# A THERAPEUTIC TRIAL OF A NEW ANTICHOLINERGIC DRUG, OXYPHENCYCLIMINE HYDROCHLORIDE, ON PATIENTS WITH PEPTIC ULCERS

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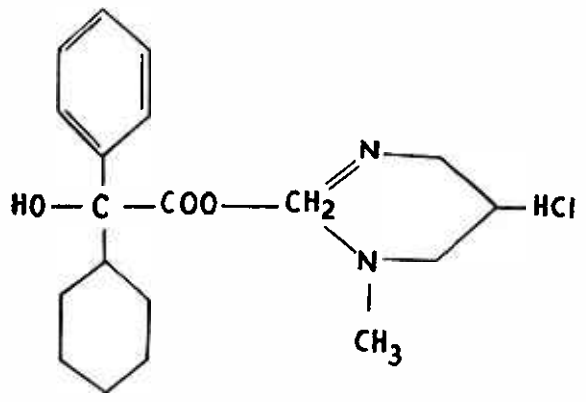
Of the numerous anticholinergic drugs tested and tried in patients with peptic ulcers, few satisfy the criteria required by the drug of choice. Ideally it should inhibit gastric secretion to the point of almost achlorhydria and at the same time produce minimal side-effects. Its duration of action should last at least eight hours so that nocturnal secretion may be effectively suppressed. It is generally accepted that using the minimal optimal dose (Sun 1955, 1956) some degree of side-effects is inevitable, and in fact is a measure of the drug's effectiveness. The new anti-cholinergic drug, oxyphencyclimine hydrochloride*, (Daricon) has been reported to have the advantage of prolonged duration of action over other preparations. Winkelstein (1959) noted good symptomatic improvement in 80 patients with duodenal ulcers, gastric ulcers, jejunal ulcers and peptic oesophagitis. Piper (1960) demonstrated its superior action over propantheline in meal-induced and hypoglycaemic-induced gastric secretion.

## PHARMACOLOGY

Structurally, oxyphencyclimine hydrochloride has a tetra-hydro-pyrimidal ring; hence it is a non-quarternised amine compound in contrast to the other anticholinergic drugs. It has the following formula:—




Finkelstein (1959) demonstrated the following properties and actions of this drug. In rats and dogs it was shown to be an effective anti-secretory drug with no concommitant mydriasis and tachycardia. Comparing it with a number of other drugs, it was most effective in inhibiting gastric secretion in the 5-hours Shay rat and in preventing rumenal ulcer formation in the 17-hours Shay rat. Given intramuscularly to dogs with chronic gastric fistula it was effective in inhibiting gastric secretion for more than 3 hours. It exerted slight inhibitory effect on salivary flow but no curare-like action on the cat sciatic nerve, and no toxicity on the central nervous system.

In human beings, the main side effect reported was diminished salivation. The dose recommended is 10 mgm. (per tablet) taken twice daily. Maximal effect was reached in 1 to 2 hours.

## OBJECTS OF PRESENT INVESTIGATION

The objects of the present investigation are to evaluate the efficacy of the drug:

1. In relieving peptic ulcer pain and dyspepsia.
2. In suppressing gastric acid secretion continuously over 24 hours.
3. In assisting the healing of peptic ulcers.

## METHOD OF INVESTIGATION

*Selection of Cases*: Cases investigated had radiologically proven duodenal or gastric ulcers, some with past histories of gastrointestinal bleeding. All had fairly severe symptoms over a period of months, and many had failed to respond to other forms of medical treatment. The trial was conducted in three parts:—

1. The first phase of the trial was a double-blind trial, using dummy and genuine tablets supplied by the drug firm. Twenty five patients were subjected to the trial for a period of four weeks each. Alternate cases were put on the dummy and real tablets. Patients were instructed to take 1 tablet twice daily, an hour before breakfast and the evening meal. The allocation of tablets was done by a different doctor from the observer (author). Patients were seen weekly at the clinic. A general diet low in roughage and spices was advised. All patients were told

*Pfizer Corporation.

to reduce smoking to less than half a dozen cigarettes per day. Besides the tablets they were given a supply of aluminium hydroxide gel, and were instructed to take a teaspoonful if their ulcer pain was more than minimal. Improvement was judged by relief of pain and dyspepsia. As a countercheck, the amount of antacid taken was used as an index of improvement or deterioration.

