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Case Study in Optimal Dosing in Duodenal Ulcer

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1. Introduction

Duodenal ulcers occur in the duodenum – the upper portion of the small intestine as it leaves the stomach. A duodenal ulcer is characterized by the presence of a well-demarcated break in the mucosa that may extend into the muscularis propria [Thompson et al, 2010]. Cimetidine (C) was the first H_2-Receptor Antagonist to receive regulatory approval (in the late 1970s) for the treatment of duodenal ulcers. When it was being developed it was widely held that duodenal ulcers were caused by excessive gastric acid production. In fact the prevailing medical opinion was *no acid, no ulcer*. Sir James Black and colleagues at SmithKline and French Laboratories are credited with the discovery of C. They discovered that histamine released by the H_2-receptor stimulated the production of gastric acid, and that C by blocking the release of this histamine would suppress both normal and food stimulated gastric acid secretion [Nayak & Ketteringham, 1986]. In a reduced acidic environment, ulcers would be able to heal. The first C regimen approved for the treatment of duodenal ulcers in the United Kingdom was 1000 mg per day, given as: 200 mg at breakfast, lunch and dinner, and 400 mg at bed time, for up to 4 weeks. The first regimen approved in the United States for this indication was 1200 mg per day, given as: 300 mg q.i.d. for up to 4 weeks. Subsequently, other indications were obtained, and dosing regimens modified; for example, 800 mg per day, given as 400 mg bid.

In the mid 1980's, based upon data from gastric acid anti-secretory studies at various doses and frequencies of dosing, there was reason to believe that a single night time (hs) dose of 800 mg of C for up to 4 weeks would be the clinically optimal regimen for treating patients with duodenal ulcers. A large, landmark, dose comparison clinical trial [Dickson et al, 1985; Peace et al, 1985; Valenzuela et al, 1985; Young et al, 1989] was undertaken to confirm the effectiveness of 800 C mg hs in the treatment of duodenal ulcers for up to four weeks. When the author was first consulted by the project physician and regulatory affairs expert, the clinical development plan consisted of two, randomized, double-blind, placebo controlled, pivotal proof of efficacy trials with single nighttime dosing for four weeks:

Trial 1: 800 mg C hs vs. Placebo, and Trial 2: 1200 mg C hs vs. Placebo.

Each trial was to enroll 150 patients per treatment group, for a total of 600 patients. One-hundred-fifty patients per group would provide a power of 95% to detect a 20% difference in cumulative four-week ulcer healing rates between the C and Placebo groups with a 1-

sided, Type I error [Peace, 1991a] of 5%. Since conducting these trials would subject ½ the patients to Placebo, the author recommended amalgamating the two trials into a single trial:

Trial 3: 1200 mg C hs vs. 800 mg C hs vs. 0 mg C hs (Placebo)

with 164 patients per treatment group, for a total of 492 patients. One-hundred sixty-four patients per treatment group would provide a power of 95% to detect a difference of 20% in four week ulcer healing rates between any two of the treatment groups with an experiment wise Type I error of 5% (1.67% per each 1-sided, pair-wise comparison). Not only would this trial require fewer patients and be less expensive to conduct, it would also provide a within trial comparison between C doses, for dose discrimination.

Further savings could be realized by incorporating into the Trial #3 protocol, a planned interim analysis after ½ the patients had been entered and completed. At the interim analysis, the efficacy comparisons: 1200 mg C vs. Placebo, and 800 mg C vs. Placebo would be tested. If both were statistically significant, then the entire study could be stopped – if efficacy of the doses were the only objective. If comparing the doses of C was also of clinical importance, then the Placebo arm could be stopped and the two C arms run to full completion to assess dose discrimination. By conducting Trial #3 (instead of the two separate trials) and incorporating the interim analysis, potential savings of up to 190 patients could be realized. Additional savings would be expected due to less time required to conduct the trial [Peace, 1990, 1991b}.

The primary objective in conducting a clinical trial of C in the treatment of duodenal ulcers with a single nighttime dose was to demonstrate that 800 mg C was clinically optimal. We therefore added a 400 mg dose and replaced the 1200 mg dose with a 1600 mg dose (a two-fold increase among consecutive doses) in the final trial protocol, which was IRB approved.

2. Materials and methods

2.1 Objective

Both primary and secondary efficacy objectives were identified in the final protocol. The primary objective addressed ulcer healing. The secondary objective addressed upper gastrointestinal (UGI) pain relief.

