



PHARMACOLOGICAL PROPERTIES AND EFFECTS OF MORPHINE ON THE HUMAN BODY

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ABSTRACT This scientific article systematically and comprehensively covers the chemical structure, pharmacokinetic and pharmacodynamic properties, and mechanisms of action of morphine — a member of the opioid analgesic group. Morphine modifies intracellular signaling via Gi/o proteins through μ -, κ -, and δ -opioid receptors, thereby inhibiting the transmission of nociceptive impulses in the central nervous system. The article also examines the drug's bioavailability, metabolic pathways, the clinical significance of M3G and M6G metabolites, adverse effects, mechanisms of dependence and tolerance, as well as its contemporary clinical applications.

Keywords: *morphine, opioid receptors, μ -receptor, pharmacodynamics, pharmacokinetics, analgesia, M6G, respiratory depression, tolerance, palliative medicine.*

INTRODUCTION

Pain is not only a protective reaction of a living organism, but also a symptom of disease that significantly reduces the quality of life of the patient. Pain management remains a pressing issue across all fields of medicine — from surgery and oncology to palliative care. In this regard, morphine has maintained its position as the most reliable and potent analgesic for centuries.

Morphine was first isolated in pure crystalline form from opium (*Papaver somniferum*) in 1804 by German chemist Friedrich Wilhelm Sertürner. Named after Morpheus, the Greek god of dreams, this substance began to be widely introduced into clinical practice from the second half of the 19th century. The invention of the syringe and the discovery of intravenous administration further increased morphine's importance in medicine.

In the 1970s, the discovery of opioid receptors by the groups of Pert, Snyder, and Simon opened entirely new perspectives for studying morphine pharmacology. Today, morphine is included in the World Health Organization (WHO) List of Essential Medicines and occupies Step 3 of the WHO pain ladder for



management of chronic pain. Nevertheless, its adverse effects, risk of dependence, and problems of misuse remain serious social and medical concerns worldwide.

CHEMICAL STRUCTURE AND PHYSICOCHEMICAL PROPERTIES OF MORPHINE

Morphine is a phenanthrene alkaloid with molecular formula $C_{17}H_{19}NO_3$ and molecular weight of 285.34 g/mol. The molecule consists of five rings and includes a piperidine nucleus. Its three-dimensional structure has a bilateral "T" shape, which precisely matches the binding pocket of opioid receptors.

The stereochemical configuration of morphine is described as 5R, 6S, 9R, 13S, 14R. The 3-hydroxyl group in the molecule has phenolic character and ensures water solubility, while the 6-hydroxyl group has an allylic structure. This 6-OH group plays a major role in metabolism: it is conjugated via a glucuronide bond to form morphine-6-glucuronide (M6G). M6G shows 45–50 times higher affinity for μ -receptors compared to morphine itself and is the primary determinant of sustained analgesic effect.

Morphine is partially soluble in water (~40 mg/mL at pH 7.4) and has low lipid solubility ($\log P = 0.89$). This property slows its passage across the blood-brain barrier. For comparison, codeine (3-methylmorphine) has greater lipid solubility and crosses the brain barrier more rapidly. The pKa of morphine is 8.0, meaning the drug exists predominantly in ionized form at physiological pH.

Analysis of structure-activity relationships among opioid alkaloids shows: methylation of the 3-OH group (producing codeine) markedly reduces analgesic activity; acetylation of the 6-OH group (producing diacetylmorphine — heroin) increases lipid solubility and brain penetration; and introduction of an N-allyl group (naloxone) confers antagonist properties. Thus, minor modifications to the morphine molecule can fundamentally alter biological activity.

PHARMACODYNAMICS: MECHANISMS OF ACTION

To understand morphine's mechanism of action, familiarity with the endogenous opioid system is essential. Endogenous opioid peptides produced naturally by the body — endorphins, enkephalins, and dynorphins — are the endogenous ligands of this system. Morphine acts as their mimetic, binding to the same receptors but producing much stronger and longer-lasting effects.

Morphine binds to opioid receptors that operate through G-proteins. These receptors are coupled to G_i/o proteins and reduce neuronal excitability through three mechanisms: first, by inhibiting adenylate cyclase, thereby decreasing intracellular cAMP; second, by closing voltage-gated Ca^{2+} channels, blocking calcium entry into the synaptosome; third, by opening Kir3 (GIRK) channels, allowing K^+ ions to exit the cell and hyperpolarize the membrane. Together, these three mechanisms sharply suppress presynaptic neurotransmitter release and postsynaptic neuronal activity.