2. Following on the double-blind trial all the 25 patients were given the real tablets. Some patients who were physically smaller were given 5 mgm. b.d. daily; the rest received 10 mgm. b.d. They were followed up for a period of five to ten months, averaging eight months. At the end of this period, repeat barium meal examination was done in nearly every case.

3. Seven patients who had previous experience with the Ryle's Tube or who did not find it unduly unpleasant were subjected to twenty four hours studies of gastric acidity. Each served as his own control. A Ryle's tube was passed into the gastric at 8 p.m. Where there was doubt, the position of the tube was checked radiologically. 5 ml. of gastric content was removed every two hours and the pH recorded with Hydrion Indicator Paper (previously checked by known pH solutions). A soft diet was allowed. Feeds and tablets were given immediately after testing of pH. Hence there was a lapse of two hours before the next aspiration. In two patients, the residual volume in the stomach was studied after 10 mgm. of the drug taken with 120 ml. of milk an hour beforehand. 5 ml. of contents was aspirated every 10 minutes for 90 minutes, and the residual content was completely aspirated and measured. The pHs were estimated with a glass electrode in the latter investigation.

The results show a trend in favour of Oxyphencyclimine Hydrochloride as the superior drug, but they are not statistically significant at the 5% level.

TABLE I. RESULTS

| DRUG | WORSE | SAME | FAIR IMPROVEMENT | GOOD IMPROVEMENT | SIDE-EFFECT DRY MOUTH | TOTAL |
|---|---|---|---|---|---|---|
| DUMMY | — | 6 | 5 | 1 | 5 | 12 |
| DARICON | — | 2 | 7 | 4 | 10 | 13 |

RESULTS OF UNCONTROLLED TRIAL — FOLLOW UP OF 25 PATIENTS FOR 5 to 10 MONTHS (AVERAGE 8 MONTHS)

TABLE II.

| IMPROVEMENT | | |
|---|---|---|
| NIL OR WORSE | FAIR | GOOD |
| 4 (16%) | 10 (40%) | 11 (44%) |

| | TROUBLE-SOME | | TOTAL |
|---|---|---|---|
| | MILD | | |
| Blurred Vision | 5 | 0 | 5 |
| Dry Mouth | 18 | 4 | 22 |
| Constipation | 4 | 0 | 4 |
| Difficult Micturition | 1 | 0 | 1 |

## ANALYSIS OF THE FAILURE CASES

All the 4 failure cases had chronic duodenal ulcers, and had previously failed to improve with medical treatment. Two of them have since had a partial gastrectomy and gastrojejunostomy; the ulcers were confirmed at the operation. One of them is symptom-free now; the fourth still complains of dyspepsia.

## ANALYSIS OF THE 3 CASES ON A DAILY DOSE OF 10 MG.

One of them was a girl 20 years old. The other two were men with physical statures below average.

The symptoms in all 3 patients responded favourably but only the one with the gastric ulcer showed radiological evidence of healing.

TABLE III. RADIOLOGICAL FOLLOW-UP OF 22 CASES

| | Total | No Change | Regression | Disappearance |
|---|---|---|---|---|
| 1. Gastric Ulcer | 3 | 1 | 2 | — |
| 2. Gastric Ulcer & Duodenal Ulcer | 1 | — | — | — |
| 3. Duodenal Ulcer | 18 | 17 (one developed pyloric ulcer) | — | 1 |

Chart 1.