The primary objective was to confirm that C given as a single nighttime dose of 800 mg for up to 4 weeks was clinically optimal in healing duodenal ulcers. Clinically optimal meant that 800 mg C was effective (significantly superior to placebo), that 800 mg C was superior to 400 mg C, and that 1600 mg C was not significantly superior to 800 mg C. Symbolically the primary (note p subscript of H) objective derives from three null and alternative hypotheses:

$$H_{p01}: P_{uh800} = P_{uh0}, \quad H_{p02}: P_{uh800} = P_{uh400}, \quad H_{p03}: P_{uh1600} = P_{uh800}$$

$$H_{pa1}: P_{uh800} > P_{uh0}, \quad H_{pa2}: P_{uh800} > P_{uh400}, \quad H_{pa3}: P_{uh1600} \neq P_{uh800}.$$

where P_{uh0}, P_{uh400}, P_{uh800} and P_{uh1600} represent the cumulative ulcer healing (uh) rates by week 4 in the Placebo, 400 mg C, 800 mg C and 1600 mg C treatment groups, respectively, under single nighttime (hs) dosing. Specifically, H_{pa1}, H_{pa2} and H_{p03} comprised the primary study objective.

Symbolically, the secondary (note s subscript of H) objective derives from the three null and alternative hypotheses:

$$H_{s01}: P_{pr800} = P_{pr0} \; , \quad H_{s02}: P_{pr800} = P_{pr400} \; , \quad H_{s03}: P_{pr1600} = P_{pr800}$$

$$H_{sa1}: P_{pr800} > P_{pr0} \; , \quad H_{sa2}: P_{pr800} > P_{pr400} \; , \quad H_{sa3}: P_{pr1600} \neq P_{pr800} \; .$$

where P_{pr0}, P_{pr400}, P_{pr800} and P_{pr1600} represent the UGI pain relief (pr) rates in the Placebo, 400 mg C, 800 mg C and 1600 mg C treatment groups, respectively, under single nighttime (hs) dosing. Specifically, H_{sa1}, H_{sa2} and H_{s03} comprised the secondary study objective.

Of the six possible pairwise comparisons among the 4 dose groups, only three comprised the study objective. The other three: 1600 mg C versus 0 mg C, 1600 mg C versus 400 mg C, and 400 mg C versus 0 mg C were not part of the study objective and thus did not exact a Type I error penalty (i.e. the overall Type I error of 5% was 'Bonferonnied' across the three pairwise comparisons comprising the study objective, and not across the 6 possible pairwise comparisons).

2.2 Designing and planning the investigation

The trial was multicenter, stratified, randomized, double-blind and Placebo (0 mg C) controlled. Neither patients, investigators nor their staff knew the identity of the C regimens. As there had been reports [Korman et al, 1981; Korman et al, 1983; Lam & Koo, *1983;* Barakat et al, 1984] of the influence of smoking on the healing of duodenal ulcers at the time of protocol development, patients were stratified by smoking status within each center prior to randomization to the treatment groups. Smoking strata were Light Smokers and Heavy Smokers. Patients who smoked at most 9 cigarettes per day comprised the Light Smoker stratum. Patients who smoked at least 10 cigarettes per day comprised the Heavy Smoker stratum.

2.3 Blinded treatment groups

Blinded treatment group medication was packaged using the existing regulatory approved 400 mg C tablet. A 400 mg Placebo tablet was formulated identical to the 400 mg C tablet except that it contained 0 mg C. Blinded trial medication for the four treatment groups was packaged in blister packs for 4 weeks of nightly treatment as identified below:

0 mg C Group:	Four 400 mg Placebo tablets
400 mg C Group:	One C 400 mg tablet + three 400 mg Placebo tablets
800 mg C Group:	Two C 400 mg tablets + two 400 mg Placebo tablets
1600 mg C Group:	Four C 400 mg tablets.

2.4 Sample size determination

The trial was designed to recruit and enter enough patients to complete one-hundred sixty-four (164) per treatment group, for a total of 656 patients. One-hundred sixty-four patients per treatment group would provide a power of 95% to detect a difference of 20% in cumulative four week ulcer healing rates between any two of the treatment groups with an experiment wise Type I error rate of 5% (1.67% per each 1-sided, pair-wise comparison). This number was inflated to account for a 15% drop out rate. A cumulative four week healing rate of 45% among Placebo treated patients [de Craen et al, 1999] in previous trials was used in the sample size determination.

2.5 Entry requirements and assessment schedule

Patients were required at entry to have an endoscopically confirmed duodenal ulcer of size at least 0.3 cm, and either daytime or nighttime UGI pain. After providing informed consent, at the preliminary examination or baseline visit, patients provided a history (including prior use of medications, particularly anti-ulcer ones or antacids), underwent a physical examination, had vital signs measured, provided blood and urine samples for clinical laboratory assessments, in addition to having UGI pain assessed and undergoing endoscopy. Patients were also instructed how to use a daily diary to record the severity of daytime or nighttime UGI pain, as well as to record any adverse experience or concomitant medication use. Diaries and trial medication were dispensed and the patients instructed to return at weeks 1, 2 and 4 of the treatment period for follow-up endoscopy, UGI pain assessment and assessment of other clinical parameters. Antacids were provided to patients for relief of severe pain during the first six days/ nights of therapy only, and were limited to 4 tablets per day of low acid-neutralizing capacity. Table 1 summarizes clinical assessments made throughout the trial.

