We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,700
Open access books available

121,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Opium Alkaloids

Mahluga Jafarova Demirkapu and Hasan Raci Yananli

Abstract

Opium alkaloids, derived from crude *Papaver somniferum L.* plant, are potent analgesic drugs, but their use is limited because of dependence and withdrawal. Opium alkaloids activate the mesocorticolimbic dopaminergic system, which project from the ventral tegmental area to the nucleus accumbens and medial prefrontal cortex, and dopamine is critically important in opioid consumption and sustaining. The reward effect resulting from the activation of the dopaminergic system leads to continued opioid consumption and occurs opioid dependence. After the development of opioid dependence, consumption continues to avoid withdrawal syndrome. Opioid dependence is accompanied with tolerance, which requires the use of high doses to achieve the same effect. When tolerance develops, the chronic consumer continues to use opioid above known toxic doses to produce the same effect, which can result in death regardless of the type of opioid used. Raw *Papaver somniferum L*. has five high-density main opium alkaloids including morphine, noscapine, codeine, thebaine, and papaverine. Some of these alkaloids bind to classical opioid receptors to produce an opioid-like effect, while the other part mediates non-opioid effects. This chapter reviews the opiod history, receptors, mechanism of action, dependence, withdrawal. In addition, general information about five main opium alkaloids, their effects, uses, routes of administration, pharmacokinetics, adverse reactions, contraindications; effects on reproduction, pregnancy, and lactation were compiled.

Keywords: morphine, noscapine, codeine, thebaine, papaverine

1. Introduction

Opium alkaloids are products obtained from the mature capsules of *Papaver somniferum L.* plant in natural way or in laboratory. Although the maintenance of *Papaver somniferum L.* is very easy, obtaining opium alkaloids naturally requires a process. Maturation of capsules occurs in May or June. First, the mature capsules are incised several times to allow the latex to flow. The exposed white latex turns brown with the effect of air. The thickened and solidified latex is collected the next day, dried under suitable conditions and made ready for use [1]. The natural way of extracting opium alkaloids for medical purposes is dried capsules [2]. The main opium alkaloids found in raw *Papaver somniferum L.* and some information are summarized in **Table 1**.

1.1 History

Papaver somniferum L. is one of the oldest medicinal plants. The first information about the production of opium alkaloids is found on Sumerian clay tablets inscribed

IntechOpen

	Density (avg%) [3]	Molecular formula	Molecular weight (g/mol)
Morphine	11.4	$C_{17}H_{19}NO_3$	285.34
Noscapine	8.1	$C_{22}H_{23}NO_7$	413.4
Codeine	3.5	$C_{18}H_{21}NO_3$	299.4
Thebaine	3.2	$C_{19}H_{21}NO_3$	311.4
Papaverine	3.1	$C_{20}H_{21}NO_4$	339.4

Table 1.
The main opium alkaloids found in crude Papaver somniferum L. *and some information.*

in Cuneiform script in about 3000 BC. The Sumerians, whose culture developed between the Tigris and Euphrates Rivers in the south of Iraq between 4000 and 3000 BC, called the opium alkaloids "Gil" ("happiness") [4].

Opium alkaloids were first isolated in 1803 by Parisian Derosne, and named 'opium salt'. Friedrich Wilhem Adam Serturner described the 'opium salt' in detail in 1817 and named "morphine', inspired by the Morpheus (Greek god of dreams). Karl Friedrich Wilhelm Meissner first used the word 'alkaloid' in 1818, which we still use. Opioids were widely used for the first time in the Franco-Prussian War and the American Civil War for medical purposes. Tincture and pills were preferred for the purpose of analgesia in wounded soldiers. Repeated use caused opioid dependence on some soldiers, and this event was first described as "soldiers' disease" [5].

1.2 Opioid receptors

Although morphine and other opioid alkaloids are exogenous substances, they show agonistic effect by binding to the receptors of endogenous opioids. Opioid receptors were first described by Beckett and Casy in 1954 [6]. In 1965, Portoghese and colleagues shared their views on the existence of multiple opioid receptor types [7]. High-affinity and stereospecific binding sites for opioid alkaloids were also found in brain in 1973 [8]. The presence of specific opioid receptors led to the discovery of endogenous ligands. They are enkephalins [9], β-endorphin [10], and dynorphins [11]. The classic opioid receptors, were discovered in 1976–1977 and named after the prototypic drugs or tissue used in these studies: μ (mu, for morphine), δ (delta, for deferens), and κ (kappa, for ketocyclazocine) [12, 13]. These receptors show seven transmembrane domain structures specific to G protein-coupled receptors, are induced by morphine and antagonized by naloxone, and had similar analgesic effect. In 1995, the fourth opioid receptor, which is similar in structure with and closely related to classic opioid receptors, was also discovered [14, 15]. Fourth opioid receptor initially identified as ORL1 or LY132, it was later updated to N/OFQ by taking the name of its endogenous ligands (nociceptin/orphanin FQ) [16]. Although the effects of N/OFQ receptor are not fully known, they do not have a similar effect on pain as classical opioid receptors, and their sensitivity to naloxone is very low. σ (sigma), ε (epsilon), and ζ (zeta) receptors and λ (lambda) site are included in other opioid receptors [17]. The σ receptor, discovered in 1976, is not coupled to G protein, and its effects are not antagonized by naloxone [12, 18, 19]. The ε receptor is sensitive to β-endorphin [20]. The λ site regulates cell growth and is not antagonized by naloxone [21, 22]. Further information on opioid receptors is summarized in **Table 2**.

According to the studies, μ receptor was also related with addiction [38], modulation of dopaminergic system [39], learning and memory [40]. The δ receptors along with μ receptors contribute to emotional sensitivity [41].

