PHARMACOLOGICAL PROPERTIES OF ALMITRINE BISMESYLATE VERSUS DOXAPRAM HYDROCHLORIDE IN EXPERIMENTAL ANIMALS

THESIS

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BY

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بسم الله الرحمن الرحيم

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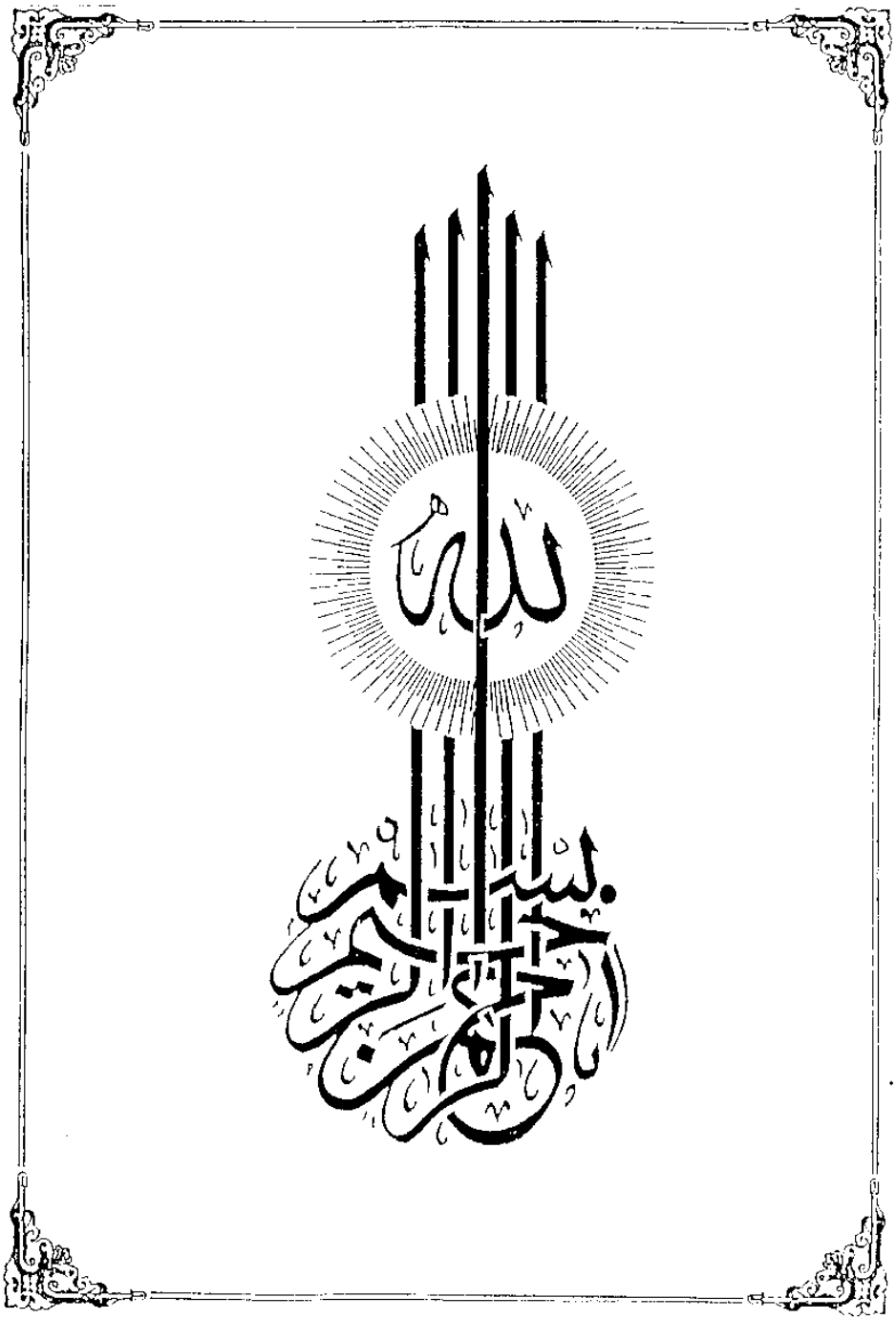
يهدي الله لنوره من يشاء ويضرب الله الأمثال للناس والله بكل شيء عليم



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CONTENTS

INTRODUCTION

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

Almitrine Bismesylate (S 2620, Vectarion) first synthesized and introduced in 1980 by Servier Research Institute, belongs to the triazine class . It is a new molecule which was claimed to act on alveolocapillary gas exchange . It has also been shown to act as a peripheral respiratory stimulant (Laubie and Schmitt, 1980; Levy-Lambert, 1980) .

Almitrine was first developed among two thousand new molecules to obtain a response from certain monoamine receptors found in the nervous system .

