USE OF NARCOTICS IN ANAESTHESIA FOR NEONATES AND CHILDREN

ESSAY SUBMITTED FOR PARTIAL FULFILMENT OF

MASTER DEGREE IN ANAESTHESIA

BY

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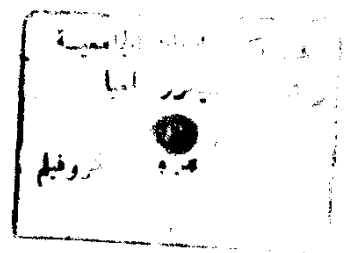

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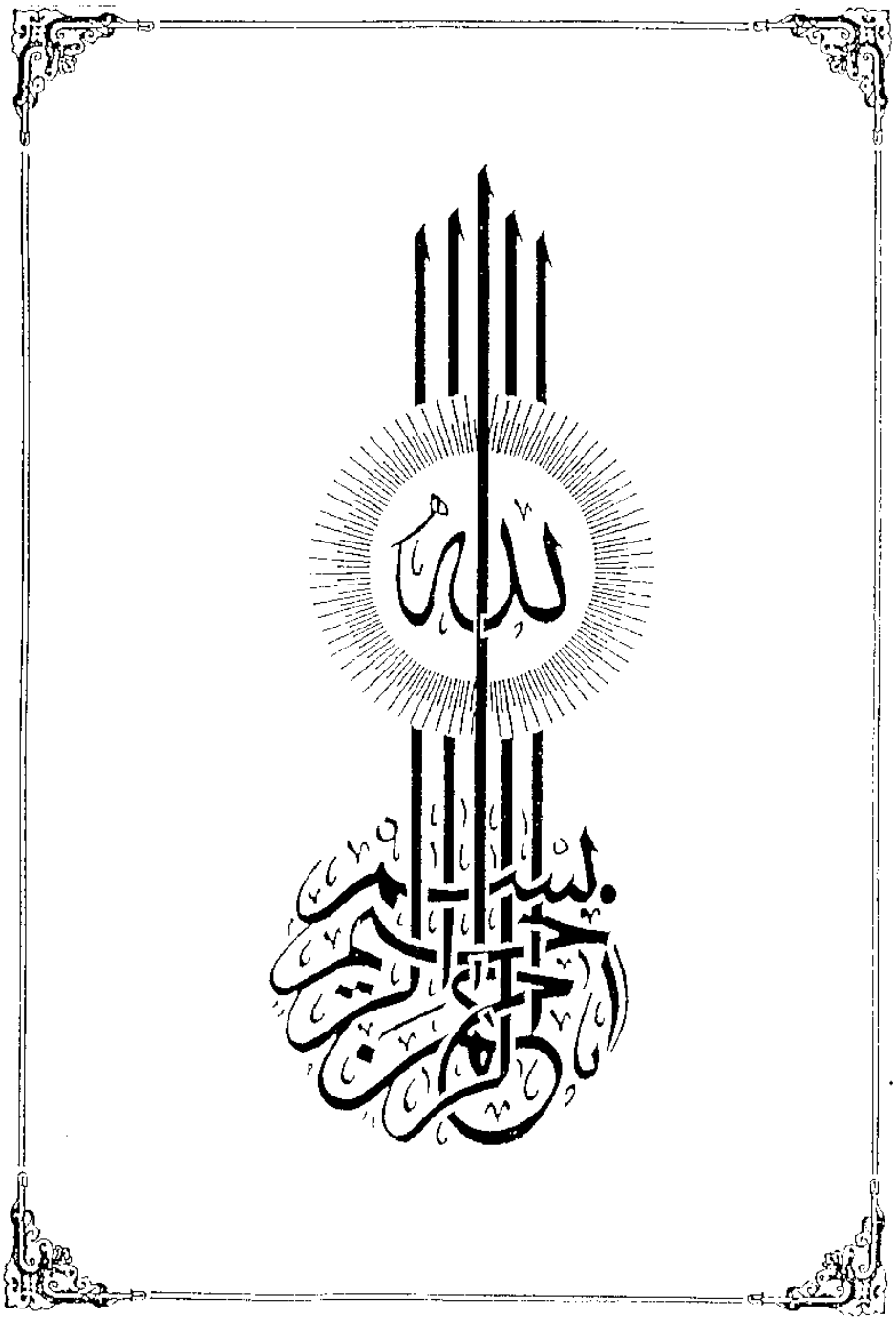
To the Soul of My Father,

To My Mother,

My Wife

& My Brothers.

