THE EFFICACY OF A BISMUTH-PROTEIN-COMPLEX COMPOUND IN THE TREATMENT OF GASTRIC AND DUODENAL ULCERS*

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SUMMARY

In a clinical trial involving a total of 86 patients, the efficacy of Bicitropeptide (BCP) in the treatment of gastric and duodenal ulcers was investigated. The gastric ulcer group was treated on a double-blind basis with gastroscopic control, while in the duodenal ulcer group radiological evidence and clinical assessment were used as criteria.

In the gastric ulcer group 60% of the patients were completely healed, while in a further 33·3% of the patients, the ulcer crater was reduced by more than two-thirds of the original size. In the control group, the corresponding figures were 8·3% and 41·6%. In the duodenal ulcer group 88% of the ulcers were considered completely healed.

The advantages of Bicitropeptide therapy are discussed and it is concluded that it has a definite place in the treatment of gastric and duodenal ulcer disease.

In spite of dramatic advances in many other fields of medicine during the past decade or two, the treatment of gastro-intestinal ulceration has remained much the same and generally in a fairly unsatisfactory state despite the appearance of a large variety of new preparations based on much the same principles as the classical anticholinergics, antacids and sedatives. Difficulties in assessing the value of new preparations, undesirable side-effects associated with the use of various drugs, general discomfort suffered by ulcer patients as a result of dietary restrictions and prolonged hospitalization as well as the psychological factors involved, have all contributed to make significant advances in this field difficult.

Although bismuth compounds were introduced into medicine as early as 1785, the value of conventional bismuth preparations in the treatment of gastric and duodenal ulcers is strictly limited due to the fact that such preparations are rapidly hydrolysed in the acidic contents of the stomach to be largely precipitated as insoluble bismuthyl (BiO) compounds.

The observation by one of us (W.J.S.) that the pepsin component in the classical 'bismuth and ammonium citrate solution cum pepsin' may react with the soluble bismuth compounds present in such solutions to form bismuth-protein-complexes under certain conditions, led us to investigate the possible use of such complexes in the treatment of peptic ulcers. It appeared that under suitable conditions, bismuth-protein-complexes which are relatively acid stable may be prepared. The clinical usefulness of such acid-stable bismuth proteinates in the treatment of peptic ulcers was demonstrated in animal experiments and on human patients (unpublished observations).

In a further study of the new class of compounds involving the systematic variation of the different variables involved, it was conclusively demonstrated that the method of preparation is critically important. The further observation that the anti-ulcer activity in such preparations may be significantly increased by increasing the concentration of the protein component (pepsin), was of utmost significance. It was finally established that optimal activity may be achieved by giving careful attention to a number of important variables which included the bismuth and citrate concentration, the type and concentration of proteins present, the type and concentration of the dye and sugar components present, the pH of the solution, etc.

It was also established that, depending on the nature of the protein component used, other compounds present and the conditions of preparation, a wide variety of soluble bismuth proteinates differing in their physical, chemical and pharmacological properties may be prepared. A bismuth proteinate preparation (Bicitropeptide) dissolved in bismuth and ammonium citrate solution, based on these

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principles, has recently become available in South Africa and in various countries overseas.

The results of a typical analysis of the preparation, showed the presence of the following constituents in 1 ml: bismuth (as Bi) 33·60mg, citric acid 22·40 mg, free NH_3 5·10 mg, total N 5·33 mg, protein (by difference) 6·96 mg, carmine 0·70 mg, and sucrose 55 mg. Different batches had pH values ranging from 9·2 to 9·8. The complexes present in the preparation were further characterized with the aid of physico-chemical methods involving electrophoresis, ultraviolet spectroscopy, gel filtration and ultracentrifugation.

MODE OF ACTION

The mechanism of action of Bicitropeptide in the treatment of peptic and duodenal ulcers is assumed at this stage to be based on the biochemical differences between the ulcerated, inflamed and regenerating tissues in the ulcer area and the surrounding normal tissues. Quantitative differences involving an increased concentration of hexosamines, hyaluronic acid, mucopolysaccharides and glycoproteins in the ulcer area are involved as well as qualitative differences in respect of the type of glycoproteins and acid mucopolysaccharides present. Many of these compounds are known to form insoluble bismuth complexes with soluble bismuth compounds. In this manner the inflamed and regenerating tissue of the ulcer surface which produces these compounds in much larger quantities and in a more readily available form for reaction than the surrounding normal tissues, becomes rapidly covered with a protecting layer of insoluble, bismuth-containing complex material. The ulcerous tissue which is thus shielded from further exposure to the damaging effects of the acidic gastric juice and pepsin, rapidly heals under the protective bismuth-containing layer which, by virtue of its bismuth content, also serves to inactivate traces of trapped pepsin.

Bicitropeptide has no significant antacid and no anticholinergic properties and it acts only in acid medium at pH 1-5, although the optimal action takes place at pH values below 4.

