Study of Naloxone Reversal of Respiratory, Circulatory, and Narcotic Effects of Some Non-opioid Agents

M.D. Thesis

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Presented By

Khadiga Abdel Fattah Mostafa

M.B., B.Ch. – M. Sc. Forensic Medicine & Toxicology

Supervised By

Prof. Dr. BAHIRA A. FAHIM
Professor of Forensic Medicine
and Toxicology
Faculty of Medicine
Ain Shams University
Director of Poison Control Center
Ain Shams University

Prof. Dr. NAILA A. EL NAYAL
Professor of Forensic Medicine
and Toxicology
Faculty of Medicine
Ain Shams University

Dr. SEHAM F. ABDEL-ALL
Lecturer of Forensic Medicine and Toxicology
Faculty of Medicine – Ain Shams University

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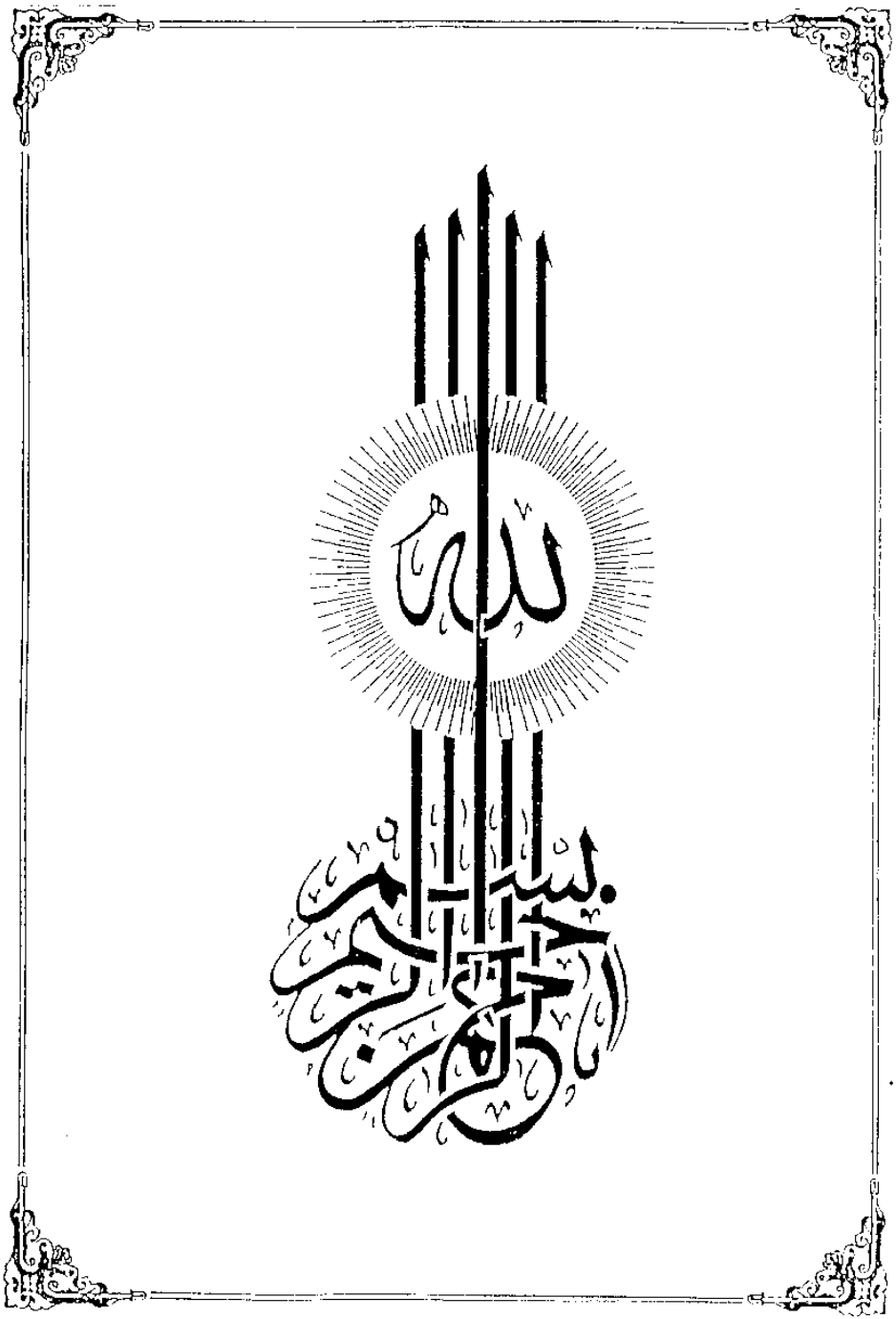

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INTRODUCTION

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Nowadays there is an alarming increase in narcotics and drug abuse, being the most reported causes of severe intoxications in developed and developing countries. Various efforts towards the evaluation of specific therapeutic antidotal measures have been exerted.