The analgesic effect manifests primarily in the central nervous system. The periaqueductal grey matter (PAG), nucleus raphe magnus, and the substantia gelatinosa Rolandi of the spinal cord are the main sites of morphine action. Upon activation of μ -receptors in the PAG, descending serotonergic and noradrenergic inhibitory pathways are engaged, suppressing nociceptive neurons in the dorsal horn of the spinal cord.

Morphine also has peripheral analgesic effects. In inflamed tissues, the density of μ - and δ -receptors increases, and local injection of morphine can produce analgesic effects. This mechanism forms the basis for intra-articular morphine administration in arthritis and postoperative pain.

PHARMACOKINETICS

Morphine absorption varies markedly depending on the route of administration. When taken orally, bioavailability is 30–40%, because a large portion of the drug is metabolized during first-pass hepatic metabolism. With intramuscular (IM) or subcutaneous (SC) injection, absorption is faster and more complete (bioavailability ~90–100%). With intravenous (IV) administration, bioavailability is 100% and onset of action occurs within 5–10 minutes.

Distribution. Morphine has a volume of distribution (V_d) of 3–4 L/kg and is widely distributed in tissues. Plasma protein binding is relatively low at ~35%, with binding mainly to albumin and γ -globulins. Owing to its low lipid solubility, passage across the blood-brain barrier is relatively slow, but in conditions of inflammation and acidosis, this barrier's permeability increases. Morphine crosses the placental barrier and passes into breast milk, requiring caution in pregnant and breastfeeding women.

Metabolism. Morphine is metabolized primarily in the liver by uridine diphosphate-glucuronosyltransferase (UGT2B7) into two main metabolites: morphine-3-glucuronide (M3G) — comprising ~60% of all metabolites, biologically inactive, and capable of antagonizing morphine's analgesic effect; and morphine-6-glucuronide (M6G) — comprising ~10%, but showing 45–50 times higher affinity for μ -receptors than morphine and serving as the primary mediator of prolonged analgesia. In patients with renal impairment, accumulation of M6G can deepen respiratory depression.

Elimination. Morphine is eliminated primarily via the kidneys (~90%) as its metabolites. Clearance rate is 20–30 mL/min/kg. The biological half-life ($T_{1/2}$) is 2–4 hours. In elderly patients and those with hepatic cirrhosis or renal insufficiency, metabolism is slowed and the risk of drug accumulation increases. In these patient categories, dose reduction and extension of dosing intervals are mandatory.

ADVERSE EFFECTS AND COMPLICATIONS

The adverse effects of morphine are multisystemic and dose-dependent. The most dangerous is respiratory depression. This occurs due to μ_2 -receptor-mediated reduction in the respiratory center's



sensitivity to CO₂. In acute overdose, bradypnea (< 12 breaths/min), hypercapnia, oxygen desaturation, and coma may develop. Naloxone 0.4–0.8 mg IV reverses respiration within 1–2 minutes, but since its duration of action (~30–90 min) is shorter than morphine's, repeated dosing may be necessary.

Gastrointestinal effects: constipation — resulting from morphine's action on muscarinic receptors and nociceptive neurons in the GI tract, slowing intestinal peristalsis and increasing transit time. Nausea and vomiting — morphine stimulates the chemoreceptor trigger zone (CTZ) in the brain stem, observed in most patients, especially in the first days of treatment. Increased tone of intestinal and biliary sphincters may produce spasm of the Sphincter of Oddi, potentially worsening biliary pain.

CNS effects: euphoria and dysphoria — mediated through μ -receptors in the limbic system; sedation — resulting from cortical inhibition; miosis (pupillary constriction) — arising from inhibition of the Edinger-Westphal nucleus in the n. oculomotorius nuclei. Cognitive impairment, particularly in elderly patients, may manifest as delirium.

Histamine release: morphine can trigger histamine release from mast cells, causing pruritus, flushing, and occasionally bronchospasm. This effect is not receptor-mediated and is not reversed by naloxone. Therefore, caution is warranted in patients with bronchial asthma.

Cardiovascular effects are generally mild — bradycardia and arterial hypotension (especially with IV administration in hypovolemic patients) may occur. Renal effects: morphine increases secretion of antidiuretic hormone (ADH), reducing diuresis; increased tone of the urinary bladder sphincter may impair micturition.

