ANAESTHESIA ON DRUG DEPENDANT PATIENTS

Thesis

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By

MAGDY MOHAMED NAFEH

M.B., B.Ch.

Supervised by

Prof. Dr. MOHAMED HAMED SHAKER

Professor of Anaesthesia

Faculty of Medicine, Ain Shams University

Dr. IBRAHIM ABD–EL GHANY

Lecturer of Anaesthesia

Faculty of Medicine, Ain Shams University

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

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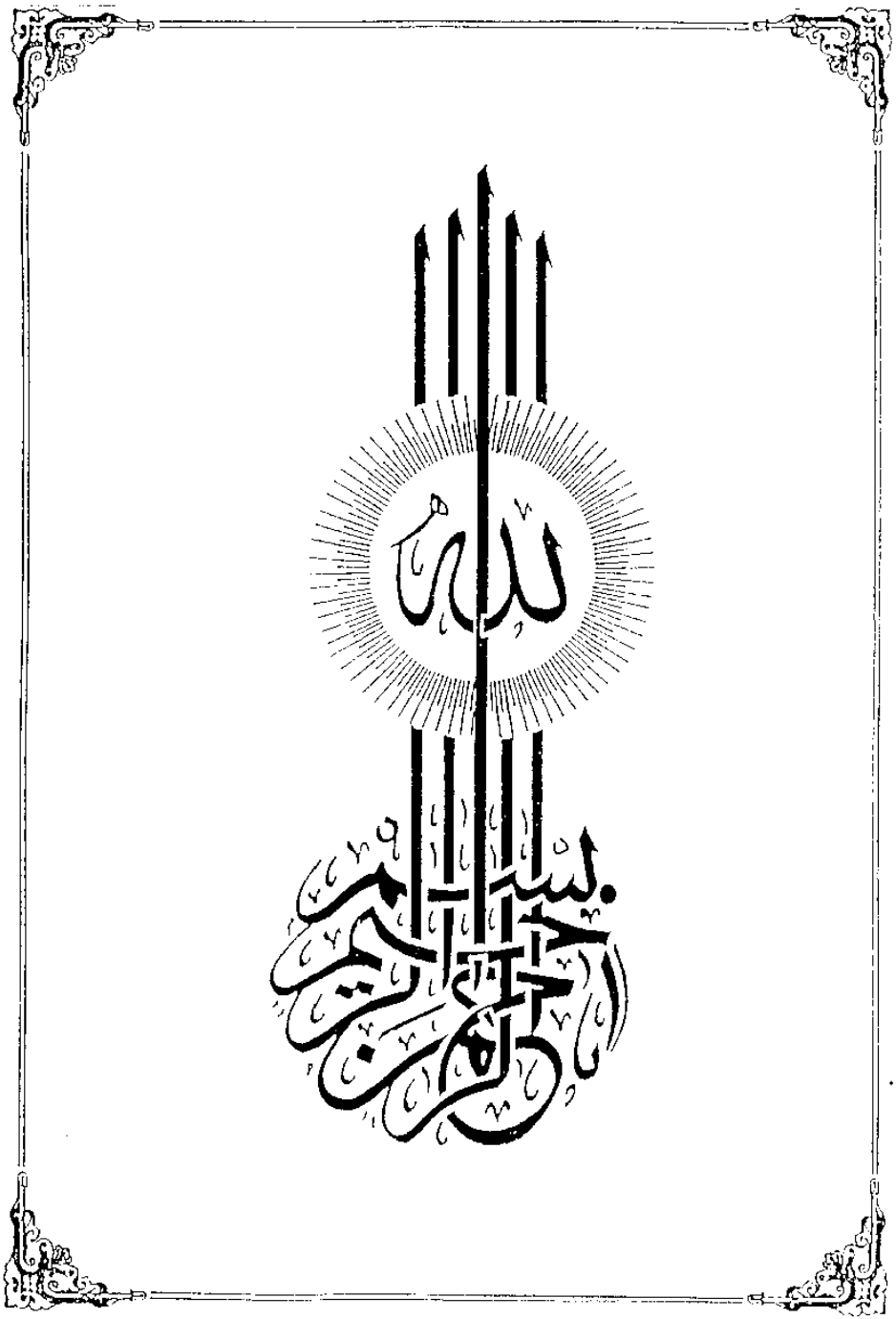

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INTRODUCTION

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All the naturally occurring sedatives, narcotics, euphoriants, hallucinogens and excitants were discovered thousands of years ago, before the dawn of civilisation.

Abuse potential of a drug is related to its capacity to produce immediate satisfaction (e.g. amphetamine and heroin give immediate effects, antidepressants do not) and to its route of administration in descending order: inhalation, intravenous, intramuscular, subcutaneous and oral.

The non-medical use of drugs (i.e., drug use that is not on generally accepted medical ground) means the continuous or occasional use of drugs by the individual, of his own choice, to achieve his own well being or to obtain an experience.