Opioid receptors		**μ receptor**	**δ receptor**	**κ receptor**	**N/OFQ receptor**
Other names		OP3, MOP, MOPr, Mu 1	OP1, DOP, DOR, DOPr, DOR-1	OP2, KOP, KOPr, KOR-1	OP4, KOR-3, NOCIR, kappa3-related, MOR-C, nociceptin receptor ORL, XOR1, NOP-r, nociceptin/ orphanin FQ, NOPr
Regions with high distribution	CNS	Thalamus Caudate putamen Neocortex Nucleus accumbens (NAc) Amygdala İnterpeduncular complex İnferior and superior colliculi [23]	Olfactory bulb Neocortex Caudate putamen NAc Amygdala [23]	Cerebral cortex NAc Claustrum Hypothalamus [23, 24]	Cerebral cortex Anterior olfactory nucleus Lateral septum Ventral forebrain Hippocampus Hypothalamus Amygdala Substantia nigra Ventral tegmental area (VTA) Locus coeruleus Brain stem nuclei [25]
	Spinal cord	Superficial layers dorsal horn of spinal cord [26]			Dorsal horn [25]
	Non-CNS	Skin [27] Immune cells [29] Pregnant uterus [31] Gastrointestinal (GI) tract [32] Cochleae [34]	Skin [28] Immune cells [30] Pregnant uterus [31] GI tract [33] Cochleae [34]	Skin[28] Immune cells [30] Pregnant uterus [31] GI tract [33] Cochleae [34]	
Types of G-protein		Primary: Gi/Go Secondary: Gq/G11	Gi/Go	Primary: Gi/Go Secondary: G12/ G13	Primary: Gi/Go
Endogenous ligands		β-endorphin Enkephalins Endomorphin-1 and -2	β-endorphin Enkephalins	Dynorphin A Dynorphin B α-neoendorphin	Nociceptin Orphanin FQ
Agonists [from main opium alkaloids]		Morphine Codeine	Morphine	Morphine	
Antagonists		Naloxone Naltrexone	Naloxone Naltrexone	Naloxone Naltrexone	[$Nphe^1$]N/OFQ-(1-13)-NH_2 UFP-101
Effects		Analgesia Respiratory functions Cardiovascular functions GI motility Neuroendocrine functions Immune system functions Feeding Mood Thermoregulation [35]	Analgesia [36] Cardiovascular functions GI motility Mood Behaviour [15]	Analgesia Neuroendocrine functions Immune system functions Diuresis Feeding [35]	Nociception Motor and aggressive behaviours Reinforcement and reward Stress response Autonomic system functions Immune system functions [37]

Table 2.
Opioid receptors and their properties.

1.3 Mechanism of action

μ, δ, and κ opioid receptors are distributed in peripheral tissue as well as CNS. Stimulation of these receptors in the CNS results in analgesia, drowsiness, euphoria, a sense of detachment, respiratory depression, nausea and vomiting, depressed cough reflex, and hypothermia. When these receptors are stimulated in peripheral tissues, miosis, orthostatic hypotension, constipation, urinary retention etc. emerges.

After stimulation of these Gi/0-coupled opioid receptors, the adenylate cyclase enzyme is suppressed and the level of cyclic AMP decreases. In addition, the voltage-gated calcium channels in the axon ends or neuron soma are closed and intracellular calcium levels are reduced, potassium channels are opened and leading to an increase in potassium conductance. As a result, inhibition and hyperpolarization of neurons occurs when opioid receptors are stimulated [42, 43].

Analgesic or antinociceptive effects, which are indicated for use of opioids, develop at the level of the brain and spinal cord. At the brain level, attenuation of impulse spread is weakened and the perception of pain is inhibited, and at the spinal cord level, the transmission of pain impulses is suppressed [44].

1.4 Opioid dependence

Opioid dependence or addiction is a chronic, recurrent disease that changes neurotransmitter systems in the CNS and affects movement [45, 46]. Opioid dependence develops in both psychic and physical dependence. Physical opioid dependence occurs both when used for treatment and as a result of abuse. Opioid abuse is a relapsing disease with high morbidity and mortality, which is used at higher doses to produce the same effect due to tolerance. The higher the exposure time to opioids, the higher the degree of dependence and tolerance. After physical dependence develops, opioid consumption is maintained to prevent withdrawal symptoms. So the treatment is long and difficult. For this purpose, opioid agonists such as methadone, buprenorphine, an opioid antagonist naltrexone or abstinence-based treatment may be preferred. This disease, referred to as 'opioid abuse and opioid dependence' in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSMIV-TR), has been changed to 'opioid use disorder' in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [47].

The estimated annual prevalence of opioids in 2010 was 0.6–0.8% of the population aged 15–64 (26×10^6 to 36×10^6). The estimated annual prevalence of opioid use is between 0.3 and 0.5% of the adult population (13×10^6 to 21×10^6 past-year users) [48].

The mesocorticolimbic dopaminergic system, which project from the VTA to the NAc and medial prefrontal cortex (mPFC) are critically important in opioid dependence [49]. Opioids act on VTA and directly or indirectly cause an increase in dopamine release in NAc region [50]. In the pathogenesis of opioid dependence, the presence of a complex mechanism including the dopaminergic system, noradrenergic, serotonergic, etc. systems should be considered [51].

1.5 Opioid withdrawal

Withdrawal is a condition that occurs when the use of an exogenous substance that is used for a long time and develops physical dependence is interrupted. In opioid dependence, the mesocorticolimbic dopaminergic system activates and induces dopamine release in the NAc region. The adaptive increase in dopaminergic

activity in CNS in opioid dependence is suppressed during withdrawal and withdrawal symptoms appear [52]. In addition to dopamine, different neurotransmitters and neuromodulators, such as noradrenaline, GABA, vasopressin, substance P, neuropeptide Y, and nitric oxide, are thought to play a role in the development of opioid withdrawal [53–55]. In opioid withdrawal syndrome, symptoms such as pain, insomnia, yawning, tremor, lacrimation, rhinorrhea, sweating, dehydration, goosebumps, mydriasis, restlessness, anorexia, nausea, vomiting, diarrhea, weight loss, hyperglycemia, hypotension, decrease in respiratory rate, hyperthermia and abdominal muscle cramps are seen [45].

2. The main opium alkaloids in raw *Papaver somniferum L.* and their pharmacological properties

2.1 Morphine

International Union of Pure and Applied Chemistry (IUPAC) name: (4R,4aR,7S,7aR,12bS)-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol.

