COMPARATIVE STUDY BETWEEN THE EFFECTS OF THE TWO RECENTLY INTRODUCED HISTAMINE H2-RECEPTOR BLOCKERS RANITIDINE AND OXMETIDINE VERSUS THE ANTICHOLINERGIC AGENTS GLYCOPYRROLATE AND PIRENZEPINE ON GASTRIC SECRETION AND MOTILITY IN EXPERIMENTAL ANIMALS

THESIS

Presented For The Ph. D. Degree (PHARMACOLOGY)

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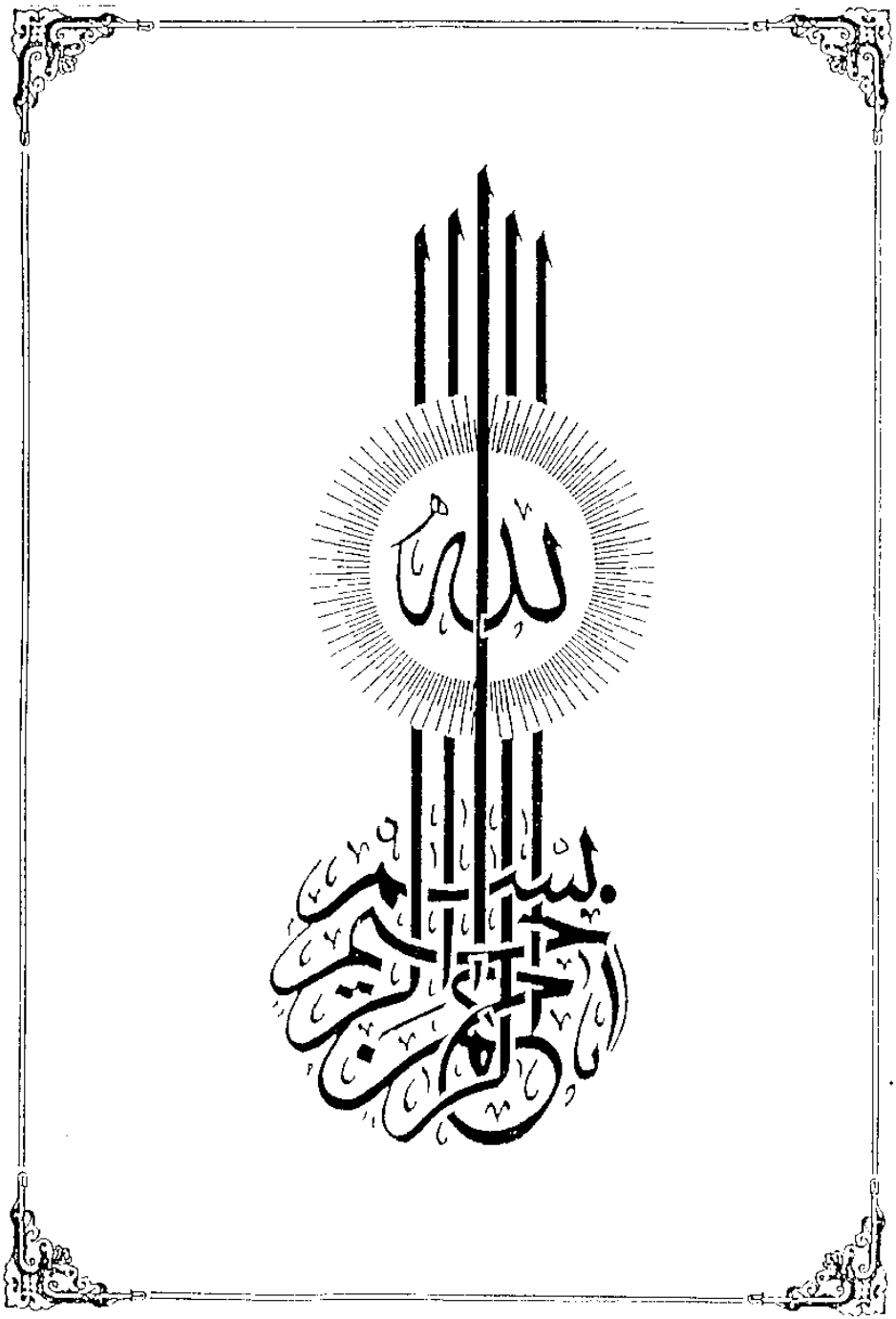
1986

