PHARMACOLOGICAL & CLINICAL EVALUATION OF A NEW MORPHINE-LIKE AGENT BUPRENORPHINE

Thesis

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By

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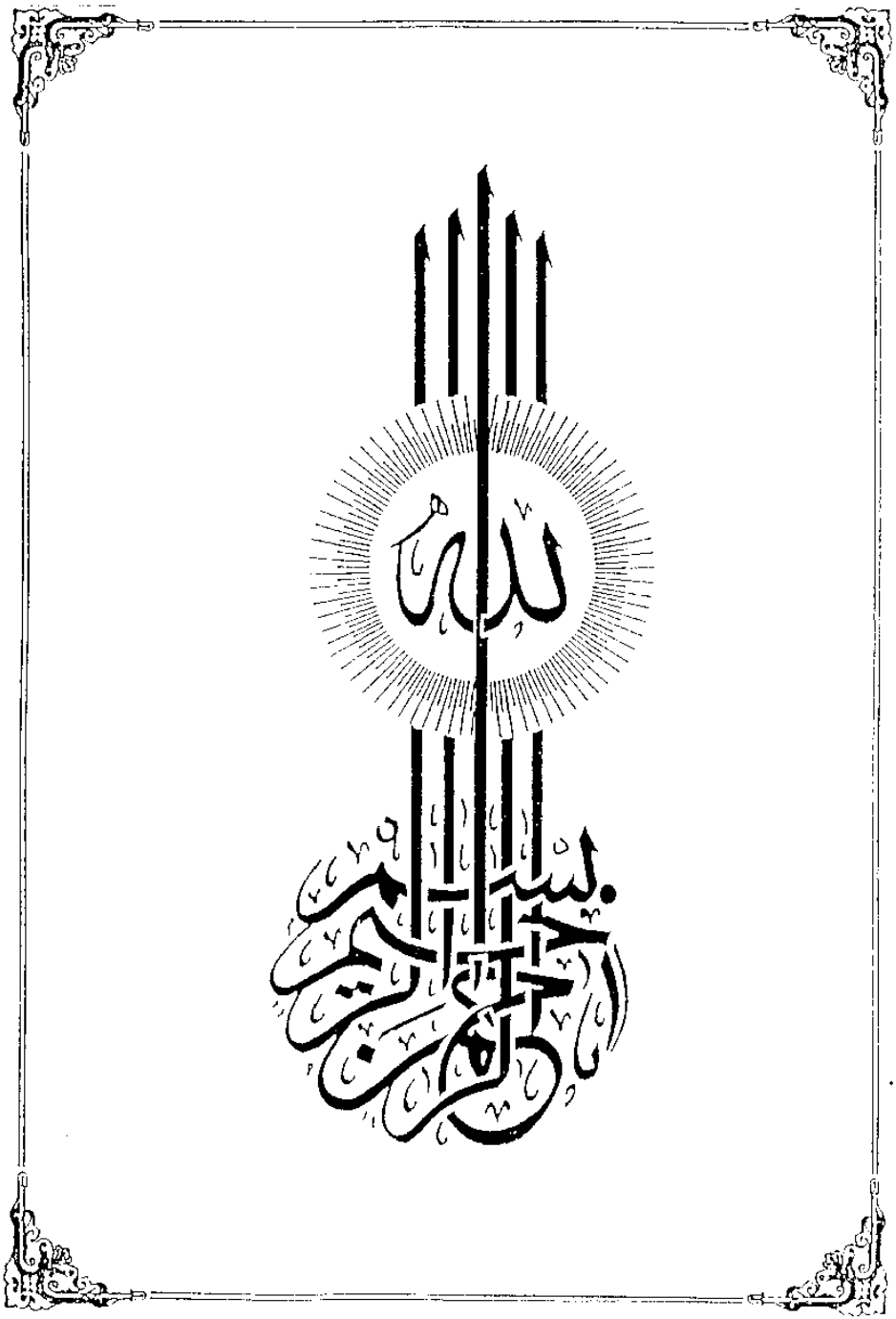

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C O N T E N T S

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INTRODUCTION

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I N T R O D U C T I O N

Man's struggle to relieve pain began with the origin of mankind. Ancient writings, both serious and fanciful, dealt with secret remedies, religious rituals, and other methods of pain relief (Charles O. Wilson, et al., 1977).