Agents aimed at increasing alkalinity such as milk, antacids and anticholinergics are, therefore, contraindicated.

Another important practical aspect is that no strict dietary restrictions are called for and even moderate consumption of alcohol and tobacco is allowed.

Acute and chronic toxicity trials involving mice, rats,* guinea-pigs and rabbits have conclusively demonstrated the absence of any side-effects, even after prolonged administration of large doses. Under these conditions, no bismuth could be demonstrated in the various organs of all experimental animals at the end of chronic trials over several months.

No acute LD_{50} values could be established due to the extremely low toxicity of the preparation.*

Histological, haematological and clinical investigations of organs and blood obtained from all the animals at the end of the chronic trials showed no abnormalities.

A series of investigations on human patients included serial barium meals, gastric juice analysis, gastroscopy, blood counts, sedimentation rate, serum protein electrophoresis, serum calcium, phosphorus, electrolytes, urea, uric acid, creatinine, iron and iron-binding capacity. All investigations were repeated 2 and 6 weeks later. The blood tests and other results showed no change following long-term therapy.

*Experiments carried out by the Biological Sciences Division of the South African Bureau of Standards.

CLINICAL TRIALS

In this article the results of a clinical trial of Bicitropeptide in 2 different groups of patients with gastric and duodenal ulcers are reported. The gastric ulcer group was treated on a double-blind basis, while the duodenal ulcer group involved a simple experiment on an outpatient basis.

In the latter case patients were accepted for trial if an unequivocal ulcer crater could be seen by the radiologist on films taken not longer than 2 weeks previously.

In the gastric ulcer group patients with a radiological diagnosis of peptic ulcer were referred to a special clinic for treatment and observation. Patients in this group were admitted to hospital for initial gastroscopy and were hospitalized for 2 weeks.

The design of the gastric ulcer trial was double-blind in nature, so that the physicians and radiologists, and also the physician performing the endoscopies did not know whether the active or placebo preparation had been given to any individual patient. Patients were allocated to the two treatment groups according to a prearranged random order. The active substance contained 0·160 g/5 ml. The placebo was similar in colour, taste and consistency (liquidity). The code was only broken on completion of the trial.

Initially, blood was taken for blood count and electrophoresis as well as for the estimation of bilirubin, urea, uric acid, creatinine, calcium, phosphorus and serum iron. Investigations were repeated after 2 and 6 weeks. No evidence of toxicity as reflected in these values was found even after long-term therapy.

The gastric ulcer group underwent gastric juice analysis and gastroscopies on two occasions, at the beginning and at the end of the trial. A barium meal was done on all patients at intervals of 2, 6 and 12 weeks.

The patients were then allocated a serial number and the appropriate container of medicine was dispensed by the hospital pharmacist. (The patient retained his serial number throughout the trial.) They were instructed to take a teaspoonful in 4 teaspoonsful of water (5 ml in 20 ml) ½-hour before each of the three main meals and on retiring. Except for the exclusion of milk, each patient followed a normal diet. Nothing was taken orally between administration of medication and mealtime. No antacids or anticholinergics were given; smoking was allowed and the advice was given 'to eat anything that does not hurt you'.

The gastric ulcer group of patients were treated for 6 weeks, the first two of which were spent in hospital. Patients were not confined to their beds.

Side-effects of the active substance were negligible, but blackening of stools and the tongue occurred due to the formation of variable amounts of bismuth sulphide. A few patients (approximately 20%) in the duodenal ulcer group complained of tiredness after 3 - 4 weeks of treatment. This could not be satisfactorily explained.

RESULTS

1. Gastric Ulcer Group

This included a total of 28 patients, of whom one was

excluded because she could not tolerate the gastroscopic examination. Of the remaining 27 patients who were admitted to the trial, 15 were randomly allocated to the active and 12 to the placebo treatment. The two treatment groups were comparable with regard to age, duration of history and sex (Table I).

TABLE I. THE TWO TREATMENT GROUPS

Gastric ulcers	*BCP Group*	*Control group (placebo)*
No. of cases	14 (9 male, 5 female—average age 58·3 yr)	12 (7 male, 5 female—average age 60·0 yr)
Average duration of illness before treatment	4 years 2 months	4 years 3 months

BCP group. Of the BCP group (15 cases) 9 showed complete healing by radiological and gastroscopic examination; 5 were improved in respect of reduction of ulcer size by one-third of original diameter and 1 constituted a failure and still showed the presence of an ulcer after 8 weeks of treatment. The results are summarized in Table II.

Thus a total of 60 out of 75 maximum attainable score was achieved in 15 patients (80%) in the BCP group.

Placebo group. Of the placebo group (13 cases) 1 case healed completely; 5 cases were improved; 6 cases remained unimproved and 1 was excluded. The results are summarized in Table III.

Thus a total of 15 out of 60 maximum attainable score was achieved in 13 patients (25%) in the control group.