ATC Code	N-Nervous system	N02-Analgesics	N02A-Opioids	N02AA-Natural opium alkaloids	N02AA01-Morphine

Morphine is one of the major opium alkaloids isolated from plant *Papaver somniferum L.*, produced synthetically and metabolized by codeine and heroin in the body. It binds to μ, δ, and κ receptors, which are widely distributed in CNS and peripheral tissue, and produce effects such as analgesia, anxiolysis, euphoria, sedation, respiratory depression, and contraction of smooth muscles of GI tract. Morphine is used in the management of severe pain, treatment of acute pulmonary edema and anesthetic procedures [56]. It can be administered orally, rectally, intramuscularly, intravenously, subcutaneously, epidurally, and intrathecally.

Absorption of morphine is variable, an almost complete absorption mainly done in the upper intestine as well as in the rectal mucosa. Morphine presents significant first-pass metabolism and oral bioavailability within 17–33% [57]. Morphine distributes to brain, skeletal muscle, liver, kidneys, lungs, intestinal tract, and spleen [58]. Hepatic metabolism occurs via glucuronic acid conjugation primarily to morphine-6-glucuronide (M6G, 10–15%) and morphine-3-glucuronide (M3G, 45–55%). Other metabolites include morphine-3,6-diglucuronide, morphine-3-ethereal sulphate, normorphine, normorphine-6-glucuronide, normorphine-3-glucuronide and codeine. M6G and normorphine show active analgesic effect by binding to opioid receptors, but M6G, which is formed more than normorphine, can contribute to analgesic effect of morphine. M3G does not contribute to the analgesic effect of morphine, because it has low affinity to opioid receptors [59]. Half-life elimination is variable according to age group: in neonates 4.5–13.3 h, in children 1–2 h, and in adults 2–4 h. Excretion occurs with urine (2–12%) and feces (7–10%).

Morphine leads to death in amounts of 0.15–0.2 g (sc) or 0.3–0.4 g (oral) in adults. Babies and young children are much more susceptible, and death has been observed at doses of 30 mg [60]. Morphine blood concentration within 10–100 μg/dL is toxically; if it is above 400 μg/dL is lethally [61].

Common adverse reactions are drowsiness, headache, constipation, nausea, vomiting, urinary retention. Although less common adverse reactions, such as depression, insomnia, paresthesia, dizziness, anxiety, abnormal dreams, confusion, seizure, myoclonus, agitation, amnesia, euphoria, pain, dyspnea, hypoventilation,

respiratory depression, tremor, fever, flu-like symptoms, rhinitis, edema, hypotension, syncope, palpitations, skin rash, amblyopia, blurred vision, conjunctivitis, diplopia, miosis, nystagmus, amenorrhea, impotence, gynecomastia, urinary hesitancy, diaphoresis, anorexia, biliary colic, dyspepsia, gastroesophageal reflux disease, hiccups, xerostomia, anemia, thrombocytopenia can be seen.

Contraindications are hypersensitivity to morphine, significant respiratory depression, acute or severe bronchial asthma in the absence of resuscitative equipment, GI obstruction.

Effects on reproduction: Prolonged morphine use can cause secondary hypogonadism, which can lead to infertility in both sexes [62].

Effects on pregnancy: It is known that, morphine crosses the placenta. Morphine exposure was associated with conoventricular septal defects, atrioventricular septal defects, hypoplastic left heart syndrome, spina bifid, and gastroschisis within a 4-month period, 1 month before and 3 months after conception [63]. In addition, the use of it in the first trimester may reduce fetal heart rate from non-teratogenic effects [64]. Use of morphine late in pregnancy may result in decreased fetal breathing movements or withdrawal signs in the newborn [65, 66]. Withdrawal signs are hypothermia, hyperthermia, diarrhea, vomiting, anorexia, weight gain, high-pitched crying, hyperactivity, increased muscle tone, increased wakefulness, abnormal sleep pattern, irritability, sneezing, seizure, tremor, yawning and etc. [67, 68].

Effects on lactation: Both morphine and an active metabolite, M6G, can be detected in breast milk [69]. According to previous study, a milk:plasma ratio of morphine was 2.85, and the estimated maximum concentration in milk was 500 ng/mL [70]. Respiratory depression or drowsiness were not common in infants of breastfeeding mothers receiving morphine [71]. Although not preferred in lactation, it should be used as soon as possible and at the lowest dose if necessary [72].

2.2 Noscapine

IUPAC name: (3S)-6,7-dimethoxy-3-[(5R)-4-methoxy-6-methyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-5-yl]-3H-2-benzofuran-1-one.

ATC Code	R-Respiratory system	R05-Cough and cold preparations	R05D-Cough suppressants, excl. combinations with expectorants	R05DA-Opium alkaloids and derivatives	R05DA07-Noscapine

Noscapine, also known as narcotine, is the second opioid alkaloid according to its density in raw *Papaver somniferum L.* plant, was first isolated by Robiquet in 1817 [73]. Noscapine has no morphine-like effect, no affect on morphine withdrawal and has mild analgesic effect [74]. It is used to suppress cough frequency and intensity in bronchial asthma and pulmonary emphysema as it has central antitussive activity such as codeine [74, 75]. It is thought that noscapine exerts its antitussive effect through σ receptor which is one of the other opioid receptors. Repeated exposure to noscapine does not lead to dependence and tolerance to its antitussive effect does not develop. The potential for antineoplastic treatment is being investigated because of its antimitotic effect [76]. In the animal study, noscapine increased histamine release, leading to bronchoconstruction and hypotension, even convulsions [77]. There are also studies showing that teratogen [78]. Noscapine is used orally in the form of a combined preparation to reduce these effects.

Noscapine in terms of antitussive potency, onset, and duration of action is similar to codeine, one of the main opium alkaloids [74]. Noscapine has a relatively low bioavailability due to a first-pass metabolism [79]. Noscapine is inactivated by

converting into meconin and o-demethylated metabolites. Meconin is major urinary metabolite of noscapine [80].