Besides, I wish to extend my deepest obligation and cordial thanks to Dr. MAHMOUD KADRI MADKOUR, Head of the Pharmacological Research Laboratories, Faculty of Medicine, Cairo University, for his co-operative spirit and proper sincerity .His valuable assistance and useful instructions in the statistical analysis and evaluation of the experimental data, in the tabulation and graphic representation of results, cannot be easily forgotten .

I wish also to express my appreciation and thanks to Dr. SAMY HOSSNI HAMED, Assistant Professor of Histology, Ain Shams University, for his proper sincerity and great help in the techniques and reading of the histological part of this thesis .

Sincere thanks to Mr. C.J. Jones; Manager, Clinical Research in A.H. Robins Company, Ltd. Redkiln Way , Horsham, West Sussex, London, RH 13 5 QR, who supplied me with the anticholinergic agent glycopyrrolate and also sent me very important references .

Deep thanks to Miss J.G. Mills and to Dr. R.J. Knox in Smith Kline and French Research Laboratories for supplying me with oxmetidine and also an information sheet on this compound .



Deepest thanks to Miss M.J. Bell, secretary in Smith Kline and French Research Laboratories , The Frythe , Welwyn Hartfordshire England AL6 9AR , who sent me an English Translate for references .

C O N T E N T S

INTRODUCTION
and
AIM OF THE WORK

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

The outstanding problem in peptic ulcer therapy is not so much to heal the ulcers as to keep them healed . However, the objectives of short-term treatment are also important, i.e. the elimination of pain (which is above all that interests the patients) and rapid healing of the mucosal lesion (which is primarily that interests the physician) (Holtermuller , 1980) . In fact, there is no proof that a painless patient with unhealed ulcer will develop complications more often than a patient with a healed ulcer . Moreover, the assumption that treatment will reduce the probability of complications is only plausible and so far untested (Grossman, 1981) .

Dobrilla et al. (1982) postulated that as far as the drug therapy of peptic ulcer is concerned, it should, on one hand, be considered prejudicially that the nature of ulcer disease is relatively benign in otherwise healthy subjects . On the other hand, there currently exists a fair number of substances which have proved active in well-conducted endoscopically assessed studies . It thus follows that among these , we should look primarily for drugs with higher safety margins as well as for those drugs characterized by a fair degree of patient compliance .

Placebo plays an important role in a number of gastro-intestinal disorders (Petersen, 1979), among which is peptic ulcer (Scherer et al., 1977 and Sircus, 1980) . In this condition, the placebo effect is relevant even if rather variable, affected as it is by numerous factors (Dobrilla and Felder, 1979) . One such factor is the geographical area where its action is studied (Peter et al., 1977 and Dobrilla et al., 1982 $_{c}$) . This variability may provide an explanation, at least in part, of the contradictory conclusions arrived at in some placebo-controlled clinical trials .

Numerous compounds with a claim to anti-ulcer efficacy have proved to be completely or partially lacking in convincing documentation in this respect . This group includes such compounds as amylopectin sulphate, deglycyrrhizinized liquorice, metoclopramide, oxyferrosorbone, pepstatin, proglumide, sulpiride and tirthiozinine (Dobrilla et al., 1982 $_{a}$) .

Antacids, in their various forms, are probably the longest and most extensively used drugs in the treatment of peptic ulcer . Contrary to the clinical impression which suggests that antacids relieve pain in peptic ulcer, objective documentation is poor . A liquid antacid was found more active than saline on ulcer pain when administered via a nasogastric tube (Lorber et al., 1978) .