Follow-up endoscopic evaluation was carried out following strict time windows (Table 1) at week 1 (Days 7-8), week 2 (Days 13-15) and week 4 (Days 26-30). Patients whose ulcers were healed at any follow-up endoscopy were considered trial completers and received no further treatment or endoscopic assessment.

Clinical Parameter	Preliminary Examination[1]	Week 1 (Days 7-8)	Week 2 (Days 13-15)	Week 4 (Days 26-30)
History	Y			
Physical Exam	Y			
Vital Signs	Y	Y	Y	Y
Adv. Events		Y	Y	Y
Con. Meds	Y	Y	Y	Y
Endoscopy	Y	Y	Y	Y
Pain Assessment	Y	Y	Y	Y
Clin. Labs.	Y	Y		Y

[1] After providing Informed Consent

Table 1. Clinical Evaluation Schedule

2.6 Primary and secondary endpoints

The **primary efficacy data** was ulcer healing at week 1, 2 or 4. Ulcer healing was defined as complete reepithelization of the ulcer crater (normal or hyperemic mucosa), documented by endoscopy. The **primary efficacy endpoint** was cumulative ulcer healing at week 4 (healed at week 1 or week 2 or week 4).

Secondary efficacy data were the severity ratings of daytime and nighttime UGI pain recorded by the patient on the daily diary card. The severity of daytime pain was recorded just prior to going to sleep at night. The severity of nighttime pain was recorded upon arising in the morning. At each follow-up visit, the physician would review the diary card

and record the most severe rating of daytime and nighttime pain since the previous clinic visit. Daytime and nighttime UGI pain were rated separately according to the following scale:

> 0 = None = I had no pain
> 1 = Mild = I had some pain, but it didn't bother me much
> 2 = Moderate = I had pain that was annoying, but it didn't interrupt my activities
> 3 = Severe = I had pain which was so bad I couldn't do my usual activities

For nighttime pain, activities reflected sleep. The **secondary efficacy endpoint** was whether the patient was free of daytime or nighttime pain at weeks 1, 2 or 4.

2.7 Conducting the investigation

When the trial was conducted, there was great pressure to complete it as quickly as possible. This was due in part to Ranitidine's rapid gains into the antiulcer market, of which C had exclusivity for several years. Approximately 60 centers were recruited. The centers were rigorously and frequently monitored for conformity to protocol and federal regulations, in an attempt to minimize violations to protocol and collection of questionable if not unusable data. Roughly half of the sites were monitored by in-house Clinical Monitoring Personnel (CRA = Clinical Research Associates). The remaining sites were monitored by an outside Contract Research Organization (CRO).

A fairly heavy advertisement campaign was initiated to recruit possible trial participants. Ads ran on television and radio and appeared in the print media. In addition circulars were posted in public areas such as supermarket and laundromat bulletin boards. The ads were targeted to adults who had been having UGI or ulcer like pain, but who were otherwise healthy.

Weekly meetings were held during the conduct of the trial to monitor progress and deal with any issues. A proactive approach to clinical data management was taken. Data collection forms (DCFs) were expressed by each clinic to the data management group (or picked up by the CRA) where they were rapidly reviewed for completeness, legibility, entered into the computerized trial database, verified and quality assured. The goal was to provide a quality assured database for statistical analysis in as short a time as possible after each patient completed the protocol.

At the time the duodenal ulcer trial was conducted, there was no commercially available 800 mg C tablet. The commercially available 400 mg C tablet was used. Therefore a blood level trial that demonstrated bioequivalence [Randolph et al, 1986a] between a new 800 mg C tablet formulation (to be marketed) and two-400 mg C commercially available tablets had to be conducted with results available by the completion of the duodenal ulcer trial. Results from these two trials as well as that from specified drug interaction studies provided the primary data to support filing a supplemental new drug application (SNDA) to the FDA for the approval of C as a single 800 mg tablet taken at bedtime for the treatment of duodenal ulcers.

2.8 Statistical analysis methods
2.8.1 Methods

Descriptive and inferential methods were used in presentations and analysis of the trial data using procedures (PROCS) in the Statistical Analysis System (SAS). Both tables and graphs reflecting the number of patients, the mean (percent for dichotomous data) and standard deviation by treatment group and time of assessment were developed.

Inferential analyses, significance tests and confidence intervals, derived from an analysis of variance model containing fixed effects of center, strata and treatment group, with contrasts specified for the pairwise comparisons of interest. P-values for the pairwise comparisons comprising the primary trial objective were used for statistical inference. Confidence intervals were used as the basis of inference for secondary trial objectives and for the three pairwise comparisons not a part of the trial objective.