During screening of its cardiovascular effects, a change in the ventilation of the dog on which this particular substance was being tested was observed . The experiment was repeated and it rapidly became clear that the blood oxygenation parameters were improving much more strongly than they had any reason to do so . The site of action was demonstrated to be peripheral . The new substance was presumed to act on the chemoreceptors. Further experiments proved its long lasting improvement in ventilation; a marked increase in the Pa O_2 could be obtained. Administration of small doses of almitrine has revealed that PaO_2 can be increased without changing other respiratory parameters, breathing rate, amplitude and the work expended by the chest muscles.

The potential importance of the selective action of almitrine on blood gases in treatment of chronic respiratory failure and in patients with obstructive lung disease was suggested . This applies to early chronic bronchitis when hypoxia alone is present (Castaing et al., 1981).

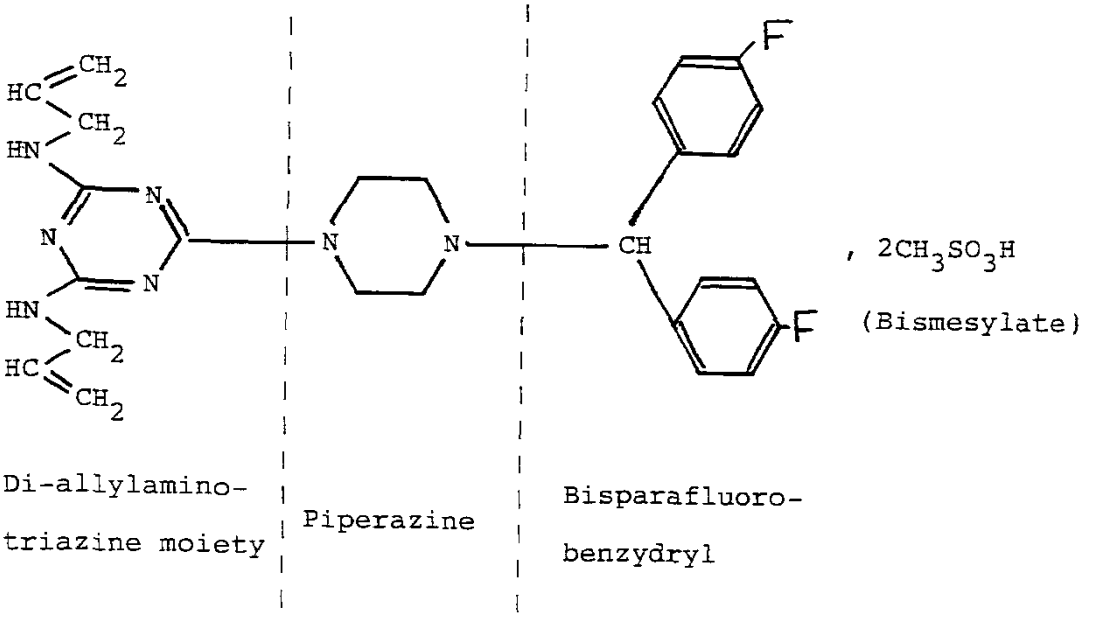
The antihypoxic action of almitrine was postulated to be due to stimulation of intrapulmonary chemo-receptors situated in the alveoli or to release of prostacyclins or other neurotransmitter serotonin-like from intraparenchymatous neuroepithelial bodies in the neighbourhood of bronchioles and blood vessels, thus producing an improvement in the ventilation perfusion relation (Levy-Lambert, 1980 ; Le ridant, 1983) .

Because almitrine is claimed to have a distinct situation in chronic respiratory failure, so the present work was designed to assess or to perform a pharmacological evaluation of the test drug in experimental animals versus doxapram, the lately introduced and clinically useful analeptic drug. Furthermore, a search for a better agent than the one mostly recommended clinically in Egypt, namely doxapram was attempted .

REVIEW OF LITERATURE

A L M I T R I N E

Almitrine bismesylate is a remarkable molecule possessing seven nitrogen atoms , thus giving a very sensitive response in a thermionic gas chromatographic detector for studying its pharmacokinetics (Bromet et al., 1980) . It is a triazine compound possessing diallyl amino triazine moiety, a piperazine nucleus and bisparafluorobenzydryl component; each moiety is claimed to be responsible for the characteristics of almitrine and also for a clear tropism for the pulmonary tract (Laubie and Schmitt, 1980 ; Labrid et al., 1983) .



Laubie and Diot (1972) first studied the effect of almitrine (Vectarion) as an injectable form in dogs . They found that it produced in the anaesthetized dog prolonged respiratory stimulation decreasing the $PaCO_2$. They also observed that the increase in ventilation varies according to the dose . They reported that the drug effects were abolished by bilateral section of the nerves of the carotid sinus or the vagi . Intravertebral injection did not change ventilation or respiratory frequency, so they considered almitrine as an analeptic drug acting at the level of chemoreceptors without any central analeptic effect .