Naloxone, a relatively new opiate antagonist, is the N-allyl (derivative of the strong acting analgesic oxymorphone ***(Foldes et al., 1969)***. It has a specific competitive antagonism at the opiate receptor site ***(Jaffe and Martin, 1980)***. It antagonizes the effects of all opioids except buprenorphine, and it is the only known antagonist for pentazocine ***(Martin, 1976)***.

Numerous clinical reports have described its antagonistic effects towards morphine ***(Evans et al., 1973)***, pethidine ***(Folds et al., 1969)***, methadone ***(Goldman and Enquist, 1973; Simon et al., 1973; and Waldron et al., 1973)***, heroin ***(Hammond, 1971)***, and pentazocine ***(Kallos and Smith, 1968; Evans et al., 1973; and Sandoval and Wang,***

1973). Lacking the agonistic effects, naloxone does not impair respiration in patients poisoned by opioids as well as by non-opioid compounds ***(Evans et al., 1973; and Evans et al., 1974)***.

Recently, it has been suggested that naloxone is useful in reversing coma and respiratory depression associated with overdoses of some benzodiazepines ***(Ho and Ho, 1979; and Walz et al., 1979)***. Regarding alcohol intoxications, it has been noticed that naloxone antagonises narcosis and impairment of behaviour ***(Sorensen and Mattison, 1978; Jeffcoate et al., 1979; and Jefferys et al., 1980)***. It also antagonised a number of pharmacological effects of ethanol, such as withdrawal and depletion of brain calcium ***(Blum et al., 1977)***. None of these actions of naloxone has, however, been satisfactorily explained. It is thus believed that the uses of naloxone might be safely extended beyond definite opioid poisoning and that it has a much wider diagnostic and therapeutic role in clinical toxicology.

Naloxone is the pivot of this work. It is aspired to evaluate its efficacy for the reversal of hazardous effects of acute intoxications. The selection of the

agents studied is based on their representation of some major categories of central depressants, while the specific choice is determined by an increasing incidence of intoxications reflecting their gaining popularity in our community ***(Poisons Information Service of Poison Control Center of Ain-Shams)***.

REVIEW OF LITERATURE

NALOXONE HYDROCHLORIDE

History

Pohl (1914), observed that substituting the allyl group for the methyl one attached to the nitrogen atom of codeine produced a compound, N-allyl-norcodeine, which antagonized the sedative and respiratory depressive effects of codeine and morphine. This observation apparently went unnoticed until 1941, when ***McCowley and his colleagues*** synthesized N-allyl-normorphine (nalorphine) in an attempt to produce a compound which would reduce the respiratory depressant and other adverse effects of an analgesic dose of morphine. In ***1942, Weijlard and Erickson*** had purified nalorphine, they noticed its strong antagonism to most of morphine actions in animal experiments. Then ***Eckenhoff et al. (1951)*** used nalorphine in clinical practice.

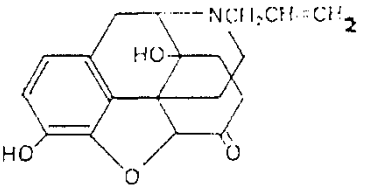
N-allyl-noroxymorphone (naloxone) was first synthesized and used by ***Foldes et al. (1963)***, as a pure opioid antagonist devoid of any agonistic activity. This was followed by many researches studying the properties of the new opiate pure antagonist which

proved its efficacy till it was introduced for commercial use in 1971 *(Avido, 1972)*.