Since there were many centers and relatively few patients per treatment group per strata per center were expected, 12 blocks reflecting smoking status (2 levels)-by-baseline ulcer size (6 levels) were defined *a priori* (Table 2). An analysis of variance model containing the fixed effects of blocks and treatment was also used to assess the effect of treatment adjusted for blocks.

Gereralizability (poolability) of treatment effects was assessed by running an analysis of variance model with block, treatment group and block-by-treatment interaction. In these analyses the sole interest was the P-value for the interaction term. The blocking factor was smoking status-by-baseline ulcer size as defined in Table 2. A separate analysis that included the factors: smoking status, baseline ulcer size, their interaction, and the interaction of each of these with treatment was also performed.

Light	[0.3]
Light	(0.3; 0.4]
Light	(0.4; 0.5]
Light	(0.5; 1.0)
Light	[1.0]
Light	(1.0; 3.0]
Heavy	[0.3]
Heavy	(0.3; 0.4]
Heavy	(0.4; 0.5]
Heavy	(0.5; 1.0)
Heavy	[1.0]
Heavy	(1.0; 3.0]

Table 2. Smoking Status by Ulcer Size (cm) Blocks

Bivariate plots of the proportion of patients with ulcers remaining unhealed and the proportion of patients with UGI pain (daytime or nighttime) by time of endoscopic evaluation and treatment group were developed. These plots illustrate the rate of ulcer healing and pain relief across the times of endoscopic evaluation.

2.8.2 Interim analysis

Prior to finalizing the protocol, we considered including an interim analysis plan. Incorporating such a plan could result in completing approximately ½ the planned number of patients. More importantly, it could reduce the time from starting the trial to filing the SNDA. The idea was accepted initially, but later rejected by upper management; so the final protocol did not include an interim analysis plan.

However after the trial started, there was a push to conduct an interim analysis. A plan was developed to conduct an interim (mid-study) analysis after ½ the patients had entered. The

plan was filed by in-house regulatory affairs personnel with the FDA. Essential features of the plan ensured preservation of the Type I error and safe guarded blindedness among investigators, patients, and in-house personnel. We hired an outside consulting group that generated dummy investigator, patient and treatment group identification. The group also computed the P-values associated with the 3 pairwise comparisons comprising the study objectives and reported them to FDA Biometrics and in-house statistical personnel. The trial was not stopped and ran to completion, eventually enrolling 768 patients. The final results, based upon more than twice the number of patients in the interim analysis, were similar to those of the interim analysis in terms of estimates of treatment effects.

3. Results and discussion

3.1 Interim or mid study analysis results
3.1.1 Numbers of patients and baseline characteristics
Table 3 summarizes the number of patients available for the mid-study, interim analysis. Three hundred and thirty-seven (337) were randomized of which 315 [Peace et al, 1985; Valenzuela et al, 1985] were considered evaluatable [Peace, 1984] for efficacy for at least one follow-up visit. The fact that 17 more patients were assigned to the 1600 mg C group illustrates that slight imbalance across treatment groups can occur in randomized trials consisting of many centers.

Table 4 contains descriptive results of data available at baseline for mid-study analysis patients by C treatment group. The treatment groups appear balanced in terms of demographic characteristics, UGI pain and ulcer size, although the 800 mg C group had patients with the largest ulcers.

	Total	0 mg	400 mg	800 mg	1600 mg
# Randomized	337	76	83	85	93
# Evaluatable					
Week 1	304	67	80	73	84
Week 2	235	46	63	60	66
Week 4	174	41	47	47	39
≥ 1 week	315	71	82	75	87

Table 3. Number of Patients by Treatment Group (Mid Study Analysis)

3.1.2 Distribution of patients according to ulcer size
Table 5 provides the distribution of patients at baseline according to ulcer size. Ten percent (10%) of patients had ulcers of size 0.30 cm; 12.5% had ulcers of size greater than 0.30 but at most 0.40 cm; 17.8% had ulcers of size greater than 0.40 cm but at most 0.50 cm; 27.2% had ulcers of size between 0.50 cm and 1.00 cm; 17.8% had ulcers 1.00 cm in size; and 14.7% had ulcers of size greater than 1.00 cm but at most 3.00 cm.

Table 6 provides the distribution of patients in the Placebo group by baseline ulcer size whose ulcers had healed by 4 weeks. Seventy-one percent (71%) of Placebo patients with ulcers of size 0.30 cm healed; 78% of Placebo patients with ulcers of size greater than 0.30 but at most 0.40 cm healed; 45% of Placebo patients with ulcers of size greater than 0.40 cm but at most 0.50 cm healed; 41% of Placebo patients with ulcers between 0.50 cm and 1.00 cm in size healed; 30% of Placebo patients with ulcers 1.00 cm in size healed; and 25% of Placebo patients with ulcers of size greater than 1.00 cm but at most 3.00 cm healed. Table 6

reflects a strong negative correlation (or trend) between baseline ulcer size and ulcer healing by 4 weeks; i.e. the smaller the ulcer, the greater is ulcer healing by 4 weeks.