Ibrahim Sabry Farid



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CONTENTS

Introduction

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Opioids have been administered for hundreds of years to allay anxiety and reduce the pain associated with surgery. Many of these compounds are not only used as intravenous analgesic supplements, but also as primary or sole intravenous anaesthetics. It has been recently suggested that, with minor modifications, a number of new synthetic opioids may qualify as the "ideal intravenous anaesthetic".

The terms "opioid, narcotic analgesic and narcotic anaesthetic" are used to describe drugs that specifically bind to any subspecies of opioid receptors and produce some opioid agonist effects.

History

The isolation of morphine from opium by **Sertunner**, in **1803**, and the introduction of the syringe and hollow needle to clinical practice by **Wood** in **1853**, finally permitted opioids to be administered in carefully measured doses. Morphine then was frequently used I.M. for preoperative medication as a supplement during ether or chloroform anaesthesia, and postoperatively for analgesia.

Late in the nineteenth century, large amounts of morphine (1 to 2 mg/kg) plus scopolamine (1 to 3 mg/70 kg) were administered in divided doses I.V., I.M., or both as a complete anaesthetic **(Foldes et al., 1964)**.

Although initially popular, this technique rapidly fell into disfavour because of an alarming increase in operative morbidity and mortality. For the next 30-40 years, anaesthetists rarely used narcotic analgesics intraoperatively.

Introduction of the ultrashort-acting barbiturates as I.V. anaesthetics and popularization of the concept of "balanced anaesthesia" led to renewed enthusiasm for the intraoperative use of opioids. Two important events in this development were the synthesis of meperidine in 1939 and its use in anaesthesia with nitrous oxide [N_2O], with or without d-tubocurarine. Many variations of the "N_2O-narcotic" technique became popular. More recently, opioids, as well as other analgesics (synthetic agonists/antagonists) and hypnotics are being administered I.V. during anaesthesia with potent inhaled anaesthetics **(Bennett & Stanley, 1979)**.

This practice is based on the belief that many of these drugs reduce the concentration of inhaled anaesthetics required for anaesthesia, and thus result in less depression of the cardiovascular and other organ systems.

Then it appeared that high doses of opioids could produce "complete" anaesthesia. Fentanyl, or morphine, was administered until consciousness was lost and then the patient was put under controlled ventilation with a high inspired concentration of oxygen. This technique did not alter the cardiovascular dynamics

in those patients who did not have cardiac disease, and in many cases improved the cardiovascular status of those with significant valvular disease. These reports led to many additional studies evaluating morphine and other opioids as the sole anaesthetic for patients with poor cardiovascular reserve undergoing a major operative procedure.

Unfortunately, problems with incomplete amnesia, histamine release, prolonged postoperative respiratory depression and increased blood requirements secondary to marked venodilatation decreased the popularity of morphine as a "complete" anaesthetic **(Stanley et al., 1973)**.

In contrast, the synthetic opioid fentanyl has become popular as a component of balanced "N_2O-narcotic" anaesthesia, as a supplement when using an inhaled anaesthetic, and in larger "anaesthetic" doses [50-150 μg/kg] as a primary or complete anaesthetic.

Unfortunately, large doses of fentanyl also cause significant postoperative respiratory depression, generally mitigating against their use in healthy patients undergoing more routine operative procedures. Nevertheless, as with anaesthetic doses of morphine, large intravenous doses of fentanyl can produce complete anaesthesia without depressing cardiovascular functions, and are ideal for patients who have little or no cardiac reserve.

In addition, fentanyl-O_2 anaesthesia produces less prolonged postoperative respiratory depression, greater cardiovascular stability, little or no histamine

release and no venodilatation, as compared with morphine **(Rosow et al., 1984)**.

Despite some problems (e.g., muscle rigidity and incomplete anaesthesia) opioids will probably remain popular as anaesthetic supplements and as complete anaesthetics in the future because of their minimal effects on most organ systems.

Chapter 1

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Pain Physiology

A. Receptors:

The receptor is an integral membrane protein which can be selectively recognized by a precise hormone or neurotransmitter called a *ligand*.

