol is the second most frequent opioid reported. Opioid users recognized tramadol as an opioid only when given in an amount that was ٦ times the therapeutic dose, but at this dose the users did not develop opioid-like clinical effects such as miosis **(Nelson, ٢٠٠٦).**

Toxicologic screening is not generally helpful in the management of patients with opioid toxicity. Screening results are not available until after significant patient management has already occurred. Recommended Tests are serum electrolytes, BUN, creatinine, creatine kinase, blood glucose, and pulse oximetry. They should be obtained in patients with altered mental status **(Epstein et al., ٢٠٠٦).**

The consequential effects of acute tramadol poisoning are central nervous system and respiratory depression. Although early support of ventilation and oxygenation is generally sufficient to prevent death,

prolonged use of bag-valve-mask ventilation and endotracheal intubation may be avoided by cautious administration of an opioid antagonist. Opioid antagonists, such as naloxone, competitively inhibit binding of opioid agonists to opioid receptors, allowing the patient to resume spontaneous respiration **(Nelson, ٢٠٠٦).**

Aim of the work

The aim of this study is to highlight tramadol toxicity through analysis of the most frequent clinical and laboratory findings associated with tramadol toxicity**.**

Chapter I

OPIOIDS

Tramadol (Ultram) is a synthetic opioid. It is an analgesic medication used to treat moderate to severe pain. It provides analgesia through a dual mechanism of action: mu-opioid receptor agonism and monoamine reuptake inhibition. The racemic parent compound, (±)-trans-٢ (dimethylaminomethyl)-١-(m-methoxyphenyl) cyclohexanol hydrochloride (tramadol), acts primarily to block the reuptake of norepinephrine and serotonin and has little opioid activity, while its hepatic metabolite, (+)-O-desmethyltramadol (M١), has mild to moderate affinity and intrinsic agonist activity at the mu opioid receptor **(Lofwall et al., ٢٠٠٧)**.

History and Epidemiology

The medicinal value of opium, the dried extract of the poppy plant Papaver somniferum, was first recorded around ١٥٠٠ B.C. in the Ebers papyrus. Raw opium typically is composed of at least ١٠٪ morphine, but extensive variability exists according to growing region. Although reformulated as laudanum (deodorized tincture of opium; ١٠ mg morphine/mL) by Paracelsus, paregoric (camphorated tincture of opium; ٠,٤ mg morphine/mL), Dover's powder (pulvis Doveri), and Godfrey's cordial in later centuries, the contents remained largely the same: phenanthrene poppy derivatives, such as morphine and codeine. Over the centuries since the Ebers papyrus, opium and its components have been exploited in two distinct manners: medically to produce profound analgesia and nonmedically to take advantage of their psychoactive effects **(Nelson, ٢٠٠٦)**.