The opium poppy is indigenous to Asia Minor, and awareness of the euphoriant effect of some part of the poppy plant is implict in the Sumerian records of 4000 B.C. (Meyers et al., 1980).

The word opium itself is derived from the Greek name for juice, the drug being obtained from the juice of the poppy, Papaver somniferum. Arabian physicians were well versed in the uses of opium. Arabian traders introduced the drug to the orient, where it was employed mainly for the control of dysentries (Jaffe and Martin, 1980).

Paracelsus (1493 - 1541) was aware of its usefulness and prepared the first tincture of opium (laudanum), but the drug had fallen into disfavour because of its toxicity. By the middle of the sixteenth century, the uses of opium that are still valid were fairly well understood, and in 1680, Sydenham wrote, "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium" (Jaffe and Martin, 1980).

In the eighteenth century opium smoking became popular in the orient. At that time the use of opiates for their subjective effects was considerably more acceptable than it is at present. In Europe, the ready availability of opium led to some degree of overuse, but the problem of opium eating never became as prevalent or as socially destructive as the abuse of alcohol.

Friedrich Sertürner (1783 - 1841) isolated morphine from opium and demonstrated for the first time that a single purified chemical substance could account for the pharmacologic effects of a natural product. Sertüner, a reluctant apprentice to a pharmacist in Prussia, was disturbed by the variable potency of available opium preparations and set out to purify and standardize it. Working at a time when neither experimental pharmacology nor the chemistry of natural products were recognized fields of endeavor, Sertürner succeeded in isolating morphine from opium. Using a bioassay in dogs, he established that morphine; as he named the alkaloid substance, was the somnifacient principle of opium. His early reports (1803) either rejected by editors or ignored after publication. He eventually tested his purified preparation on himself and 3 friends and observing the vomiting, flush, and near coma. This work was finally published in 1817 and attracted the interest of the influential French chemist Gay-Lussac. The work of Sertürner influenced Pelletier and Caventou, and in the same year other pure

principles from plant sources were successfully isolated (Meyers et al., 1980).

The discovery of other alkaloids in opium (codeine by Robiquet in 1832 & papaverine by Merck in 1848) quickly followed that of morphine. By the middle of the nineteenth century the use of pure alkaloids rather than crude opium preparations began to spread throughout the medical world.

The invention of hypodermic needle and the parentral use of morphine tended to produce a variety of compulsive drug use. In the United States, the extent of the opioid-use problem was accentuated by the influx of opium-smoking Chinese laborers, the widespread use of morphine among wounded Civil War soldiers, and the unrestricted availability of opium that prevailed until the early years of this century.

The problem of addiction stimulated a search for potent analgesics that would be free of the potential to produce addiction. In 1915, Pohl observed that N-allyl nor codeine prevented or abolished morphine-and heroin - induced respiratory depression. More than 25 years elapsed before Unna as well as Hart and McCawley independently described the more pronounced morphine-antagonizing properties of nalorphine. The clinical significance of this antagonistic effect was not explored until 1951, when Eckenhoff and Co-workers reported the use of nalorphine as

an antidote for morphine poisoning in man. By this time chemists had synthetized a number of entities that were chemically quite distinct from morphine but produced almost the same pattern of pharmacological effects, including addiction. In 1953, Wikler and associates demonstrated that nalorphine would precipitate acute abstinence syndromes in post addicts who had received opioids for brief periods, and that in the majority of nonaddicted subjects large doses of nalorphine produced dysphoria and anxiety rather than euphoria. Shortly thereafter, Lasagna and Beecher in 1956, noted that although nalorphine antagonized the analgesic effects of morphine, it was, nevertheless, an effective analgesic when given to patients with postoperative pain. The dysphoric side effects produced by nalorphine make it unsuitable for clinical use as an analgesic; however, since the low abuse potential of nalorphine had already been observed, the report of its analgesic effects raised the hope that other narcotic antagonists might be free of these dysphoric effects and still have analgesic activity (Musto, 1973).