Run and Zachariassen (1979) stated that, acute relief of duodenal pain in duodenal ulcer patients obtained by a liquid antacid preparation by mouth, was found significantly better than the effect of placebo, but the therapeutic gain was small .
A comparative study with aluminium hydroxide and placebo yielded controversial results (Littman et al., 1977) . In other trials conducted by Hollander and Harlan (1973), Peterson et al. (1977), Sturdevant et al. (1977), Lam et al. (1979), no significant differences between liquid antacid and placebo in relieving duodenal ulcer pain were found . Probably low-dose antacid regimen, if their efficacy is confirmed by further and longer studies, may pass less hazards for patients and may prove more acceptable to them (Drake and Hollander , 1981) .

Anticholinergics reduce basal acid output by approximately 40 - 50 % , pentagastrin-stimulated secretion by about 40 % and food-stimulated secretion by about 30 % (Ivey, 1975; Christensen et al., 1977; Feldman et al., 1977) . In order to obtain a decrease in basal and maximal acid secretion, high doses, usually higher than those recommended by the manufacturer, are employed (Ivey, 1975). At these high doses, the inhibitory effect on food-stimulated secretion has, surprisingly, not always been found to be more than a low-dose regimen (Feldman et al., 1977) .

Well-known side effects are observed including blurred vision and dry mouth . In addition to the disadvantage of important side effects, anticholinergics also present another theoretical disadvantage as they inhibit pancreatic secretion of bicarbonate (Duthie and Wormsley , 1979) . Furthermore, the delaying effect of anticholinergics on gastric emptying and their action on the lower oesophageal sphincter, should be considered in an attempt to define the therapeutic role of these compounds (Dobrilla et al., 1982 $_a$) .

Clinical trials performed to establish the anti-ulcer effectiveness of anticholinergics were all pre-endoscopic and, therefore, assessment was principally made by evaluating relief of symptoms and clinical recurrence rate (Piper , 1973 and Ivey, 1975) . These are not necessarily correlated with ulcer healing . At any rate, the results in terms of healing are controversial both in gastric ulcer (Doll, 1964 and Baume et al.,1972) and in duodenal ulcer (Bowers et al., 1977 and Cheli et al., 1978) .

In view of their well-known contraindications (prostatic obstruction , acute angle glaucoma , gastric outlet obstruction , reflex oesophagitis) and the more recent availability of H_2-receptor antagonists, the debate on anticholinergics seems at the present time somewhat academic .

Glycopyrrolate, another anticholinergic, had been shown to have longer acting and more potent actions than atropine (Wyant and Kao, 1974) . Being a quaternary ammonium compound, the drug crosses the blood-brain-barrier to a limited extent, compared with atropine and should not therefore, exert the central effects sometimes associated with atropine (Proakis and Harris, 1978) .

McCubbin et al. (1979) demonstrated that, when glycopyrrolate was used as a premedicant, it produced a lower initial heart rate . In a comparative study between glycopyrrolate and atropine conducted by Mirakhur et al., (1978_a), it was found that glycopyrrolate produces a decreased frequency of arrhythmias on induction of anaesthesia . It offers protection similar to atropine against the cardiac effects resulting from intermittent administration of suxamethonium (Cozanitis et al., 1980) .

It produces a more stable heart rate with a reduced frequency of tachycardia and arrhythmia, when used in a mixture with neostigmine, for antagonism of neuromuscular blockade (Dundee and Clark, 1977) .

Cotton and Smith (1981) showed that glycopyrrolate decreases barrier pressure to an extent similar to atropine and this effect on the LOS (lower oseophageal sphincter) is likely to be more prolonged .

Clark and Seager (1983) conducted a double-blind study of the effects of glycopyrrolate or atropine when given intravenously, on gastric emptying in pregnant and non-pregnant women . Following the administration of glycopyrrolate gastric emptying was delayed in the non-pregnant patients and delayed further in the pregnant patients .

Carbenoxolone synthesized from glycyrrhinizic acid, a constituent of liquorice root, works by strengthening the mucosal defence factors via multiple and complex mechanisms of action (Dobrilla et al., 1982$_a$) . A thorough assessment of the therapeutic role of carbenoxolone has been made by Avery et al. (1978) .