The motives for drug abuse include:

1. Relief of anxiety, tension or depression.
2. Fun, amusement or excitement.
3. Fear of missing something.

Drug abusers will need special anaesthetic management.

PHARMACOLOGY OF NARCOTIC ANALGESICS

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The term narcotic is an imprecise, since narcosis signified a stuporous state whereas the opiate produces analgesia without loss of consciousness. The term opiate was once used to designate drugs derived from opium-morphine, codiene and the many semisynthetic entities with morphine-like actions. The word opioid was introduced to refer in a generic sense to all drugs, natural and synthetic, with morphine-like actions *(Lewis et al., 1971)*.

Classification

- Opioids are usually classified as naturally occurring, semisynthetic and synthetic. Morphine, codeine and papaverine the only naturally occurring opioids of clinical significance are obtained from Poppy plant. "Papaver somniferum". These compounds can be classified into chemical classes, the phenanthrenes (morphine and codeine) and the benzylisoquinoline (papaverine).

- The semisynthetic opioids are derivatives of morphine in which any one of several changes has been made, such as etherification of one hydroxyl group (codeine) or esterification of both hydroxyl groups (heroin).

- The synthetic compounds resemble morphine but are usually entirely synthesized. They are divided into four groups:

* Morphine derivatives, e.g. levorphanol (discovered by *Grewe, 1948*).
* Phenylpiperidine derivatives, e.g. meperidine and its congeners (discovered by *Eisleb and Schaumann, 1939*).
* Diphenylpropylamine derivatives, e.g. methadone and its congeners (originated by *Bockmuhl and Ehrhart, 1948*).
* Benzomorphan derivatives, e.g. phenazocine, pentazocine (originated by *May and Murphy, 1955*).

Site of Action "Opiate Receptors"

Opioids act as agonists interacting with receptors in the brain and other tissues. In 1973 three independent investigators described the presence of an "opioid receptor" in nervous tissue and hypothesized that endogenous substances probably stimulate this structure *(Pert and Snyder, 1973)*.

A few years later, the endogenous opiates were discovered. A lock and key analogy for the receptor-agonist opioid interaction although surely an over simplification, appears to be reasonably accurate. While agonist and antagonist opioid have both been described as fitting into the lock, only the agonist is able to "turn" in the lock. The pure antagonist opioids have intrinsic activities of 1, some opioids (i.e., mixed agonist antagonist) exhibit intermediate intrinsic activities *(Pasternak and Childens, 1984)*.

Receptor	Effects produced by agonists	Agonists		Antagonist
		Endogenous	Synthetic	
μ "mu" μ_1 μ_2	* Supraspinal analgesia * Miosis * Stimulation then depression of respiratory rate * Bradycardia * Hypothermia * Physical dependence * Euphoria. * ++++ Antinociceptive effect * Decrease flexor and skin twitch reflexes	* B-endorphin * methionine-enkephalin	* Morphine	* Naloxone * Pentazocine
K "kappa"	* Spinal analgesia * Miosis * No change in respiratory rate * No change in heart rate * No change of body temperature * Sedation * +++ Antinociceptive effect	* Ketocyclazocine * Dynorphin	* Morphine * Pentazocine * Ethyl-ketazocine * Bremazocine * Nalbuphine * Butorphenal	* Nalaxone
σ Sigma	* Mydriasis * Stimulation of ventillation * Tachycardia * Hallucination * Dysphoria * 0 to + Antinociceptive effect		* N-allyl normetazocine * Pentazocine	* Naloxone
δ delta	* Modulation of μ receptor activity * Supraspinal analgesia	* Leucine-enkephalin * Methionine-enkephalin	* Pentazocine	* Naloxone
ϵ		* B-endorphin		

Opiate receptors according to *Pasternak and Childers, 1984.*

Opiate receptors are found in many areas of the CNS, including the cerebral cortex, the limbic cortex (anterior and posterior amygdala and hippocampus), hypothalamus, medial thalamus, midbrain (periaqueductal gray), extra pyramidal area (caudate striatum and putamen), substantia gelatinosa and sympathetic preganglionic neurons.

Morphine and most opioids are effective in relieving dull, boring poorly localized visceral type of pain but are not nearly as effective in influencing highly localized somatic pain. The lateral thalamic nuclei are involved with highly localized pain. As might be expected, higher concentrations of opiate receptors are found in medial than lateral thalamic nuclei *(Goldstein, 1974)*.

Endogenous Opiates

The discovery of opioid receptors in the CNS led to the hypothesis, and later the discovery of endogenous opiate like substances. *Hyghes et al., 1975* first described two brain pentapeptides, methionine-enkephalin and leucine-enkephalin, that had potent affinities for opiate binding sites, and whose opiate effects were reversed by naloxone. Larger endogenous opioid peptides, β endorphin, and dynorphin were also described.

Opiates interact with opioid receptors to modulate pain perception and produce analgesia. Regulation of pain perception is likely a role for endorphins. It is speculated that brain contains an endogenous pain suppression system in which "analgesia" is mediated by endorphin release. Those who tolerate pain will do so because they have a more active or highly developed pain suppression system *(Buchsbaum et al., 1977)*.

