

NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION

Drugs and Human
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Morphine and heroin are white, crystalline powders. Illicit heroin may vary in color from white to dark brown due to impurities, or may appear as a black tar-like material.

Synonyms: *Morphine:* Astramorph®, Duramorph®, Infumorph®, Kadian®, Morphine Sulfate®, MSIR®, MS-Contin®, Oramorph SR®, Roxanol®. *Heroin:* diacetylmorphine, diamorphine; Mexican brown or Mexican black tar heroin; bags, blue-steel, China white, H, horse, junk, no-name, silk, skag, smack. Scramble (cut heroin), bone (uncut heroin for smoking), chippers (occasional users).

Source: Morphine is a naturally occurring substance extracted from the seedpod of the poppy plant, *Papaver somniferum*. The milky resin that seeps from incisions made in the unripe seedpod is dried and powdered to make opium, which contains a number of alkaloids including morphine. Morphine concentration in opium can range from 4-21%. An alternate method of harvesting morphine is by the industrial poppy straw process of extracting alkaloids from the mature dried plant, which produces a fine brownish powder. Morphine is a schedule II controlled substance and is available in a variety of prescription forms: injectables (0.5-25 mg/mL strength); oral solutions (2-20 mg/mL); immediate and controlled release tablets and capsules (15-200 mg); and suppositories (5-30 mg). Heroin is a schedule I controlled substance and is produced from morphine by acetylation at the 3 and 6 positions. The majority of heroin sold in the U. S. originates from Southeast Asia, South America (Columbia) and Mexico. Low purity Mexican black tar heroin is most common on the West coast, while high purity Columbian heroin dominates in the East and most mid-western states.

Drug Class: Narcotic analgesic.

Medical and Recreational Uses: Morphine is used medicinally for the relief of moderate to severe pain in both acute and chronic management. It can also be used to sedate a patient pre-operatively and to facilitate the induction of anesthesia. Heroin has no currently accepted medical uses in the U.S., however, it is an analgesic and antitussive.

Potency, Purity and Dose: The dosage of morphine is patient-dependent. A usual adult oral dose of morphine is 60-120 mg daily in divided doses, or up to 400 mg daily in opioid tolerant patients. Recreationally, daily heroin doses of 5-1500 mg have been reported, with an average daily dose of 300-500 mg. Addicts may inject heroin 2-4 times per day. Depending on the demographic region, the street purity of heroin can range from 11-72% (average U.S. purity is ~38%). Heroin may be cut with inert or toxic adulterants such as sugars, starch, powdered milk, quinine, and ketamine. Heroin is often mixed with methamphetamine or cocaine ("speedball") and injected; or co-administered with alprazolam, MDMA (Ecstasy), crack cocaine, or diphenhydramine.

Route of Administration: *Morphine:* oral, intramuscular, intravenous, rectal, epidural, and intrathecal administration. Morphine tablets may be crushed and injected, while opium can be smoked. *Heroin:* smoked, snorted, intravenous ("mainlining"), and subcutaneous ("skin popping") administration. Black tar heroin is typically dissolved, diluted and injected, while higher purity heroin is often snorted or smoked.

Pharmacodynamics: Morphine produces its major effects on the CNS primarily through m-receptors, and also at k- and d-receptors. m 1-receptors are involved in pain modulation,

analgesia, respiratory depression, miosis, euphoria, and decreased gastrointestinal activity; μ -2-receptors are involved in respiratory depression, drowsiness, nausea, and mental clouding; κ -receptors are involved in analgesia, diuresis, sedation, dysphoria, mild respiratory depression, and miosis; and δ -receptors are involved in analgesia, dysphoria, delusions, and hallucinations. Heroin has little affinity for opiate receptors and most of its pharmacology resides in its metabolism to active metabolites, namely 6-acetylmorphine, morphine, and morphine-6-glucuronide.

Pharmacokinetics: The oral bioavailability of morphine is 20-40%, and 35% is bound in plasma. Morphine has a short half-life of 1.5 - 7 hours and is primarily glucuroconjugated at positions 3 and 6, to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), respectively. A small amount (5%) is demethylated to normorphine. M6G is an active metabolite with a higher potency than morphine, and can accumulate following chronic administration or in renally impaired individuals. The half-life of M6G is 4 +/- 1.5 hours. Close to 90% of a single morphine dose is eliminated in the 72 hours urine, with 75% present as M3G and less than 10% as unchanged morphine. **Heroin has an extremely rapid half-life of 2-6 minutes, and is metabolized to**

6-acetylmorphine and morphine. The half-life of 6-acetylmorphine is 6-25 minutes. Both heroin and 6-acetylmorphine are more lipid soluble than morphine and enter the brain more readily.