Characteristic	Statistic	0 mg	400 mg	800 mg	1600 mg
Age (yr)	Mean	42	40	44	42
Height (in)	Mean	67	67	67	67
Weight (lb)	Mean	169	160	163	160
Sex	Male (N)	50	62	51	55
	Female (N)	26	21	34	38
Race	Caucasian(N)	44	50	58	61
	Black (N)	24	21	18	24
	Other (N)	8	12	9	8
Day Pain	Mean	2.89	3.13	2.91	2.92
Night Pain	Mean	2.68	2.84	2.80	3.05
Ulcer Size(cm)	Mean	0.76	0.71	0.85	0.75
Smoking	Heavy (N)	40	45	45	48
	Light (N)	36	38	40	45

Table 4. Baseline Characteristics (Mid Study Analysis)

Ulcer Size (cm)	% Patients
[0.30]	10.0%
(0.30; 0.40]	12.5%
(0.40; 0.50]	17.8%
(0.50; 1.00)	27.2%
[1.00]	17.8%
(1.00; 3.00]	14.7%

Table 5. Distribution by Ulcer Size - Mid Study Analysis

Ulcer Size (cm)	Healed
[0.30]	71%
(0.30; 0.40]	78%
(0.40; 0.50]	45%
(0.50; 1.00)	41%
[1.00]	30%
(1.00; 3.00]	25%

Table 6. Cumulative 4-week Ulcer Healing Rates: Mid Study Analysis Placebo Patients

3.1.3 Influence of smoking and ulcer size on ulcer healing

Figure 1 provides a summary of the cumulative proportion of patients across all treatment groups with healed duodenal ulcers by week of endoscopy and smoking status. Figure 1 reflects a strong negative correlation between smoking status and ulcer healing; i.e. light smokers have a higher percentage of healed ulcers than do heavy smokers at all weeks of endoscopy.
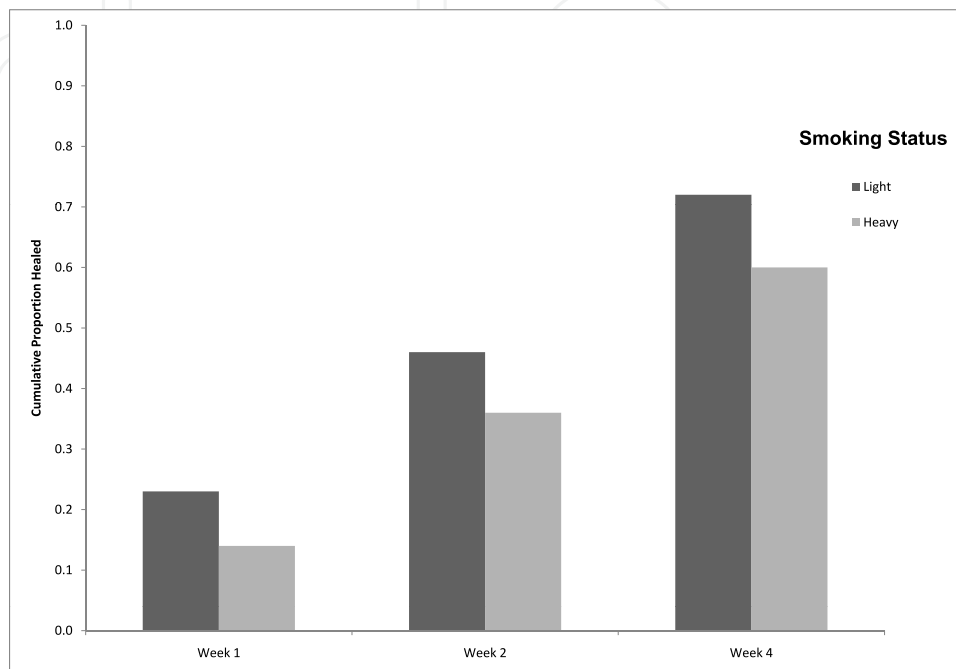