Adverse reactions are not expected when used in therapeutic doses [74]. When taken in high doses, drowsiness, headache, nausea, vasomotor rhinitis, conjunctivitis may be seen [81].

Effects on reproduction and pregnancy is unknown.

Effects on lactation: It is thought to have no negative effects on infant [82].

2.3 Codeine

IUPAC Name: (4R,4aR,7S,7aR,12bS)-9-methoxy-3-methyl-2,4,4a,7,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-ol

ATC Code	R-Respiratory system	R05-Cough and cold preparations	R05D-Cough suppressants, excl. combinations with expectorants	R05DA-Opium alkaloids and derivatives	R05DA04-Codeine

Codeine, a 3-methylether derivative of morphine, is the third opioid alkaloid according to its density in the raw *Papaver somniferum L.* plant, was first isolated by Robiquet in 1833. Codeine and its metabolite, morphine, act by stimulating opioid receptors. The main effects are analgesia (lighter than morphine), central antitussive and antidiarrheal effects [83]. It can also do sedation, drowsiness, and respiratory depression. Codeine is used in the management of mild to moderate pain, in the treatment of cough, persistent diarrhea and restless leg syndrome. Codeine is taken orally and intramuscularly.

Absorption is rapidly in oral use and bioavailability is higher due to less first-pass metabolism (about 53%). Codeine is distributed to a variety of tissues, with priority being to the liver, spleen and kidney [84]. Codeine-6-glucuronide, morphine, and norcodeine is formed as a result of hepatic metabolism. Morphine is then metabolized to M3G and M6G, and contributes to analgesic effects of codeine. The half-life elimination is about 3 h and excretion is mostly done through urine and with less feces.

In adults 7–14 mg/kg, in children more than 5 mg/kg intake leads to death [85]. Codeine blood concentration within 20–50 μg/dL is toxically, if it is above 60 μg/dL is lethally [86].

Abnormal dreams, insomnia, depression, paresthesia, agitation, anxiety, ataxia, dizziness, disorientation, sedation, euphoria, fatigue, hallucination, headache, bradycardia, tachycardia, circulatory depression, flushing, pruritus, skin rash, urticaria, bronchospasm, dyspnea, respiratory depression, abdominal cramps, anorexia, constipation, diarrhea, nausea, urinary hesitancy, urinary retention, blurred vision, diplopia, miosis, nystagmus, laryngospasm, muscle rigidity, tremor, hypogonadism, etc. may occur due to codeine use.

Contraindications are hypersensitivity to codeine, pediatric patients <12 years of age, postoperative management in pediatric patients <18 years of age who have undergone tonsillectomy and/or adenoidectomy, significant respiratory depression, acute or severe bronchial asthma in the absence of resuscitative equipment, GI obstruction.

Effects on reproduction: Prolonged codeine use can cause secondary hypogonadism, which can lead to infertility in both sexes [62].

Effects on pregnancy: It is known that, codeine crosses the placenta. The use in the first trimester can lead to respiratory tract malformation, pyloric stenosis, inguinal hernia, neural tube defects, cardiac and circulatory system defects, and cleft lip and palate [63, 87]. The use of codeine late in pregnancy may result in neonatal

withdrawal syndrome, characterized by tremor, jitteriness, diarrhea, and poor feding [88].

Effects on lactation: Both codeine and an active metabolite, morphine, can be detected in breast milk [89]. A milk: plasma ratio of codeine is unknown. Respiratory depression, sedation and withdrawal signs can be seen in infants of breastfeeding mothers receiving codeine [90].

2.4 Thebaine

IUPAC Name: (4R,7aR,12bS)-7,9-dimethoxy-3-methyl-2,4,7a,13-tetrahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinoline.

Thebaine, also known as paramorphine, which is not used for medicinal purposes and is used for the production of other opioids, is the fourth opioid alkaloid according to its density in the raw *Papaver somniferum L.* plant. Thebaine exposure can be addictive as in the use of morphine, as well as strychnine-like convulsions [91].

2.5 Papaverine

IUPAC name: 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline

ATC Code	A-Alimentary tract and metabolism	A03-Drugs for functional gastrointestinal disorders	A03A-Drugs for functional gastrointestinal disorders	A03AD-Papaverine and derivatives	A03AD01-Papaverine
	G-Genito urinary system and sex hormones	G04-Urologicals	G04B-Urologicals	G04BE-Drugs used in erectile dysfunction	G04BE02-Papaverine

Papaverine, which has no opioid-like effect, is the fifth opioid alkaloid based on its density in the raw *Papaver somniferum L.* plant, first isolated from opium by Merck in 1848. Papaverine affects the heart muscle and vascular smooth muscle by blocking non-selective phosphodiesterase and calcium channels [92]. Papaverine suppresses conduction and prolongs the refractory period in the heart. Vasodilatation occurs with direct effect on vascular smooth muscles including coronary and pulmonary arteries. Papaverine-mediated relaxation in smooth muscles is independent of muscle innervation and therefore does not cause paralysis in the muscles. Papaverine-mediated these effects are more pronounced especially in ischemia with arteriospasm [93]. Papaverine is used in the treatment of myocardial infarction, angina, peripheral and pulmonary embolism, peripheral vascular disease, cerebral angiospastic states. It can also be used in hypertension, urinary incontinence, prostate hyperplasia and erectile dysfunction [94]. Papaverine also has antiviral activity, which is particularly pronounced against respiratory syncytial virus, cytomegalovirus and HIV [95]. Papaverine is taken orally, intramuscularly, intravenously, and intra-arterially.

Absorption is nearly total in oral use. Oral bioavailability is higher due to less first-pass metabolism (about 54%). Papaverine is distributed to a variety of tissues, with priority being to the adipose tissue and liver. 6-Desmethylpapaverine (6-DMP, major metabolite) and 4′,6-didesmethylpapaverine (4,6-DDMP) is formed as a result of hepatic metabolism [96]. Half-life elimination is 0.5–2 h. The excretion of papaverine is through primarily urine [97]. No information on toxic blood concentrations is available. The oral median lethal dose in rats is 360 mg/kg, unknown in humans [98].