In the treatment of duodenal ulcer, carbenoxolone has been used in recent trials in the form of special positioned-release capsules, designed to deliver the compound in a concentrated form into the duodenal bulb (Hunt, 1975) . Up till now, it has not been adequately demonstrated that the positioned-release capsule is a Sine Qua non* for the efficacy of carbenoxolone in duodenal ulcer (Langman, 1978; Dobrilla and Valentini, 1980) . The analgesic effect of carbenoxolone is judged to be positive by certain authors (Abrahamsson and Dotevall , 1979), relatively poor by others (Bardhan,1981) and slower than with cimetidine in yet other studies (Domschke and Domschke, 1982) .

* Something absolutely essential .

Unfortunately, carbenoxolone has aldosterone-like effects leading to troublesome and sometimes serious side-effects. At the dose of 300 mg per day, hypertension, headache , salt and water retension and hypokalaemia occur in more than 30 % of patients (Langman, 1978) .

Tri-potassium di-citrato bismuthate, which is a stable colloidal bismuth salt complex, chelates with proteins (including pepsin) at an acid pH and is believed to be active principally by forming a protective coating at the site of the ulcer crater (Brogden et al., 1976) . Gastric acid precipitates bismuth oxide, which has an affinity for the granulating tissue of the base of the ulcer crater .

The few side-effects reported after oral colloidal bismuth include darkening of the tongue and the stools. Moreover , patient compliance is usually reduced by the ammoniacal taste of the bismuth preparation , if administered as a liquid rather than in tablet form . Tri-potassium di-citrato bismuthate contains relatively small amounts of bismuth in soluble form ; therefore, significant absorption and consequent neurotoxicity have not been described . Nevertheless, it is not recommended in severe renal disease . Milk and antacids may interfere with the action of the drug (Salmon et al., 1974) .

Sucralfate is an aluminium salt of sulfated sucrose and is thought to act with a mechanism similar to that of the colloidal bismuth. In fact, this compound at the dose of 1 g four times daily, may enhance healing of both gastric and duodenal ulcer by forming a chemical complex that binds to the ulcer crater. It forms a protective barrier against pepsin and bile. The barrier may also block the back-diffusion of HCl at the site of the ulcer . Therefore, it has no systemic effects and particularly does not interfere with the blood-clotting mechanisms (Bighley and Giesing, 1979).

Trimipramine is a tricyclic antidepressant with anti-ulcer activity probably due both to its action on the central nervous system and its anti-secretory effects . As this compound can produce dry mouth and blurred vision, it was believed that its anti-secretory action was due to an anti-cholinergic mechanism. However, dose-response studies suggested a decrease in parietal cell sensitivity , an effect which resembles that of high selective vagotomy (Domschke and Domschke , 1982) . No serious side-effects occurred with " trimipramine " , but side-effects such as tiredness , drowsiness and dryness of the mouth were found more frequently in the patients receiving trimipramine (Fritsch et al., 1980) .

Pirenzepine is a new tricyclic anticholinergic compound showing a selective antagonism on muscarinic receptors (Hammer and Koss, 1980) . Konturek et al. (1982) postulated that pirenzepine distinguishes between different subclasses of muscarinic receptors . This was based only on receptor binding studies .

During the last few years, a variety of new investigations on the mode of action of pirenzepine has been published including further reports on receptor binding, pharmacological investigations on isolated tissues and studies in man (Hammer et al., 1982) . Pirenzepine, used as an anti-secretory drug in peptic ulcer disease has shown its potency to heal both gastric (Barbara et al., 1979 ; Gasbarrini et al., 1979 ; Morreli et al., 1979 ; Osselladore et al., 1979) and duodenal ulcer in many therapeutic trials (Barbara et al., 1979; Bianchi et al., 1979 ; D'Imperio et al., 1979 ; Osselladore et al. 1979).

Clinical experience with pirenzepine may count now on a fairly sizeable number of trials which have been recently carefully reviewed (Bianchi and Petrillo, 1982). There is less agreement in published studies with regard to the results relating to improvement in symptoms. Side effects, too, are affected by the dosage employed; at doses lower than 75 mg per day, side effects are rare and rarely necessitate withdrawal of therapy . At higher doses , however ,