24 HOURS pH STUDIES WITH OXYPHENCYCLMINE.

C. K T.

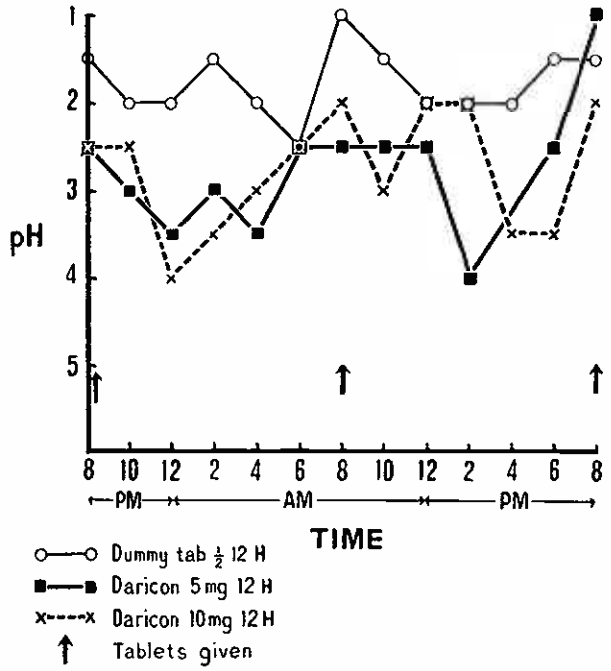



Chart 3.

24 HOURS pH STUDIES WITH OXYPHENCYCLIMINE.

Q. S. L.

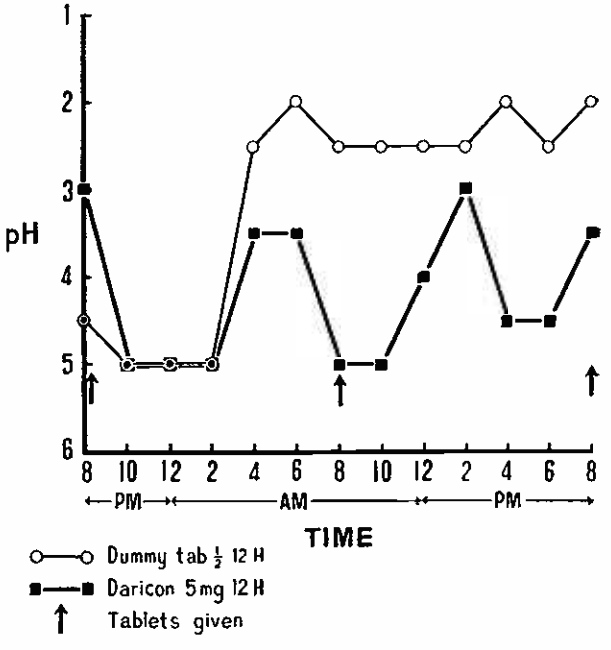



Chart 2.

24 HOURS pH STUDIES WITH OXYPHENCYCLIMINE.

Y. C. T.

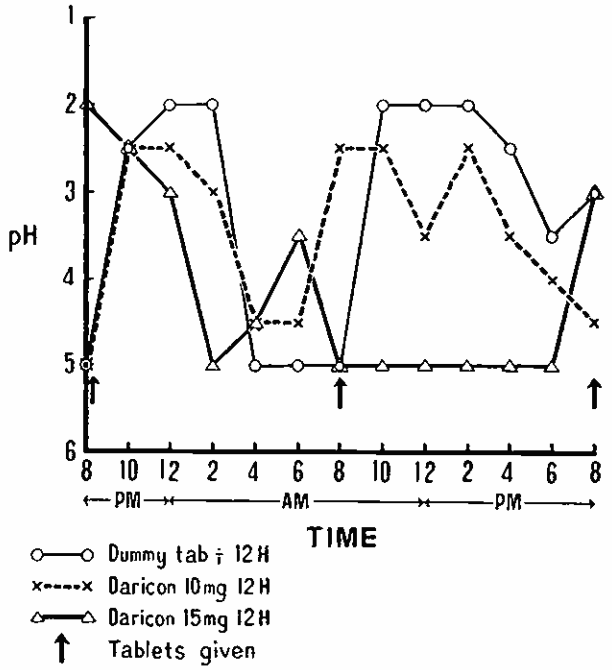
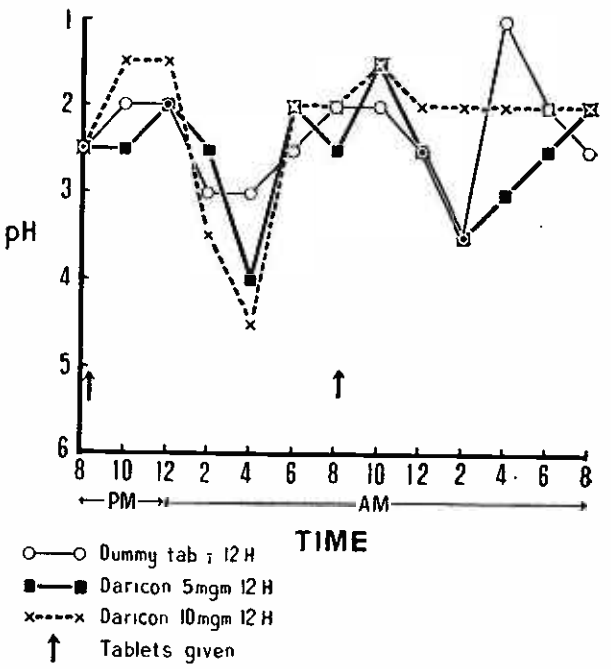