Adverse reactions are flushing, hypertension, tachycardia, headache, malaise, sedation, abdominal distress, anorexia, constipation, etc.

Use in the complete AV block is contraindicated.

Effects on reproduction and lactation is unknown.

Effects on pregnancy: It is not considered to have a adverse effect on infants.

3. Conclusions

Although information about opium alkaloids was about 3000 BC, it was first isolated in the 1800s. Opioid-like effects occur after opioid alkaloids bind to conventional opioid receptors, such as μ, δ, and κ. In particular, as a result of the agonistic effect on μ receptors, strong analgesia, physical dependence, tolerance and increased dopaminergic activity develop in the mesocorticolimbic system responsible for dependence. Increased dopaminergic activity in the mesocorticolimbic system, is a sign of developing physical dependence, decreases in the absence of opium alkaloids, leading to withdrawal syndrome. Hypogonadism in opium alkaloids users supports the idea that it has a suppressive effect on reproduction. In addition to the risk of teratogenicity, use in both pregnancy and lactation may lead to the development of abstinence syndrome in infants.

Conflict of interest

The authors declare no conflict of interest.

Author details

Mahluga Jafarova Demirkapu[1] and Hasan Raci Yananli[2*]

1 Department of Pharmacology, Faculty of Medicine, University of Tekirdag Namık Kemal, Tekirdag, Turkey

2 Department of Pharmacology, School of Medicine, University of Marmara, Istanbul, Turkey

*Address all correspondence to: hasanyananli@yahoo.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Mishra BK, Rastogi A, Siddiqui A, Srivastava M, Verma N, Pandey R, et al. Opium Poppy: Genetic Upgradation Through Intervention of Plant Breeding Techniques. Plant Breeding from Laboratories to Fields. Sven Bode Andersen. IntechOpen; 22 May 2013. DOI: 10.5772/53132. Available from: https://www.intechopen.com/books/plant-breeding-from-laboratories-to-fields/opium-poppy-genetic-upgradation-through-intervention-of-plant-breeding-techniques

[2] Booth M. Opium-A History [Internet]. 1998. Available from: http://.www.nytimes.com/books/first/b/booth-opium.html

[3] United Nations International Drug Control Programme. Laboratory Section. Recommended Methods for Testing Opium, Morphine and Heroin. New York: United Nations; 1998. p. 4

[4] Wink M. A short history of alkaloids. In: Roberts MF, Wink M, editors. Alkaloids. Boston, MA: Springer; 1998. pp. 35-37. DOI: 10.1007/978-1-4757-2905-4_2

[5] Mann J. Murder, Magic, and Medicine. Oxford, UK: Oxford University Press; 1992. pp. 173-186

[6] Beckett AH, Casy AF. Synthetic analgesics: Stereochemical considerations. Journal of Pharmacy and Pharmacology. 1954;**6**:986-1001. DOI: 10.1111/j.2042-7158.1954.tb11033.x

[7] Portoghese PS. A new concept on the mode of interaction of narcotic analgesics with receptors. Journal of Medicinal Chemistry. 1965;**8**:609-616. DOI: 10.1021/jm00329a013

[8] Pert CB, Snyder SH. Opiate receptor: Demonstration in nervous tissue. Science. 1973;**179**:1011-1014. DOI: 10.1126/science.179.4077.1011

[9] Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. Nature. 1975;**258**:577-580. DOI: 10.1038/258577a0

[10] Cox BM, Goldstein A, Hi CH. Opioid activity of a peptide, beta-lipotropin-(61–91), derived from beta-lipotropin. Proceedings of the National Academy of Sciences of the United States of America. 1976;**73**:1821-1823. DOI: 10.1073/pnas.73.6.1821

[11] Goldstein A, Tachibana S, Lowney LI, Hunkapiller M, Hood L. Dynorphin-(1–13), an extraordinarily potent opioid peptide. Proceedings of the National Academy of Sciences of the United States of America. 1979;**76**: 6666-6670. DOI: 10.1073/pnas.76.12.6666

[12] Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. The Journal of Pharmacology and Experimental Therapeutics. 1976;**197**: 517-532

[13] Lord JA, Waterfield AA, Hughes J, Kosterlitz HW. Endogenous opioid peptides: Multiple agonists and receptors. Nature. 1977;**267**:495-499. DOI: 10.1038/267495a0

[14] Meunier JC, Mollereau C, Toll L, Suaudeau C, Moisand C, Alvinerie P, et al. Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. Nature. 1995;**377**: 532-535. DOI: 10.1038/377532a0

[15] Reinscheid RK, Nothacker HP, Bourson A, Ardati A, Henningsen RA, Bunzow JR, et al. Orphanin FQ:

A neuropeptide that activates an opioidlike G protein-coupled receptor. Science. 1995;**270**:792-794. DOI: 10.1126/science.270.5237.792

[16] Mollereau C, Parmentier M, Mailleux P, Butour JL, Moisand C, Chalon P, et al. ORL1, a novel member of the opioid receptor family. Cloning, functional expression and localization. FEBS Letters. 1994;**341**:33-38. DOI: 10.1016/0014-5793(94)80235-1

[17] Zagon IS, Gibo DM, McLaughlin PJ. Zeta (zeta), a growth-related opioid receptor in developing rat cerebellum: Identification and characterization. Brain Research. 1991;**551**:28-35. DOI: 10.1016/0006-8993(91)90909-f

[18] Manallack DT, Beart PM, Gundlach AL. Psychotomimetic sigma-opiates and PCP. Trends in Pharmacological Sciences. 1986;**7**: 448-451

[19] Hanner M, Moebius FF, Flandorfer A, Knaus HG, Striessnig J, Kempner E, et al. Purification, molecular cloning, and expression of the mammalian sigma1-binding site. Proceedings of the National Academy of Sciences of the United States of America. 1996;**93**:8072-8077. DOI: 10.1073/pnas.93.15.8072

[20] Wüster M, Schulz R, Herz A. Specificity of opioids towards the mu-, delta- and epsilon-opiate receptors. Neuroscience Letters. 1979;**15**:193-198. DOI: 10.1016/0304-3940(79)96112-3