Neukirch et al. (1974) studied the effects of the less well known oral form of almitrine (at that time) in a group of patients suffering from chronic obstructive lung disease (COLD) approaching the stage of respiratory failure. It was a trial run for a fortnight and they observed a significant improvement in the blood gases in this group of patients ; however, they measured neither ventilation nor any other parameter . They compared their results with a placebo group . Their investigation had pointed out that one of the possible mode of action of almitrine could be at the level of the regulation of the ventilation perfusion ratio of lung units .

Guillerm and Radziszewski, in the same year(1974), studied the respiratory analeptic action of almitrine in healthy volunteers . They attributed this action to stimulation of the peripheral chemoreceptors and they also reported the inhibition of the respiratory effects of almitrine by hyperoxia . In addition, they noticed the improvement of the pulmonary gas exchange .

Sergysels et al. (1978), four years later, carried out a functional evaluation of the new analeptic drug almitrine as an injectable form , in patients with chronic hypoxemia and hypercapnia in case of chronic obstructive lung disease (COLD) reaching respiratory failure . They noticed that almitrine increased ventilation and improved arterial blood gases (increased $Pa\ O_2$ and decreased $Pa\ CO_2$) . The changes in $Pa\ O_2$ were out of proportion of the increase in ventilation , so they suggested that almitrine has a local role either through locally-released mediators or through a direct action of the drug or one of its mediators at the level of ventilation-perfusion ratios . They continued their study and in 1980, they pointed out the dissociation between ventilation and blood gases during almitrine infusion in chronic and acute stages of chronic obstructive lung disease .

Schrijen and Romero-Colomer (1978) studied the haemodynamic effects of almitrine in patients with chronic pulmonary lung disease . They documented that it has a potent vasoactive action on the pulmonary circulation without affecting the cardiac output and the pulmonary capillary pressure . Using an infusion of almitrine, they observed no increase in the pulmonary artery pressure, so they suggested that almitrine could act at the level of ventilation-perfusion ratios .

The works of Maestracci et al. (1978), Sabathie (1978) and Torrens (1979) have succeeded in proving that the use of almitrine during the immediate post-operative phase when hypoxemia associated with hypercapnia were found, is of great benefit . Hypoventilation in this area is related to the length of the operation, the position during operation, the site of incision, the regional adjustments in ventilation-perfusion ratios and the delayed elimination of anaesthetic drugs . Furthermore, Sadoul (1978) reported that almitrine is particularly effective in the intensive care units in acute respiratory failure. In addition, Gay (1979), Germouty and Dalage (1979) and Marsac et al. in the same year (1979) emphasized that almitrine as a specific stimulant to the peripheral chemoreceptors, is an effective ventilatory analeptic in an injectable form .

In the study of Sergysels (1979), good evidence has been raised that almitrine given intravenously is a pulmonary vasoactive drug .

Hannhart et al. (1979) also demonstrated that almitrine is able to increase ventilation in patients affected by chronic obstructive lung disease (COLD), when it was given by the intravenous route .

Laubie and Schmitt in the same year (1979), have observed that the hyperventilation following infusion of almitrine in anaesthetized dog is accompanied by an increase in the electrical activity of the afferent fibres in Herings nerve .

Most of the studies on almitrine related the change in PaO_2 and $PaCO_2$ to the increase in ventilation, but Prefaut (1979) has observed that there was a significant increase in PaO_2 without or before any change in $PaCO_2$. Such an observation was explained by the possibility of a direct effect by almitrine on the ventilation-perfusion ratio. By further ongoing research, Prefaut (1980) noticed a moderate but significant rise of pulmonary vascular resistance, after a single oral dose of almitrine, when given to patients with hypercapnic chronic obstructive lung diseases, thus evoking the hypothesis of an improvement in gas exchange by redistribution of pulmonary blood flow .

Chardon (1980) by putting patients with (COLD) under constant ventilation, observed a greater elimination of CO_2 after perfusion of almitrine which was attributed to a non-ventilatory effect .

Laubie and Schmitt (1980) continued their study on almitrine to evaluate the precise role of its respiratory effects on the aortic and carotid chemoreceptors . They found that in dogs anaesthetized with pentobarbital , almitrine induced a dose-dependent increase in respiratory frequency and minute ventilation associated with a rise in PaO_2 and a fall in $PaCO_2$. The respiratory actions of almitrine were inhibited by carotid sinus and vagal nerve section. The ventilatory response disappeared after destruction of the nucleus of the tractus solitarius. They also found that intracarotid perfusion of almitrine in weak doses strongly stimulated respiration and increased the frequency of the fibre discharge from chemoreceptors. Besides, the inhalation of pure oxygen decreased almitrine activity, so they concluded that almitrine is a powerful stimulant of chemoreceptors and it differs from other agents by its prolonged action.

Further experiments by Denavit et al. (1980) proved that in cats, almitrine applied micro-electrophoretically did not change the frequency of discharge from respiratory neurones in the medulla or pons .