Twelve patients on Bicitropeptide treatment and 3 on placebo had no complaints during the trial period, while 3 patients on Biciptropeptide and 9 on placebo complained of pain 1 - 14 days after commencement of the trial.

Of the 15 patients on BCP, only 8 developed black tongues.

The possibility of complications in the interpretation of the results due to malignancy in some of the patients in one or both groups was excluded on the basis of the gastroscopic examinations (and in some cases biopsies) before and after the trial which were done on all the patients, thus the 6 cases in the placebo group which showed no improvement during the trial were classified as benign on this basis.

2. Duodenal Ulcer Group

This was a simple trial consisting of 59 patients, of which 7 had to be excluded for lack of co-operation (they did not return for control barium meals). These patients were selected on the basis of clinical symptoms suggesting

TABLE II. GASTRIC ULCERS: BCP GROUP*

Patients			*Reduction in size by ⅓ diameter*	*Reduction in size by ⅔ diameter*				*Total score (maximum attainable = 5)*
Age	*Sex*	*No change*			*Healed*	*Clinical*	*X-ray*	
43	M	—	—	—	3	1	1	5
58	M	—	—	—	3	1	1	5
54	M	—	—	2	—	1	—	3
60	M	—	—	2	—	1	1	4
78	M	—	—	—	3	1	1	5
43	M	—	—	—	3	1	1	5
32	F	—	—	2	—	1	1	4
57	F	—	—	—	3	1	1	5
75	F	—	—	—	3	1	1	5
60	F	0	—	—	—	—	—	0
62	F	—	—	2	—	—	—	2
52	F	—	—	—	3	1	1	5
75	M	—	—	—	3	1	1	5
68	M	—	—	2	—	—	—	2
58	M	—	—	—	3	1	1	5
								60/75

*Scoring of gastroscopic changes: 0 = no change; 1 = reduction by ⅓ diameter in size; 2 = reduction by ⅔ diameter in size; 3 = healed; + 1 for disappearance on barium meal examination, and 1 for clinical assessment. Total maximum attainable score = 5.

TABLE III. GASTRIC ULCERS: PLACEBO GROUP*

Patients			*Reduction in size by ⅓ diameter*	*Reduction in size by ⅔ diameter*				*Total score (maximum attainable = 5)*
Age	*Sex*	*No change*			*Healed*	*Clinical*	*X-ray*	
66	M	—	—	—	3	1	1	5
75	F	0	—	—	—	—	—	0
48	M	0	—	—	—	—	—	0
52	F	—	1	—	—	—	1	2
58	M	—	1	—	—	1	—	2
73	F	0	—	—	—	—	—	0
58	M	—	1	—	—	1	—	2
84	F	0	—	—	—	—	—	0
48	M	0	—	—	—	—	—	0
45	M	0	—	—	—	—	—	0
54	F	—	1	—	—	—	1	2
63	M	—	1	—	—	1	—	2
								15/60

*For scoring of gastroscopic changes see footnote to Table II.

chronic peptic ulceration and positive barium meals. They were treated as outpatients and received the trial material together with a sedative or tranquillizer in the form of diazepam or fluphenazin. Instructions similar to those given to the gastric ulcer patients were given.

Results were judged on clinical grounds. Disappearance of pain, heartburn, epigastric discomfort and dyspepsia were considered significant and the appearance of the ulcer crater on barium-meal examination was noted. The course lasted 12 weeks, at which stage control films were taken (Table IV). The course of treatment was 12 weeks in the duodenal ulcer group as compared with 6 weeks duration in the gastric ulcer group, because the former group was judged on clinical impressions and radiological evidence

TABLE IV. DUODENAL ULCER GROUP (ACTIVE)

No. of cases	59	
Male	43	
Female	16	
Average age	41·8	years
Average duration of illness before treatment	7	years
Number healed	46	
Number not healed	3	
Recurrence	1	
Referred for surgery	2	
Did not return for follow-up	7	

without hospitalization, while the latter group was hospitalized for at least 2 weeks and the results were assessed directly by means of gastroscopy.

Of the 52 cases retained in the trial, all but 3 had definite clinical improvements within the first week of treatment and the ulcer had disappeared on the control barium-meal films taken after 12 weeks. Even the case of re-occurrence and the 2 cases referred for surgery, improved clinically after 2 weeks. Thus 46 cases healed completely as judged by clinical and radiological assessment (88%).

On the basis of the results presented here and on further clinical impressions gained over the past year, we conclude that BCP-compound has a definite place in the armamentarium of ulcer treatments, the safety factor in the use of the drug being particularly impressive. It is a new approach to the peptic ulcer problem, easy to administer, does not entail any hospitalization or dietary restrictions and has no side-effects. It has, therefore, many advantages over established regimens and is of definite clinical value in the treatment of gastric and duodenal ulcer disease.

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TYPHOID FEVER IN AN ENDEMIC AREA: A 'GREAT IMITATOR'*