Chart 4.

24 HOURS pH STUDIES WITH OXYPHENCYCLIMINE.

M. B H.



Three patients did not have repeat barium meal examination. Two were failure cases and were subsequently subjected to partial gastrectomy and one failed to turn up.

## STUDY OF GASTRIC ACIDITY

The following charts illustrate the types of responses seen in the investigation:

*Chart 1* illustrates moderate lowering of acidity with 5 mgm. b.d. and 10 mgm. b.d. of Oxyphencyclimine Hydrochloride.

*Chart 2* illustrates response only with a higher dosage, that is, 15 mgm. b.d.

*Chart 3* illustrates good response with low dosage, that is, 5 mgm. b.d.

*Chart 4* illustrates poor response with low and medium dosage.

*Chart 5*. The values represent the mean of the recordings in two patients investigated, to study the effect of the drug on residual gastric volume. The results show a lowering of gastric acidity without significant difference in residual volumes. This suggests that the drug acts by inhibiting gastric secretion, and not by reducing gastric emptying time. Delay in gastric emptying would increase the residual volume which exerts a buffering action on gastric secretion.

Chart 5.

THE EFFECT OF DUMMY OR 10mgm OXYPHENCYCLIMINE WITH 120 mL. OF MILK TAKEN AN HOUR PREVIOUSLY ON THE PH OF GASTRIC SAMPLES AND ON THE RESIDUAL VOLUME. THE RESULTS ARE THE MEAN OF READINGS TAKEN IN 2 PATIENTS