Fig. 1. Cumulative Proportion Healed: Light vs Heavy Smokers, Combined Treatment Groups
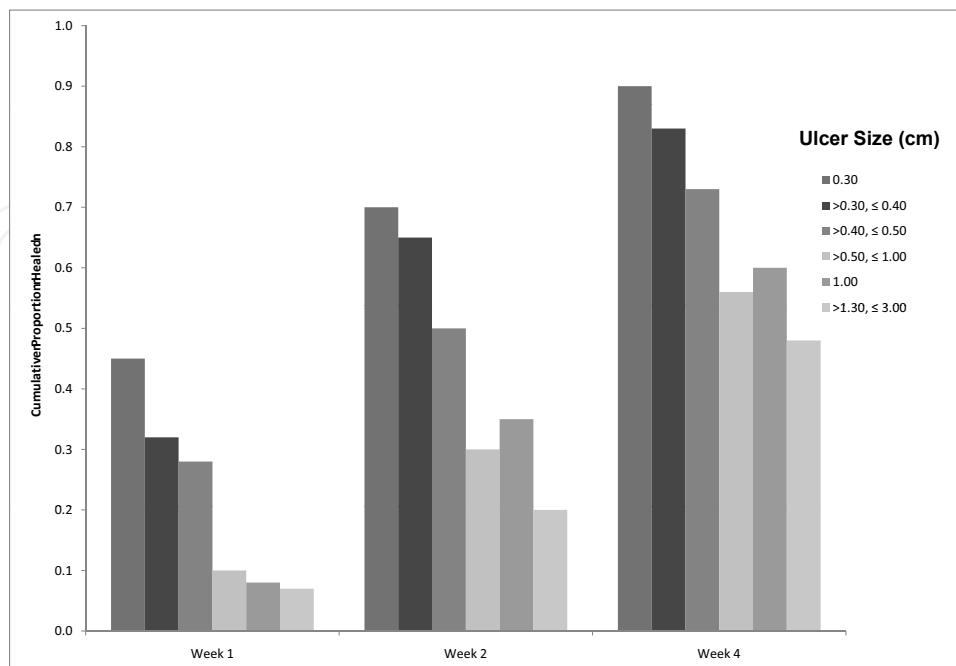
Fig. 2. Cumulative Proportion Healed by Ulcer Size, Combined Treatment Groups

Figure 2 provides a summary of the cumulative proportion of patients across all treatment groups with healed duodenal ulcers by week of endoscopy and baseline ulcer size. Figure 2 reflects a strong negative correlation between ulcer size and ulcer healing; i.e. patients with smaller ulcers have a higher percentage of healed ulcers than do patients with larger ulcers at all weeks of endoscopy. Note that the categories of ulcer size in Figure 2 are those that were defined *a priori*.

The negative correlation between ulcer size and healing is sharpened when collapsing the six ulcer size categories into three (Figure 3).
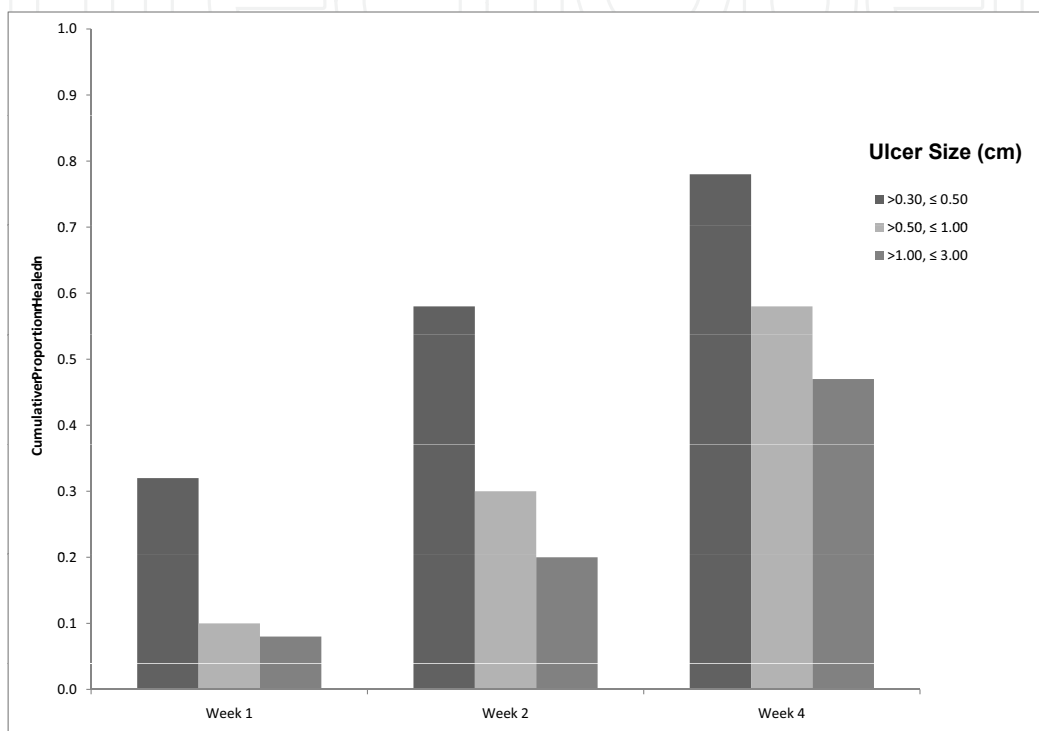
Fig. 3. Cumulative Proportion Healed by Ulcer Size, Combined Treatment Groups