[21] Grevel J, Yu V, Sadée W. Characterization of a labile naloxone binding site (lambda site) in rat brain. Journal of Neurochemistry. 1985;**44**: 1647-1656. DOI: 10.1111/j.1471-4159.1985.tb08808.x

[22] Zagon IS, Verderame MF, Allen SS, McLaughlin PJ. Cloning, sequencing, expression and function of a cDNA encoding a receptor for the opioid growth factor, [Met(5)]enkephalin. Brain Research. 1999;**849**:147-154. DOI: 10.1016/s0006-8993(99)02046-6

[23] Mansour A, Khachaturian H, Lewis ME, Akil H, Watson SJ. Autoradiographic differentiation of mu, delta, and kappa opioid receptors in the rat forebrain and midbrain. The Journal of Neuroscience. 1987;**7**:2445-2464

[24] Kitchen I, Slowe SJ, Matthes HW, Kieffer B. Quantitative autoradiographic mapping of mu-, delta- and kappa-opioid receptors in knockout mice lacking the mu-opioid receptor gene. Brain Research. 1997;**778**:73-88. DOI: 10.1016/s0006-8993(97)00988-8

[25] Neal CR Jr, Mansour A, Reinscheid R, Nothacker HP, Civelli O, Akil H, et al. Opioid receptor-like (ORL1) receptor distribution in the rat central nervous system: Comparison of ORL1 receptor mRNA expression with (125)I-[(14)Tyr]-orphanin FQ binding. The Journal of Comparative Neurology. 1999;**412**:563-605

[26] Besse D, Lombard MC, Zajac JM, Roques BP, Besson JM. Pre- and postsynaptic distribution of mu, delta and kappa opioid receptors in the superficial layers of the cervical dorsal horn of the rat spinal cord. Brain Research. 1990;**521**:15-22. DOI: 10.1016/0006-8993(90)91519-m

[27] Ständer S, Gunzer M, Metze D, Luger T, Steinhoff M. Localization of mu-opioid receptor 1A on sensory nerve fibers in human skin. Regulatory Peptides. 2002;**110**:75-83. DOI: 10.1016/s0167-0115(02)00159-3

[28] Salemi S, Aeschlimann A, Reisch N, Jüngel A, Gay RE, Heppner FL, et al. Detection of kappa and delta opioid receptors in skin—Outside the nervous system. Biochemical and Biophysical Research Communications. 2005;**338**: 1012-1017. DOI: 10.1016/j.bbrc.2005.10.072

[29] Chuang TK, Killam KF Jr, Chuang LF, Kung HF, Sheng WS, Chao CC, et al. Mu opioid receptor gene expression in immune cells. Biochemical and Biophysical Research Communications. 1995;**216**:922-930. DOI: 10.1006/bbrc.1995.2709

[30] Gavériaux C, Peluso J, Simonin F, Laforet J, Kieffer B. Identification of kappa- and delta-opioid receptor transcripts in immune cells. FEBS Letters. 1995;**369**:272-276. DOI: 10.1016/0014-5793(95)00766-3

[31] Zhu Y, Pintar JE. Expression of opioid receptors and ligands in pregnant mouse uterus and placenta. Biology of Reproduction. 1998;**59**:925-932. DOI: 10.1095/biolreprod59.4.925

[32] Bagnol D, Mansour A, Akil H, Watson SJ. Cellular localization and distribution of the cloned mu and kappa opioid receptors in rat gastrointestinal tract. Neuroscience. 1997;**81**:579-591. DOI: 10.1016/s0306-4522(97)00227-3

[33] Pol O, Palacio JR, Puig MM. The expression of delta- and kappa-opioid receptor is enhanced during intestinal inflammation in mice. The Journal of Pharmacology and Experimental Therapeutics. 2003;**306**:455-462. DOI: 10.1124/jpet.103.049346

[34] Jongkamonwiwat N, Phansuwan-Pujito P, Sarapoke P, Chetsawang B, Casalotti SO, Forge A, et al. The presence of opioid receptors in rat inner ear. Hearing Research. 2003;**181**:85-93. DOI: 10.1016/s0378-5955(03)00175-8

[35] Dhawan BN, Cesselin F, Raghubir R, Reisine T, Bradley PB, Portoghese PS, et al. International Union of Pharmacology. XII. Classification of opioid receptors. Pharmacological Reviews. 1996;**48**:567-592

[36] Guan JS, Xu ZZ, Gao H, He SQ, Ma GQ, Sun T, et al. Interaction with vesicle luminal protachykinin regulates surface expression of delta-opioid receptors and opioid analgesia. Cell. 2005;**122**:619-631. DOI: 10.1016/j.cell.2005.06.010

[37] Borsodi A, Bruchas M, Caló G, Chavkin C, Christie MJ, Civelli O, et al. Opioid receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database. UPHAR/BPS Guide to Pharmacology CITE. 2019(4). DOI: 10.2218/gtopdb/F50/2019.4

[38] Hutcheson DM, Matthes HW, Valjent E, Sánchez-Blázquez P, Rodríguez-Díaz M, Garzón J, et al. Lack of dependence and rewarding effects of deltorphin II in mu-opioid receptor-deficient mice. The European Journal of Neuroscience. 2001;**13**:153-161. DOI: 10.1111/j.1460-9568.2001.01363.x

[39] Tien LT, Park Y, Fan LW, Ma T, Loh HH, Ho IK. Increased dopamine D2 receptor binding and enhanced apomorphine-induced locomotor activity in mu-opioid receptor knockout mice. Brain Research Bulletin. 2003;**61**:109-115. DOI: 10.1016/s0361-9230(03)00077-7

[40] Jamot L, Matthes HW, Simonin F, Kieffer BL, Roder JC. Differential involvement of the mu and kappa opioid receptors in spatial learning. Genes, Brain, and Behavior. 2003;**2**:80-92. DOI: 10.1034/j.1601-183x.2003.00013.x

[41] Filliol D, Ghozland S, Chluba J, Martin M, Matthes HW, Simonin F, et al. Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. Nature Genetics. 2000;**25**:195-200. DOI: 10.1038/76061