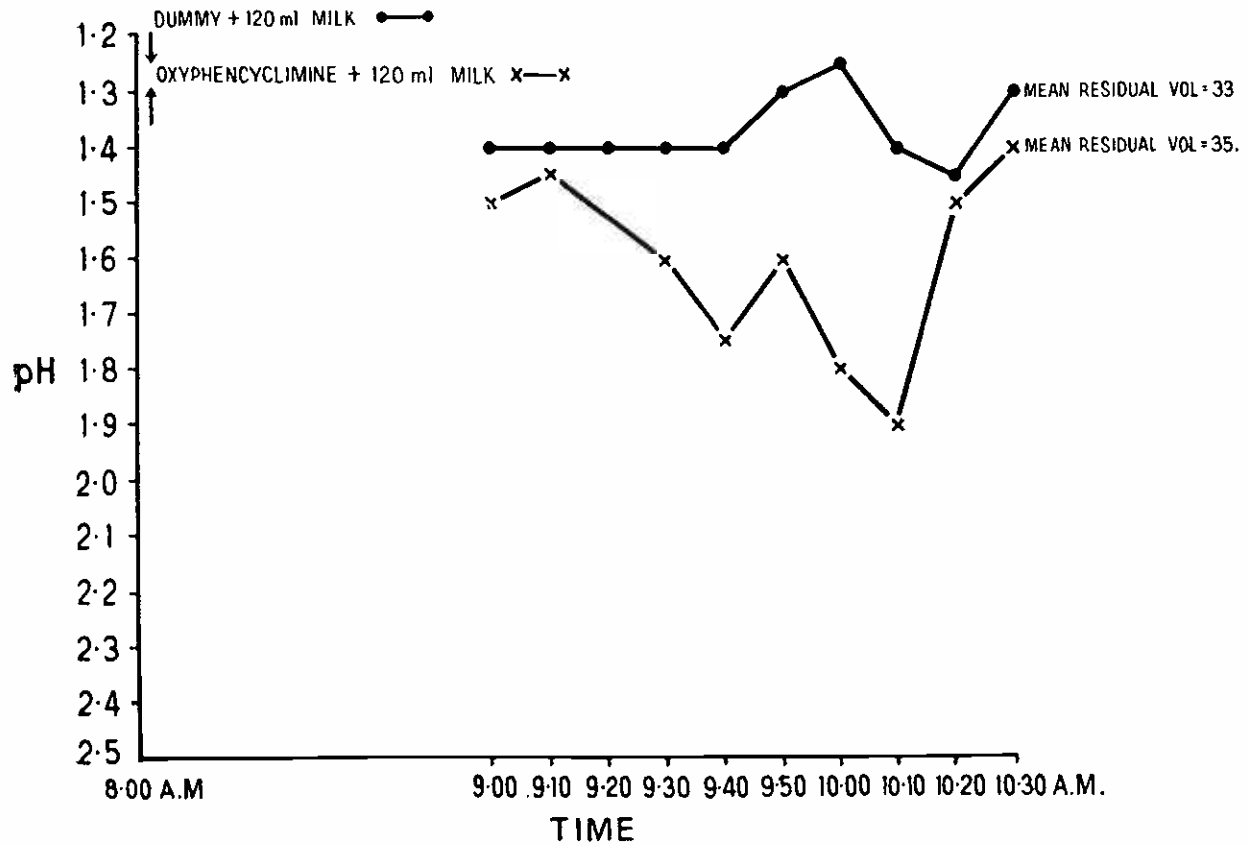


TABLE IV.
CORRELATION OF CLINICAL RESULTS AND pH STUDIES IN 7 PATIENTS

| | |
|---|---|
| 2 with good improvement showed good | lowering of acidity. |
| 1 with fair improvement showed good | — do — |
| 2 with fair improvement showed moderate | — do — |
| 2 with no improvement showed no | — do — |
| 1 with good improvement showed no | — do — |

## DISCUSSIONS

Clinical trials of drugs in chronic disorders are faced with problems of natural remission, relapses and exacerbation. This is particularly so with chronic peptic ulceration. So many external and personal factors affect the symptom complex and natural history of peptic ulceration that perfectly controlled studies are very difficult. Seasonal variations make long term follow-up necessary. Unlike hypertension, there is no accurate quantitative measurement that one could rely upon to evaluate changes. Barium studies, at best, give only a crude visual impression of improvement or deterioration.

Pharmacological and clinical investigations into anticholinergic drugs have often produced conflicting results. Preliminary favourable reports sometimes turned out to be unfounded by more prolonged clinical follow-up studies. The reason for this anomaly rests partly on the unphysiological condition under which the human experiments were conducted. The response to a drug during fasting state in an experiment may be quite different from its response under conditions in which it is used in clinical practice (Rowland 1952). Again, a drug like hexamethonium may produce varying results in the same patient at different times; or in different patients. Differences in diets also influence the response (Bingle 1960). Bearing these facts in mind, attempts were made to conduct the present investigation under as physiological conditions as feasible.

The double-blind trial was mainly a trial of symptomatic improvement. It was felt that if acid-pepsin activity could be reduced symptomatic improvement should be noticed fairly early. For this reason the trial covered only 4 weeks. Extension of the trial beyond this period may cause patients to be dissatisfied with the continuation of the trial. The results suggest oxyphencyclimine hydrochloride to be superior to the dummy tablets, though not statistically significant (See Table I). It is possible that if the number of cases were increased, the level of 5% significance may be reached.