TOLERANCE, PHYSICAL DEPENDENCE, AND PSYCHOLOGICAL ADDICTION

Tolerance to morphine refers to the adaptation of the organism to the drug such that the effect of the previous dose decreases and a higher dose is required to achieve the same effect. The molecular mechanisms of tolerance are multifaceted: desensitization of μ -receptors — uncoupling of the receptor protein from G-protein; internalization — withdrawal of receptors into the cell; ectopic signaling — compensatory upregulation of the cAMP pathway; and alterations in synaptic plasticity.

Physical dependence inevitably develops with prolonged morphine use. Abrupt discontinuation or administration of naloxone produces acute withdrawal syndrome (abstinence) in three phases: acute phase (6–24 hours) — tachycardia, diaphoresis, agitation, diarrhea; subacute phase (1–3 days) — myalgia, restlessness, insomnia; prolonged phase (weeks) — dysphoria, decreased libido, vagotonia symptoms.

Psychological addiction is formed through activation of opioid receptors in the limbic reward system (nucleus accumbens, VTA) and disruption of dopamine release. In clinical practice, when used



under medical supervision for pain management, the risk of psychological addiction is relatively low, but extreme caution is essential in patients with a history of substance abuse.

CLINICAL APPLICATIONS AND DOSING PRINCIPLES

The clinical indications for morphine are broad: postoperative pain — oral or parenteral administration at doses corresponding to pain score; myocardial infarction — IV 2–4 mg in divided doses, with monitoring of respiration and hemodynamics; oncological pain — dose titration according to the WHO three-step analgesic ladder based on pain intensity; dyspnea — subanalgesic doses reduce the sensation of breathlessness in pleural effusion and pulmonary edema; palliative medicine — first-choice drug for managing pain and dyspnea in the terminal stage of life.

Dosing principles. Dosing is individualized and carried out as follows: assessment of pain on a numeric scale (0–10); initial dose — 2.5 mg in elderly patients, 5–10 mg orally in adults; "rescue" dose — 10–15% of the total 24-hour dose as a prn dose; transition to sustained-release formulations (e.g., MS Contin) is preferred in chronic pain; reduction of dose and extension of intervals is mandatory in patients with renal and hepatic impairment.

Contraindications: acute bronchial asthma and airway obstruction, paralytic ileus, raised intracranial pressure in head injury, overdose or depressed conscious states. Special caution is required in neonates and young children, and during pregnancy and lactation. Concurrent use with MAO inhibitors is extremely dangerous — serotonin syndrome may develop.

CONCLUSION

Morphine is an indispensable part of modern medicine, possessing a deep and multifaceted pharmacological profile. Its molecular structure, effects on Gi/o signaling pathways via μ -, κ -, and δ -receptors, pharmacokinetic parameters, and clinical pharmacology have been extensively studied. The ability of the M6G metabolite to provide a delayed component of analgesia, and the possibility of its accumulation in renal disease, are of clinical significance.

Respiratory depression, gastrointestinal adverse effects, and the development of tolerance and dependence characterize morphine as a drug requiring constant medical supervision. However, when used according to correct indications, with individualized dosing and regular patient monitoring, morphine remains one of the most effective and reliable tools for pain management. Contemporary research is leveraging the experience of morphine to develop safer opioid analgesics.



REFERENCES

1. Katzung B.G., Trevor A.J. Basic and Clinical Pharmacology. 14th ed. New York: McGraw-Hill Education, 2018. 1235 p.
2. Rang H.P., Dale M.M., Ritter J.M. et al. Rang and Dale's Pharmacology. 9th ed. Edinburgh: Elsevier, 2020. 808 p.
3. Trescot A.M., Datta S., Lee M., Hansen H. Opioid pharmacology. Pain Physician. 2008; 11(2 Suppl): S133–S153.
4. Pasternak G.W., Pan Y.X. Mu opioids and their receptors: evolution of a concept. Pharmacol Rev. 2013; 65(4):1257–1317.
5. Stein C. Opioid receptors. Annu Rev Med. 2016; 67:433–451. DOI: 10.1146/annurev-med-062613-093100.
6. World Health Organization. WHO Model List of Essential Medicines. 23rd List. Geneva: WHO, 2023. 60 p.
7. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw-Hill, 2018. 1440 p.
8. Nishonov N.T., Rakhimova G.A. Fundamentals of Clinical Pharmacology. Tashkent: Medicine, 2019. 480 p.
9. Inturrisi C.E. Clinical pharmacology of opioids for pain. Clin J Pain. 2002; 18(4 Suppl):S3–13.
10. Olson K.R. Poisoning & Drug Overdose. 7th ed. New York: McGraw-Hill, 2018. 1106 p.