NARCOTIC AGONISTS

Morphine

Morphine is the prototype narcotic analgesic most widely used.

Absorption, distribution and excretion

Morphine may be administered via the oral, subcutaneous, intramuscular or intravenous injection. Morphine is readily absorbed from the gut, but plasma levels are considerably lower after oral administration than after parenteral administration. This is secondary to uptake and metabolism of morphine by liver prior to reaching the central circulation. Intravenous morphine bypasses the absorption process. Peak plasma levels are higher than by any other routes.

Free morphine rapidly leaves the blood and is taken up by the parenchymatous tissues and skeletal muscles. At pH of 7.4, one-third of morphine is bound to plasma proteins mostly serum albumin. Morphine is not lipid soluble so penetration and exit from CNS is delayed. This is the most important reason for the long duration of action of the drug. Clearance of morphine from the body is largely dependent on hepatic bio-transformation and renal excretion. The elimination half life of morphine is 2-4 hours *(Dohlstom et al., 1982)*.

Pharmacological Actions

Respiratory Actions

All μ-receptor stimulating opioids result in a dose dependant depression of respiration *(Hickey and Severinghaus, 1981)*, primarily through a direct action on the brain-stem respiratory center. The responsiveness of the brain stem respiratory centers to CO_2 is significantly reduced by opioids. The apneic threshold ($Paco_2$ below which spontaneous ventilation is not initiated without hypoxia) is increased by opioids *(Kryger et al., 1976)*. Pain, particularly surgically induced, counteracts the respiratory depressant effects of narcotic compounds *(Keats and Girgis, 1968)*.

Cardiovascular Actions

Clinical doses of morphine (0.1-0.2 mg/kg) in normal supine patients has little effect, but postural hypotension may occur due to peripheral vasodilatation and venous pooling. The vasodilatation is attributed to:

1. Histamine release.
2. Direct vasodilatation, and
3. Neural mediation.

Histamine release result in decreased arterial blood pressure and systemic vascular resistance. Fentanyl, sufentanil and alfentanil do not produce changes in plasma histamine *(Roscow et al., 1984)*.

Morphine causes a rapid decrease in pulmonary artery flow and pressure, left ventricular end diastolic pressure and result in increased myocardial contractility. Morphine and other narcotics have a negative

chronotropic effect (with exception of meperidine), due to stimulation of the central vagal nucleus in the medulla *(Reitan et al., 1978)*.

Central Nervous System

In man, morphine produces analgesia, drowsiness, changes in mood and mental clouding. Analgesia without loss of consciousness is a significant feature. Patients also experience euphoria and if the external situation is favourable sleep may ensue. When morphine is given to normal, pain free individual, the experience is not always pleasant. Nausea, vomiting, feeling of drowsiness, inability to concentrate and lessened physical activity may ensue *(Van Ree, 1977)*. Morphine causes constriction of pupil due to excitatory action on autonomic segment of the nucleus of the oculomotor nerve. Nausea and vomiting produced by morphine and its derivatives are unpleasant side effects caused by direct stimulation of chemoreceptor trigger zone for emesis *(Lee and Wang, 1975)*. Extremely high doses of morphine produces convulsions, that can be reversed by naloxone *(Frenk et al., 1978)*.

In patients who are undergoing surgery, opioids inhibit the stress induced release of ACTH *(Fishman, 1978)*. Opioids suppress the secretion of luteinising hormone leading to decrease in the concentration of testosterone in plasma. So, males maintained on methadone exhibit decreased sexual drive, as well as decreased motility of sperm and volume of ejaculate. Plasma ADH rises significantly during morphine (1 mg/kg) plus nitrous oxide anaesthesia in humans during surgery before cardio-pulmonary bypass and increases further during bypass *(Philbin et al., 1976)*.

Effects on the Gastrointestinal Tract

Morphine delays gastric emptying time and decreases intestinal motility in the terminal ileum. Biliary tract pressure is increased, but it is of little clinical significance. Increases in biliary tract pressure are easily antagonized by naloxone *(Radnay et al., 1984)*.

Effects on the Kidney

The addition of surgical stress to nitrous oxide narcotic anaesthesia may result in very high plasma ADH levels with a decrease in glomerular filtration rate and urine output *(Philbin and Coggins, 1978)*.

Heroin

Heroin is the 3,6-diacetyl derivative of morphine. Heroin is readily absorbed from the gastrointestinal tract and through nasal mucous membrane. Except that heroin is 2 to 3 times more potent and has more rapid onset of action, the effects of this drug are essentially similar to those of morphine *(Jaffe, 1975)*.

Codeine

Codeine is a naturally occurring alkaloid of opium (0.5%). As an analgesic it is 1/2 to 1/10 as potent as morphine. Dependence liability of codeine is reported to be less than that of morphine, and physical dependence occurs only rarely from its oral use as an analgesic. The codeine abstinence syndrome is milder than that of morphine *(Jaffe, 1980)*.