[42] Jordan B, Devi LA. Molecular mechanisms of opioid receptor signal transduction. British Journal of Anaesthesia. 1998;**81**:12-19. DOI: 10.1093/bja/81.1.12

[43] North RA, Williams JT, Surprenant A, Christie MJ. Mu and delta

receptors belong to a family of receptors that are coupled to potassium channels. Proceedings of the National Academy of Sciences of the United States of America. 1987;**84**:5487-5491. DOI: 10.1073/pnas.84.15.5487

[44] Malaivijitnond S, Varavudhi P. Evidence for morphine-induced galactorrhea in male cynomolgus monkeys. Journal of Medical Primatology. 1998;**27**:1-9. DOI: 10.1111/j.1600-0684.1998.tb00061.x

[45] Eddy NB, Halbach H, Isbell H, Seevers MH. Drug dependence: Its significance and characteristics. Bulletin of the World Health Organization. 1965; **32**:721-733

[46] Koob GF, Le Moal M. Opioids. In: Neurobiology of Addiction. London: Academic Press; 2006. pp. 121-171

[47] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition (DSM-5). Arlington: American Psychiatric Association; 2013. pp. 541-546

[48] World Drug Report. New York: United Nations Office on Drugs and Crime; 2012. p. 1

[49] Koob GF. Drugs of abuse: Anatomy, pharmacology and function of reward pathways. Trends in Pharmacological Sciences. 1992;**13**:177-184. DOI: 10.1016/0165-6147(92)90060-j

[50] Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;**35**: 217-238. DOI: 10.1038/npp.2009.110

[51] Gómez-Milanés I, Almela P, García-Carmona JA, García-Gutiérrez MS, Aracil-Fernández A, Manzanares J, et al. Accumbal dopamine, noradrenaline and serotonin activity after naloxone-conditioned place aversion in morphine-dependent mice. Neurochemistry International. 2012;**61**:433-440. DOI: 10.1016/j.neuint.2012.06.011

[52] Diana M, Pistis M, Muntoni A, Gessa G. Profound decrease of mesolimbic dopaminergic neuronal activity in morphine withdrawn rats. The Journal of Pharmacology and Experimental Therapeutics. 1995;**272**: 781-785

[53] Yananli H, Gören MZ, Berkman K, Aricioğlu F. Effect of agmatine on brain L-citrulline production during morphine withdrawal in rats: A microdialysis study in nucleus accumbens. Brain Research. 2007;**1132**:51-58. DOI: 10.1016/j.brainres.2006. 11.028

[54] Topkara B, Yananli HR, Sakallı E, Demirkapu MJ. Effects of injection of gamma-aminobutyric acid agonists into the nucleus accumbens on naloxone-induced morphine withdrawal. Pharmacology. 2017;**100**:131-138. DOI: 10.1159/000477548

[55] Jafarova Demirkapu M, Yananli HR, Kaleli M, Sakalli HE, Gören MZ, Topkara B. The role of adenosine A1 receptors in the nucleus accumbens during morphine withdrawal. Clinical and Experimental Pharmacology & Physiology. DOI: 10.1111/1440-1681. 13224

[56] Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. The Journal of Pain. 2009;**10**: 113-130. DOI: 10.1016/j.jpain.2008. 10.008

[57] Masood AR, Thomas SH. Systemic absorption of nebulized morphine compared with oral morphine in healthy subjects. British Journal of Clinical Pharmacology. 1996;**41**:250-252. DOI: 10.1111/j.1365-2125.1996.tb00192.x

[58] Hunt A, Joel S, Dick G, Goldman A. Population pharmacokinetics of oral morphine and its glucuronides in children receiving morphine as immediate-release liquid or sustained-

release tablets for cancer pain. The Journal of Pediatrics. 1999;**135**:47-55. DOI: 10.1016/s0022-3476(99)70326-4

[59] Christrup LL. Morphine metabolites. Acta Anaesthesiologica Scandinavica. 1997;**41**:116-122. DOI: 10.1111/j.1399-6576.1997.tb04625.x

[60] Harvey AL. Natural and Synthetic Neurotoxins. London, England: Academic Press; 1993. p. 263

[61] Gossel TA. In: Gossel TA, Bricker JD, editors. Principles of Clinical Toxicology. 3rd ed. New York: CRC Press; 1994. p. 421

[62] Brennan MJ. The effect of opioid therapy on endocrine function. The American Journal of Medicine. 2013; **126**:S12-S18. DOI: 10.1016/j.amjmed.2012.12.001

[63] Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, Honein MA; National Birth Defects Prevention Study. Maternal treatment with opioid analgesics and risk for birth defects. American Journal of Obstetrics and Gynecology. 2011;**204**:314.e1-11. DOI: 10.1016/j.ajog.2010.12.039

[64] Schmid M, Kuessel L, Klein K, Metz V, Fischer G, Krampl-Bettelheim E. First-trimester fetal heart rate in mothers with opioid addiction. Addiction. 2010;**105**:1265-1268. DOI: 10.1111/j.1360-0443.2010.02982.x

[65] Kopecky EA, Ryan ML, Barrett JF, Seaward PG, Ryan G, Koren G, et al. Fetal response to maternally administered morphine. American Journal of Obstetrics and Gynecology. 2000;**183**:424-430. DOI: 10.1067/mob.2000.105746

[66] Cobrınık RW, Hood RT Jr, Chusıd E. The effect of maternal narcotic addiction on the newborn infant; review of literature and report of 22 cases. Pediatrics. 1959;**24**:288-304

[67] Dow K, Ordean A, Murphy-Oikonen J, Pereira J, Koren G, Roukema H, et al. Neonatal abstinence syndrome clinical practice guidelines for Ontario. Journal of Population Therapeutics and Clinical Pharmacology. 2012;**19**:e488-e506

[68] Hudak ML, Tan RC, Committee On Drugs, Committee on Fetus and Newborn, American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics. 2012;**129**:e540-e560. DOI: 10.1542/peds.2011-3212

[69] Baka NE, Bayoumeu F, Boutroy MJ, Laxenaire MC. Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. Anesthesia and Analgesia. 2002;**94**:184-187. DOI: 10.1097/00000539-200201000-00035