Molecular Interactions / Receptor Chemistry: The uridine 5'-diphosphate-glucuronosyltransferase (UGT) 2B7 isoform is primarily involved in the metabolism of morphine. Potential inhibitors of this UGT isoform could decrease the rate of morphine elimination if administered concurrently, while potential inducers could increase the rate of elimination.

Blood to Plasma Concentration Ratio: Morphine 1.02; M6G 0.57; M3G 0.59

Interpretation of Blood Concentrations: Tolerance makes interpretation of blood or plasma morphine concentrations extremely difficult. Peak plasma morphine concentrations occur within an hour of oral administration, and within 5 minutes following intravenous injection. Average plasma concentrations of 0.065 mg/L are necessary for adequate therapeutic analgesia in ambulatory patients. Anesthetic concentrations can reach beyond 2 mg/L in surgical patients. Following oral doses of 10-80 mg, corresponding peak morphine concentrations in serum were 0.05-0.26 mg/L. Following an intravenous dose of 8.75g/70 kg, a peak serum concentration of 0.44 mg/L was reached. In 10 intravenous drug fatalities, where morphine was the only drug detected, postmortem whole blood morphine concentrations averaged 0.70 mg/L (range 0.20-2.3 mg/L). Following a single 12 mg intravenous mg dose of heroin, a peak heroin concentration of 0.141 mg/L was obtained at 2 minutes, while the 6-acetylmorphine and morphine concentrations were 0.151 and 0.044, respectively. A single 5 mg intravenous dose of heroin produced a peak plasma morphine concentration of 0.035 mg/L at 25 minutes, while intravenous doses of 150-200 mg have produced plasma morphine concentrations of up to 0.3 mg/L. Intranasal administration of 12 mg heroin in 6 subjects produced average peak concentrations of 0.016 mg/L heroin in plasma within 5 minutes; 0.014 mg/L of 6-acetylmorphine at 0.08-0.17 hours; and 0.019 mg/L of morphine at 0.08-1.5 hours.

Interpretation of Urine Test Results: Positive morphine urine results generally indicate use within the last two to three days, or longer after prolonged use. Detection of 6-acetylmorphine in the urine is indicative of heroin use. High concentrations may indicate chronic use of the drug. It is important to hydrolyze urine specimens to assess a urine morphine concentration.

Effects: Depends heavily on the dose of morphine or heroin, the route of administration, and previous exposure. Following an intravenous dose of heroin, the user generally feels an intense surge of euphoria ("rush") accompanied by a warm flushing of the skin, dry mouth, and heavy extremities. The user then alternates between a wakeful and drowsy state ("on the nod").

Psychological: Euphoria, feeling of well-being, relaxation, drowsiness, sedation, lethargy, disconnectedness, self-absorption, mental clouding, and delirium.

Physiological: Analgesia, depressed heart rate, respiratory depression, CNS depression, nausea and vomiting, reduced gastrointestinal motility, constipation, flushing of face and neck due to dilatation of subcutaneous blood vessels, cramping, sweating, pupils fixed and constricted, diminished reflexes, and depressed consciousness.

Side Effect Profile: Drowsiness, inability to concentrate, apathy, lessened physical activity, constipation, urinary retention, nausea, vomiting, tremors, itching, bradycardia, severe respiratory depression, and pulmonary complications such as pneumonia. Medical complications among abusers arise primarily from adulterants found in street drugs and in non-sterile injecting practices, and may include skin, lung and brain abscesses, collapsed veins, endocarditis, hepatitis and HIV/AIDS. Overdose can include slow, shallow breathing, clammy skin, convulsions, extreme somnolence, severe respiratory depression, apnea, circulatory collapse, cardiac arrest, coma, and death.

Duration of Effects: Depending on the morphine dose and the route of administration, onset of effects is within 15-60 minutes and effects may last 4-6 hours. The duration of analgesia increases progressively with age although the degree of analgesia remains unchanged. Following heroin use, the intense euphoria lasts from 45 seconds to several minutes, peak effects last 1-2 hours, and the overall effects wear off in 3-5 hours, depending on dose.