3.1.4 Cumulative ulcer healing

The cumulative duodenal ulcer healing rates are summarized [Peace et al, 1985; Valenzuela et al, 1985] in Figure 4 by week of endoscopy and treatment group. The healing rates were: 19%, 18%, 16% and 21% at week 1; 29%, 37%, 38% and 49% at week 2; and 41%, 62%, 72% and 74%; for the Placebo, 400 mg C, 800 mg C and 1600 mg C groups respectively. At week 4: 800 mg C was effective (P = 0.0002) as compared to Placebo; 800 mg C was marginally superior to 400 mg C (P = 0.1283); and 1600 mg C provided no clinically significant greater benefit {δ = 0.0156: 90% CI on ratio of 1600 mg C/ 800 mg C = (0.86; 1.18)} than did 800 mg C. Even though 800 mg C healed 10% more ulcers than did 400 mg C, the P-value for this comparison did not achieve statistical significance. Therefore, the mid-study analysis did not demonstrate that 800 mg C was clinically optimal as formulated in the trial objective.

3.1.5 Generalizability assessment

Table 7 provides a summary of the assessment of generalizability (poolability) of treatment effect across smoking status, baseline ulcer size and smoking status-by-baseline ulcer size.

All of the P-values are large and therefore provide no evidence of lack of generalizability of treatment effects across these subpopulations.
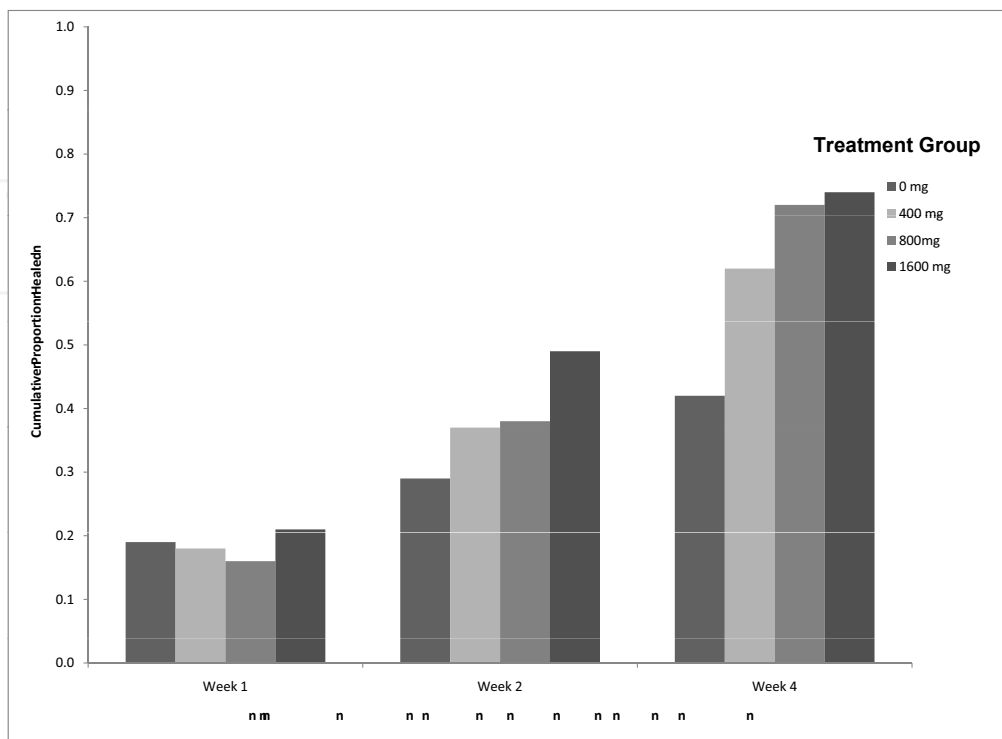

Fig. 4. Cumulative Proportion of Patients with Healed Ulcers by Week and Treatment Group

Source	F-value	P-value
Smoke x Size	1.11	0.3559
Smoke x Dose	0.40	0.7518
Size x Dose	1.12	0.3359
Smoke x Size x Dose	0.78	0.7038

Table 7. Assessment of generalizability: Smoking Status by Ulcer Size Subpopulations, Mid Study Analysis