The search for useful compounds led to the discovery of new drugs, such as the relatively pure antagonist naloxone and compounds with mixed actions (e.g. pentazocine, butorphanol, nalbuphine and buprenorphine). Such agents not only have enlarged the range of available

therapeutic entities but also, in conjunction with the subsequent discovery of receptors for opioids and endogenous peptides that bind to these receptors, have helped to change our views about the actions of the opiates (Jaffe and Martin, 1980).

Review of Literature

ANATOMY & PHYSIOLOGY OF PAIN

Pain may serve a number of useful functions. It may be protective, defensive or diagnostic. The protective effect is most obvious in avoiding trauma. The defensive function is seen in the body's natural desire to immobilize an inflamed part or broken bone, which not only alleviates pain but also promotes healing. There are many conditions, however, such as carcinomatosis with bony metastases, where pain serves no useful function at all, and only makes a sad situation harder to bear. Pain is one of the commonest symptoms to lead a patient to seek medical advice, and whatever the cause, it demands relief (Churchill-Davidson, 1984).

Pain Pathways:

Pain receptors appear to consist of peripheral plexuses of unmyelinated nerves (A δ and C fibres), activated by high-intensity stimuli which may be thermal, mechanical, electrical or chemical (Table 1) and they do not manifest adaptation (Perl ER, 1971; Iggo, 1974).

Table(1) Types of nerve fibers

Fibre type	Function: Sensory	Function: Motor	Fibre diameter µm.	Conduction speed m/sec.
A α	Proprioception	Somatic	12-20	70-120
β	touch, pressure		5-12	30-70
γ		muscle spindle	3-6	15-30
δ	pain, temperature		2-5	12-30
B		preganglionic	13	3-15
C	pain, reflex	post-ganglionic	0.3-1.3	0.5-2.3

After Franz and Perry (1974)

N.B.: µm = micromilli
m/sec = meter/second

Some nociceptors are responsible chiefly to mechanical injury, these are called pricking receptors and the peripheral nerves carrying these impulses are the small myelinated A-fibres (Burgess, 1974). Others, the polymodal receptors, are responsible to heat and chemical irritation as well as the mechanical injury, the peripheral nerves carrying these impulses are chiefly the unmyelinated C fibres (Hallin and Torebjork, 1974).

A δ fibres are finely myelinated and relatively rapidly conducting (12-30 m/sec.). They would appear to conduct the sharp pain produced by pinprick or electrical stimulation, as well as thermal stimuli, and are responsible for the withdrawal reflex. A δ-conducted pain is felt quickly and is well localised (Mayer and Price, 1979).

C fibres are very fine non-myelinated fibres which conduct at a very slow rate of 2.3 m/sec or less. Their threshold for stimulation is higher than that of Aδ fibres and they would appear to be responsible for more delayed and truly noxious burning or throbbing pain. There is, however, considerable overlap in the activation of Aδ and C fibres.

Peripheral sensory nerves have their cell bodies in the dorsal root ganglion, and the central projections of Aδ and C fibre neurones enter the dorsal horn in the lateral division of the dorsal root (Bowsher, 1978).

In the grey matter of the spinal cord, cell bodies are arranged in a series of laminae, some of which have classical names, but which are more simply, given Roman numerals by Rexed (Rexed, 1952), starting with I at the tip of the dorsal horn. Aδ and C primary afferent fibres terminate principally in the marginal layer (lamina I) and the substantia gelatinosa (lamina II) (Fig. 1). Some of the neurones of lamina I which synapse with Aδ fibres, give off axons which ascend in the contralateral anterior columns without synapsing with neurones from deeper layers. The majority of pain fibres, however, synapse in the substantia gelatinosa with intermediate neurones which send projections to deeper layers, or with the dendrites of neurones whose cell bodies reside in deeper layers, principally in lamina V (Fig. 2) (Bowsher, 1978).