[70] Feilberg VL, Rosenborg D, Broen Christensen C, Mogensen JV. Excretion of morphine in human breast milk. Acta Anaesthesiologica Scandinavica. 1989; **33**:426-428. DOI: 10.1111/j.1399-6576.1989.tb02938.x

[71] Wittels B, Scott DT, Sinatra RS. Exogenous opioids in human breast milk and acute neonatal neurobehavior: A preliminary study. Anesthesiology. 1990;**73**:864-869. DOI: 10.1097/00000542-199011000-00012

[72] Martin E, Vickers B, Landau R, Reece-Stremtan S. ABM clinical protocol #28, peripartum analgesia and anesthesia for the breastfeeding mother. Breastfeeding Medicine. 2018;**13**: 164-171. DOI: 10.1089/bfm.2018.29087.ejm

[73] Willette RE. Analgesic agents. In: Delgado JN, Remers WA, editors. Textbook of Organic Medicinal and Pharmaceutical Chemistry. 10th ed.

Philadelphia, PA: Lippincott-Raven; 1998. pp. 687-711

[74] Osol A, Hoover JE, et al. Remington's Pharmaceutical Sciences. In: Osol A, Hoover JE, editors. 15th ed. Easton, Pennsylvania: Mack Publishing Co.; 1975. p. 805

[75] Ramanathan VS, Chandra P. Recovery, separation and purification of narcotine and papaverine from Indian opium. Bulletin on Narcotics. 1981;**33**: 55-64

[76] National Cancer İnstitute. Noscapine [Internet]. 2019. Available from: https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C80589

[77] Goodman LS, Gilman A. In: Goodman LS, Gilman A, editors. The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc.; 1975. p. 279

[78] Gutstein HB, Akil H. Opioid analgesics. In: Hardman JG, Limbird LE, Gilman AG, McGraw-Hill, editors. The Pharmacological Basis of Therapeutics. 10th ed. New York, NY; 2001. pp. 569-611

[79] Dahlström B, Mellstrand T, Löfdahl CG, Johansson M. Pharmacokinetic properties of noscapine. European Journal of Clinical Pharmacology. 1982;**22**:535-539. DOI: 10.1007/bf00609627

[80] Tsunoda N, Yoshimura H. Metabolic fate of noscapine. II. Isolation and identification of novel metabolites produced by C—C bond cleavage. Xenobiotica. 1979;**9**:181-187. DOI: 10.3109/00498257909038719

[81] American Medical Association, AMA Department of Drugs. AMA Drug Evaluations. 3rd ed. Littleton, Massachusetts: PSG Publishing Co., Inc.; 1977. p. 667

[82] American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics. 1994;**93**:137-150

[83] Troy DB. In: Troy DB, editor. Remmington: The Science and Practice of Pharmacy. 21st ed. Philadelphia, PA: Lippincott Williams & Williams; 2005. p. 1527

[84] Baselt RC, Cravey RH. Disposition of Toxic Drugs and Chemicals in Man. 4th ed. Foster City, CA, USA: Chemical Toxicology Institute; 1995. pp. 191-194

[85] Dart RC. In: Dart RC, editor. Medical Toxicology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins.; 2004. p. 761

[86] Gossel TA, Bricker JD. Principles of Clinical Toxicology. 3rd ed. New York, NY: Raven Press, Ltd.; 1994. p. 298

[87] Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstetrics and Gynecology. 2013;**122**:838-844. DOI: 10.1097/AOG.0b013e3182a6643c

[88] Nair V, Soraisham AS, Akierman A. Neonatal withdrawal syndrome due to maternal codeine use. Paediatrics & Child Health. 2012;**17**:e40-e41. DOI: 10.1093/pch/17.5.e40

[89] Meny RG, Naumburg EG, Alger LS, Brill-Miller JL, Brown S. Codeine and the breastfed neonate. Journal of Human Lactation. 1993;**9**:237-240. DOI: 10.1177/089033449300900423

[90] Lam J, Matlow JN, Ross CJ, Hayden MR, Carleton BC, Madadi P. Postpartum maternal codeine therapy and the risk of adverse neonatal

outcomes: The devil is in the details. Therapeutic Drug Monitoring. 2012;**34**: 378-380. DOI: 10.1097/FTD.0b013e31825da19f

[91] The Merck Index. 11th ed. Title 21 Part 1308.12. 1985

[92] Kaneda T, Takeuchi Y, Matsui H, Shimizu K, Urakawa N, Nakajyo S. Inhibitory mechanism of papaverine on carbachol-induced contraction in bovine trachea. Journal of Pharmacological Sciences. 2005;**98**:275-282. DOI: 10.1254/jphs.fpj05013x

[93] Stiefel MF, Spiotta AM, Udoetuk JD, Maloney-Wilensky E, Weigele JB, Hurst RW, et al. Intra-arterial papaverine used to treat cerebral vasospasm reduces brain oxygen. Neurocritical Care. 2006;**4**:113-118. DOI: 10.1385/NCC:4:2:113

[94] Pfizer New Zealand Limited. DBL Papaverine hydrochloride injection product data sheet [İnternet]. 2017. Available from: http://www.medsafe.govt.nz/profs/Datasheet/d/dblPapaverineHydrochlorideinj

[95] National Cancer İnstitute. Papaverine [Internet]. 2019. Available from: https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C726

[96] Wolf CE, Pierce KL, Goldfine BL, Nanco CR, Poklis JL, Korzun WJ. Using papaverine and its metabolites, 6-desmethyl papaverine and 4',6-didesmethyl papaverine as biomarkers to improve the detection time of heroin use. Journal of Analytical Toxicology. 2019;**43**:600-606. DOI: 10.1093/jat/bkz069

[97] US Natl Inst Health; DailyMed. Current Medication Information for Papaverine hydrochloride injection, solution, 2012. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=9e5e2ce4-7a57-4c61-a826-64c8d11d038e

[98] RxList. Papaverine injection [Internet]. 2019. Available from: https://www.rxlist.com/papaverine-injection-drug.htm#overdosage