Naloxone was used to treat non-opioid coma with respiratory depression by *Moss (1973)*, who reported naloxone reversal of apnea produced by combined ingestion of barbiturate, alcohol and diazepam. later on, many workers used naloxone in some non-opioids, e.g. alcohol *(Sorensen and Mattison, 1978; Mac Kenzie, 1979; Reding and Cornil, 1980; Guerin et al., 1981; Barros and Rodriguez, 1981; Lyon and Antony, 1982; Jefferys and Volans, 1983; and Ryle et al., 1985)*, benzodiazepines *(Ho and Ho, 1979; Christensen and Huttel, 1979; Bell, 1980; Malizia et al., 1980; and Jefferys and Volans, 1983)*, clonidine overdose *(Kuling et al., 1982)*, and some anaesthetic drugs like nitrous oxide, enflurane and cyclopropane *(Harper et al., 1978)*.

PHARMACOKINETICS

Chemical Formula of Naloxone



Naloxone
(cf. oxymorphone)

N-allyl-7,8,-dihydroxynor-morphinone hydrochloride (Nalxone hydrochloride)
(Quoted from Pharmaceutical Codex, 1979).

Naloxone hydrochloride is a white powder which is soluble in water, dilute acids and strong alkalies, slightly soluble in alcohol, but insoluble in chloroform and ether. It has to be stored in air-tight containers and to be protected away from light ***(Trissel, 1980).***

Dosage Forms

Naloxone hydrochloride is prepared for the parenteral use as solutions of 20 µg/ml in 2 ml ampoules for neonates and 400 µg/ml in 1 ml ampoules, 1 ml prefilled syringes, and 10 ml vials for adults ***(Martindale, 1982)***.

Routes of Administration

The main route of administration for naloxone hydrochloride is the intravenous one as one shot, infusion or through umbilical vein in neonates. It may be injected by the intramuscular or the subcutaneous routes if venous line is so difficult to obtain ***(Martindale, 1982)***. Sublingual administration may be life saving in hypotensive patients with hypoperfusion where the parenteral routes will not be effective ***(Kersh and Schwartz, 1973)***. ***Tandberg and Abercombie (1982)*** reported the effective administration of naloxone through endotracheal tube in severely shocked patients with heroin poisoning where the venous access was difficult to obtaine and subcutaneous and/or intramuscular routes might result

in delayed or erratic therapeutic response. They proved that, with the use of endotracheal naloxone, its serum levels and rate of elimination were similar to those obtained after intravenous administration.

Naloxone hydrochloride is 100 - 1000 times less potent orally than parenterally ***(Bowman and Rand, 1980)***. Combined formulations of orally active analgesics with naloxone have been prepared on the ground that the low oral activity of naloxone will not prevent the analgesic effect of the mixture when taken orally ***(Zaks et al., 1971)***. Oral administration of naloxone has been given for the treatment of opiate dependence in single daily doses of 2.4 to 3 gm ***(Kurland et al., 1976)***.

Doses

The adult initial dose needed for the treatment of narcotic overdosage is 0.4 - 2 mg I.V., which may be repeated at 2 - 3 minutes intervals, if the desired degree of counteraction and improvement in respiratory functions are not obtained ***(Bennett et al., 1983)***. Naloxone can be given by continuous I.V. infusion of 2 mg added to 500 ml normal saline in a rate of 100 ml of the solution every 30 minutes ***(Waldron et al.,***

1973). In treatment of opiate toxicity, if no response is observed after 10 mg naloxone have been administred, the diagnosis should be questioned ***(Bennett et al., 1983)***. Naloxone may be needed in very small doses to reverse narcotic depression following surgery, 0.1 - 0.2 mg I.V. initially given, which may be repeated at 2 - 3 minutes intervals until the desired degree of reversal is achieved (adequate ventilation and alertness) without significant pain or discomfort. Larger doses will result in reversal of analgesia ***(Valsses and Fraker, 1974)***.

The paediatric initial dose is 10 µg/kg given intravenously and, if the desired clinical improvement does not occur, a subsequent dose of 100 µg/kg may be administered. Naloxone may be also given intramuscularly or subcutaenously in divided doses ***(Fisher and Cook, 1974)***. ***Sesso and Rodzvilla (1975)*** used naloxone infusion in opiate respiratory depressed children in a dose of 0.4 mg/hour (17 µg/kg/hour).

Naloxone is safely used during neonatal period of life ***(Fisher and Cook, 1974)***. ***Evans et al. (1976)*** used naloxone in a dose of 10 µg/kg given through the umbilical vein of the respiratory depressed