Tolerance, Dependence and Withdrawal Effects: Both morphine and heroin have high physical and psychological dependence. With regular use, tolerance develops early to the duration and intensity of euphoria and analgesia. Withdrawal symptoms may occur if use is abruptly stopped or reduced. Withdrawal can begin within 6-12 hours after the last dose and may last 5-10 days. Early symptoms include watery eyes, runny nose, yawning and sweating. Major withdrawal symptoms peak between 48-72 hours after the last dose and include drug craving, restlessness, irritability, dysphoria, loss of appetite, tremors, severe sneezing, diarrhea, nausea and vomiting, elevated heart rate and blood pressure, chills alternating with flushing and excessive sweating, goose-flesh, abdominal cramps, body aches, muscle and bone pain, muscle spasms, insomnia, and severe depression.

Drug Interactions: Alcohol increases the CNS effects of morphine such as sedation, drowsiness, and decreased motor skills. There is a higher risk of respiratory depression, hypotension and profound sedation or coma with concurrent treatment or use of other CNS depressant drugs such as barbiturates, benzodiazepines, hypnotics, tricyclic antidepressants, general anesthetics, MAO inhibitors, and antihistamines. Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Small doses of amphetamine substantially increase the analgesia and euphoriant effects of morphine and may decrease its sedative effects. Antidepressants may enhance morphine's analgesia. Partial agonists such as buprenorphine, nalbuphine, butorphanol, and pentazocine will precipitate morphine withdrawal.

Performance Effects: Laboratory studies have shown that morphine may cause sedation and significant psychomotor impairment for up to 4 hours following a single dose in normal individuals. Early effects may include slowed reaction time, depressed consciousness, sleepiness, and poor performance on divided attention and psychomotor tasks. Late effects may include inattentiveness, slowed reaction time, greater error rate in tests, poor concentration, distractibility, fatigue, and poor performance in psychomotor tests. Subjective feelings of sedation, sluggishness, fatigue, intoxication, and body sway have also been reported. Significant tolerance may develop making effects less pronounced in long-term users for the same dose. In a laboratory setting, heroin produced subjective feelings of sedation for up to 5-6 hours and slowed reaction times up to 4 hours, in former narcotic addicts. Euphoria and elation could also play a role on perception of risks and alteration of behaviors.

Effects on Driving: The drug manufacturer states that morphine may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car, and patients must be cautioned accordingly. Driving ability in cancer patients receiving long-term morphine analgesia (mean 209 mg daily) was considered not to be impaired by the sedative effects of morphine to an extent that accidents might occur. There were no significant differences between the morphine treated cancer patients and a control group in vigilance, concentration, motor reactions, or divided attention. A small but significant slowing of reaction time was observed at 3 hours. In several driving under the influence case reports, where the subjects tested positive for morphine and/or 6-acetylmorphine, observations included slow driving, weaving, poor vehicle control, poor coordination, slow response to stimuli, delayed reactions, difficulty in following instructions, and falling asleep at the wheel.

DEC Category: Narcotic Analgesic.

DEC Profile: Horizontal gaze nystagmus not present; vertical gaze nystagmus not present; lack of convergence not present; pupil size constricted; little or no reaction to light; pulse rate

down; blood pressure down; body temperature down. Other characteristic indicators may include presence of fresh injection marks, track marks, flaccid muscle tone, droopy eyelids, drowsiness or "on-the-nod", and low raspy slow speech.

Panel's Assessment of Driving Risks: Classification of risk depends on tolerance, dose, time of exposure, acute or chronic use, presence or absence of underlying pain, physiological status of individual, and the presence of other drugs. Moderately to severely impairing in non-tolerant individuals. Mild to moderately impairing if morphine is used as medication on a regular basis for chronic pain. Severely impairing in acute situations if used orally, or as an intravenous medication, or if either drug is taken illicitly.

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Physicians' Desk Reference What is MMUCC MMUCC Committee MMUCC Documents What is MMUCC? The Model Minimum Uniform Crash Criteria (MMUCC) is a minimum set of crash data elements with standardized definitions that are relevant to injury control, highway and traffic safety. Not all of the MMUCC data elements need to be collected by police at the scene. Instead, some can be created from other data elements, such as the Vehicle Identification Number, to identify a specific vehicle characteristic. Or they can be obtained after linkage to other traffic records, such as injury or roadway inventory data to describe injury outcome or a specific roadway characteristic. FOR MORE INFORMATION ON THE MMUCC, PLEASE CLICK ON www-nrd.nhtsa.dot.gov/departments/nrd-30/ncsa/MMUCC.html Top of Page
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MMUCC Documents To visit the MMUCC Homepage, please click on the following link: Model Minimum Uniform Crash Criteria--Improving Crash Data for Safer Roadways The following links will take you to several documents related to the MMUCC effort. Download a PDF of the Final Guidelines (522KB) for Minimum Standardized Crash Data Reporting , Medical Economics Company, Montvale, NJ, 2002.

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