Ligands are known as agonists when they activate the receptor to transduce a response. An antagonist is a drug that interacts with a receptor, causing it to remain in the inactive form, and thus, by occupying the receptor, diminishes or aborts the effect of an agonist **(Maze, 1981)**.

NATURAL LIGANDS:

There are three separate families of natural or endogenous peptide opioid receptor ligands: enkephalins, endorphins and dynorphins. They are derived from three different prohormone families: proenkephalin, proopiomelanocortin and prodynorphin.

1- Proenkephalin Family:

The first opioid peptides are characterized by being pentapeptides with the structures: Tyr-Glyc-Glyc-Phe-Met called methionine-enkephalin, or [Met]-enkephalin; and Tyr-Gly-Gly-Phe-Leu, called leucin-enkephalin, or [Leu]-enkephalin.

The precursor, also known as proenkephalin A, was demonstrated to have two polypeptides in a fixed ratio of six [Met]-enkephalin sequences to one [Leu]-enkephalin.

Proenkephalin-containing cells are widely spread throughout the brain, spinal cord and in peripheral sites, such as the adrenal medulla and gastrointestinal tract **(Hughes et al., 1975)**.

2- Proopiomelanocortin Family:

Proopiomelanocortin [POMC] is a multifactorial prohormone which is the common precursor of opioid beta-endorphin and non-opioid hormones: adrenocorticotrophic hormone and alpha and beta melanocyte stimulating hormones. While the pituitary gland is the major site for POMC synthesis, POMC is found also in limited areas of the brain, such as the hypothalamus, and in the periphery **(Smyth, 1983)**.

3- Prodynorphin Family:

Prodynorphin, which was known as proenkephalin B, contains [Leu]-enkephalin sequences, but no [Met]-enkephalin sequences.

The opioid peptides derived from this precursor include the dynorphins, beta neoendorphins and leumorphins **(Imura et al., 1985)**, all of which contain the [Leu]-enkephalin sequence at the amino terminals.

Prodynorphin, in common with proenkephalin, is synthesized throughout the C.N.S. in a wide variety of neuronal systems **(Khachaturian et al., 1985)**. Distribution of dynorphins and enkephalins is often contiguous, and it may participate, via separate receptors, in related C.N.S. functions. In common with enkephalins, the prodynorphin family is also found in peripheral tissues **(Pleuvry, 1991)**.

Opioid Receptors:

The original classification of opioid receptors into mu, kappa and sigma **(Martin et al., 1976)** was based on the activity, in spinal dogs, of 3 unnatural or at least exogenous ligands: morphine [mu], ketocyclazocine [kappa] and SKF 10,047 (N-allylnormetazocine) [sigma]. Subsequently, the [delta] receptor, to which [Leu]-enkephalin binds preferentially, was added. This receptor is particularly abundant in the mouse's vas deferens **(Lord et al., 1977)**. The final Greek letter

used to annotate opioid receptors was [epsilon]. This receptor, originally described in the rat's vas deferens **(Wuster et al., 1978)**, is sensitive to beta endorphin.

Naloxone has antagonistic properties at all opioid receptors, but it antagonizes mu-receptor activation in a smaller concentration.

- **Mu-Receptors [μ]:**

While products from all three opioid genes have affinity for this receptor, no selective natural ligand has been isolated. In contrast, the dynorphins have selectivity for kappa-receptors, and [Leu]-enkephalin has selectivity for delta-receptors. It may be that the mu site is a universal opioid receptor, or that a mu-receptor's selective ligand has yet to be discovered **(Pleuvry, 1991)**.

Based on the results of radioligand binding studies, **Pasternak**, in **1982**, has suggested the existence of mu-receptors in two affinity states. The high-affinity state being designated mu_1 and the low-affinity state mu_2. Using an antagonist thought to be selective to mu_1 site (naloxone), it was suggested that opioid analgesia, but not respiratory depression, was associated with the mu_1 site. Mu_1-receptors mediate supraspinal analgesia, while mu_2-receptors have a role in spinal analgesia **(Paul et al., 1989)**. Mu opioid receptors are widely distributed, and the most dense sites are in regions of the brain associated with pain regulation and sensorimotor integration **(Mansour et al., 1988)**.