In the uncontrolled follow-up studies, 11 out of 25 cases (44%) did well. They were either symptom-free or had only minimal dyspepsia. 10 cases (40%) improved moderately; that is, they obtained some measure of relief but were not free of pain, and they required less antacids than before the trial. Of the 4 patients who did not improve or who got worse, 2 have had a partial gastrectomy, the other 2 refused surgery. It must be emphasised again that the cases selected for this trial had severe symptoms and complications. This is necessary as evaluation of symptomatic improvement in mild cases is extremely difficult, if not impossible. Less severe cases or ordinary cases of dyspepsia without proven lesion may well do better.

Among the side effects, dryness of mouth was most frequently met with. It was severe in 4 cases and mild in 18 cases. It commenced about one hour after taking the drugs and lasted about 3 to 4 hours, sometimes much longer. Associated with dryness of mouth there was a sticky feeling in the throat. The latter seemed more troublesome to the patient than just a dry mouth. However this side effect diminished in intensity as time went on, and most patients would put up with it when warned about it initially. When the dryness was unbearable, the dose was reduced by 5 mg. daily. This was invariably followed by amelioration of the side effect. 5 patients complained of slight blurring of vision, but this rarely persisted or was severe enough to interfere with their normal routine. Constipation, when it occurred, was not severe and was successfully relieved by a more liberal fluid and fruit intake. Only 1 patient, who was about 60 years old, complained of hesitancy with micturition at the beginning. No incidence or urinary retention was encountered.

In the continuous studies of gastric acidity by a sampling technique a soft but ordinary diet was given. Patients who found it difficult

to tolerate the Ryle's tube were excluded, as the attempted passage of a tube in an unhappy patient in itself will inhibit gastric secretion. Sun et al stressed the importance of raising the pH to 4.5. They found suppression of acid secretions to this level not possible without concommitant dryness of mouth and that the effect of the same dose was not constant in the same patient.

3 out of 7 cases investigated showed good lowering of acidity, the pH of gastric secretion was between 3.5 to 4.5 for most times of the day. One case showed moderate lowering of acidity; 3 cases showed no significant changes. The dose required varied from patient to patient. Patient Q.S.L. (see Chart 3) required only 5 mg. b.d.; whereas patient Y.C.T. (see Chart 2) required 15 mg. b.d. Differences in response may be due to varying interplay of neuronal and humoral mechanisms. If the humoral mechanism predominates in a patient, then an anticholinergic drug is not likely to reduce acid secretion significantly. Piper demonstrated a decrease in hypoglycaemia and meal stimulated acid secretion but noted a rise in the pepsin concentration. The significance of this latter finding is not understood.

Table IV suggests a significant correlation between the effect of lowering of gastric acidity and clinical improvement, with the exception of one case. This is not surprising as patients with peptic ulcer may show symptomatic improvement without reduction in acidity. Following a milk feed, relief of pain is not related to a rise in pH. In fact, milk and cream act as gastric stimulants (Kasich 1958). Hence the mechanism for the relief of pain must either rests on its demulcent property or in its ability to modify gastric motility. It is now appreciated that subtle disturbance of gastric motility may be responsible for dyspeptic symptoms rather than secretion alone (Rowland 1960).

In view of the difficulty in interpreting changes in duodenum, only marked improvement or complete disappearance was accepted as significant. Mensuration of ulcers radiologically has been shown to be full of pitfalls. Fortunately, regression in gastric ulcer is much easier to detect. Follow-up of radiological studies show improvement in only 4 out of 22 cases; of these 4, 2 had gastric ulcers, one had a duodenal ulcer. Only 1 out of 18 cases of duodenal ulcers showed complete regression of the ulcer. The poor radiological improvement suggests that healing of large chronic ulcers is slow and difficult. Many of the cases showing apparently no radiological improvement were symptom free; the cicatrised ulcer might have been epithelialised and become inactive. Whether withdrawal of the drug at this stage would hasten relapse or not is an interesting point and merits further follow-up studies.

Experience gained in the trial suggests that oxyphencyclimine hydrochloride has a more prolonged duration of action than the usual anticholinergic drugs. The dose required varied from 10 mgm. to 20 mgm. daily in two or three divided doses, depending on the weight of the patient, the degree of inhibition of gastric secretion and the severity of side-effects. More than 80% of cases obtained some measure of relief in their symptoms but this beneficial effect was not necessarily accompanied by radiological evidence of healing.

## SUMMARY

1. A double-blind trial of oxyphencyclimine ("Daricon") conducted on twenty five patients with duodenal or gastric ulcers for four weeks showed that the drug probably had favourable effect on the symptoms of patients with peptic ulcers though results were not statistically significant at the 5% level.

2. An eight months follow-up showed that 44% of cases obtained complete or almost complete relief of pain and dyspepsia, whilst 40% obtained fair to moderate relief.

3. Studies on the effect of the drug on continuous gastric acid secretion in 7 cases demonstrated variable response from patient to patient. The varying interplay between neuronal and humoral control of secretion probably accounts for the unpredictable response. With the exception of one case, secretory response seemed to correlate well with symptomatic relief.

4. Radiological follow-up showed complete healing or regression of ulcers in only four out of twenty two patients.

5. The main side effect was dryness of mouth and throat. Nearly 90% of patients complained of it to varying extent. Generally this symptom abated with time.

6. The dose recommended is 5 mgm. b.d. or 8-hourly, or 10 mgm. b.d. Occasional patient may need and tolerate up to 30 mg. daily.

7. It is emphasized that the therapeutic trial was conducted on patients with chronic and severe symptoms.

## ACKNOWLEDGEMENT

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## REFERENCES

1. Bingle, J.P., & Lennard-Jones, J.E. (1960) Some Factors in the Assessment of Gastric Antisecretory Drugs by a sampling technique, Gut. Vol. 1, 337.
2. Finkelstein, M., P'an, S.Y., Neisler, V.N., Johnson, C.A., Schneider, J.A. (1959) On the Pharmacology of Oxyphencyclimine Hydrochloride, J. of Pharmacol. & Exp. Therap. Vol. 125, 8144.
3 Kasich, A.M. & Argyros, T.G. (1958) The Effect of a Prolonged Acting Form of Propantheline Bromide (Probanthine) on the Hydrogen Ion Concentration of Gastric Juice as observed in Forty Eight Hour Gastric Analysis, Gastroenterology, Vol. 34, 292.
4. Lopusniak, M.S., Berk, J.E. (1948) The Comparative Effect of Casein Hydrolysate, Milk and Milk-Cream on Gastric and Duodenal Bulb Activity in Duodenal Ulcer Patients, Gastroenterology, Vol. 11, No. 6, 891.
5. Piper, D.W., Elliott, F.M., Sietsma, A.S. & Pryor, A.W. (Feb. 13, 1960) The Effect of a New Anticholinergic Agent, Oxyphencyclimine Hydrochloride on Gastric Secretion, Med. J. Aust., 236.
6. Rowlands, E.N., Wolff, H.H. & Atkinson, M. (1952) Clinical Assessment of Drugs which inhibit gastric secretion, with special reference to Hexamethonium, Lancet, Vol. 2, 1154.
7. Rowlands, E.N. (1960) Clinical Assessment of Gastric Function, Postgraduate Medical Journal, Vol. 36, 714.
8. Sun, D.C.H., Shay, H. & Ciminera, J.L.C. (1955) Relative Effectiveness of Anticholinergic Drugs on Basal Gastric Secretion, J.A.M.A., Vol. 158, 713.
9. Sun, D.C.H., Shay, H. (1956) Optimal Effective Dose of Anticholinergic Drug in Peptic Ulcer Therapy, Arch. Int. Med. Vol. 97, 442.
10. Winkelstein, A. (1959) The Clinical Evaluation of Oxyphencyclimine in Patients with Peptic Ulcers, Am. Journal of Gastroenterology, Vol. 32, No. 1, 66.