3.1.6 Complete UGI pain relief and ulcer healing

To illustrate changes in duodenal ulcer healing and complete relief of UGI pain jointly, bivariate plots (Figure 5 and Figure 6) were generated. To develop these plots, the means (proportions) of each endpoint were computed by treatment or dose group and each endoscopy evaluation. The means, corresponding to each endoscopy evaluation and dose group identification, along with the ranges (0; 1) of each endpoint, were output to a data file. The data file was accessed by a graphical software package and a plot generated of the mean pairs by dose group. In generating the plots, the horizontal axis reflects the range of one endpoint and the vertical axis reflects the range of the other endpoint. In plotting the pairs of means for each dose group, the endoscopy evaluation corresponding to each pair appears as a floating index on the graph of each dose group.
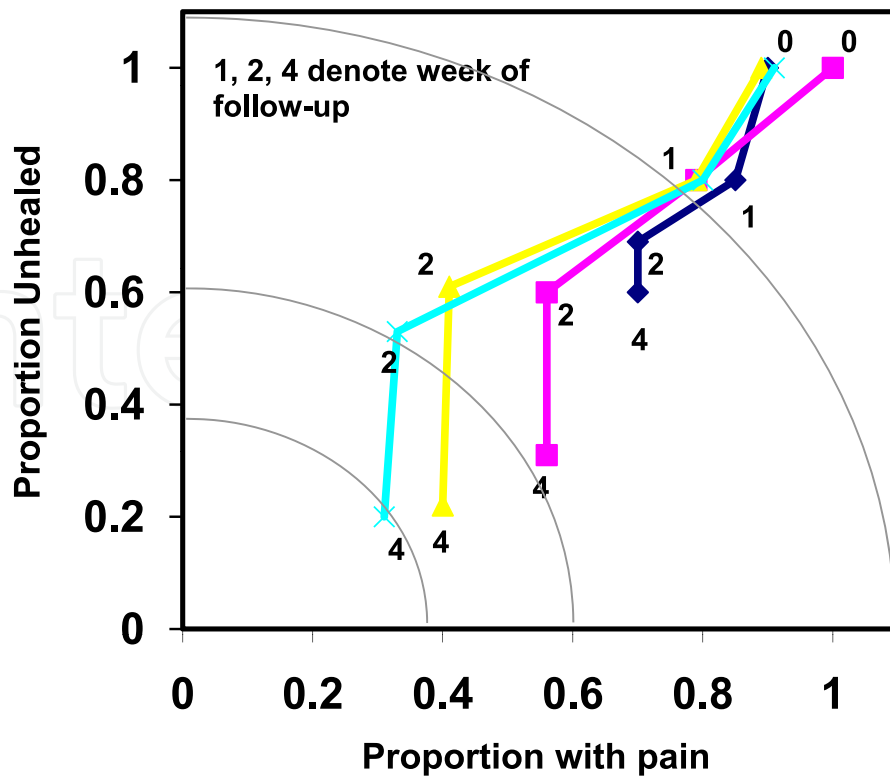
Fig. 5. Proportions of patients with Daytime Pain and Unhealed Ulcers, by Treatment Group (Mid-Study Analysis)
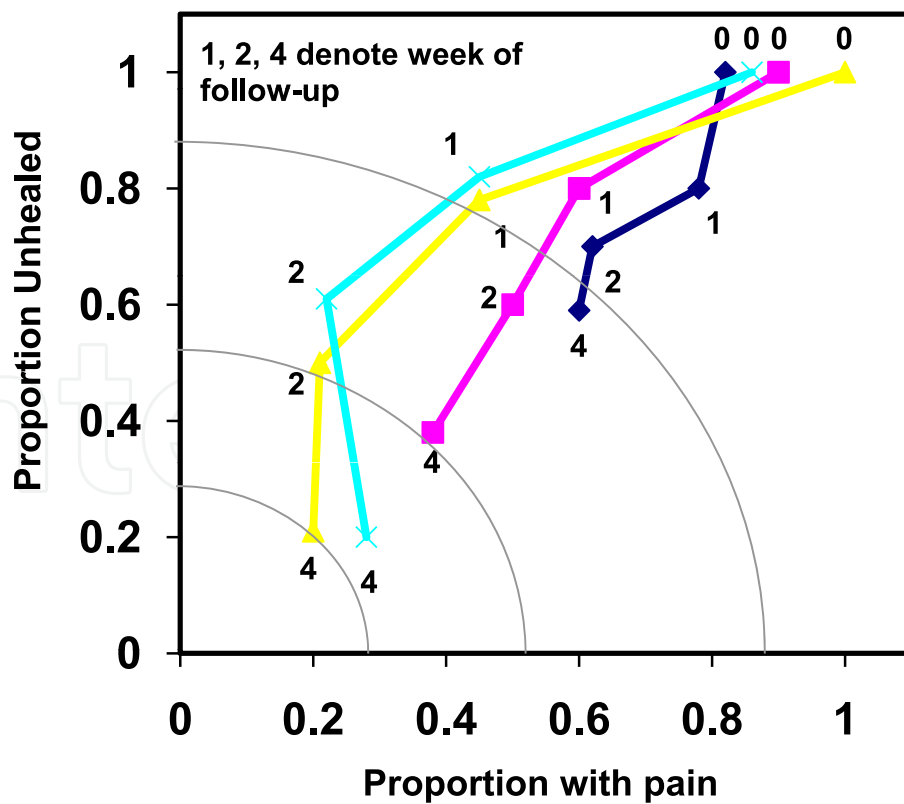

Fig. 6. Proportions of Patients with and Unhealed Nighttime Pain Ulcers, by Treatment Group (Mid-Study Analysis)

In Figures 5 and 6, the horizontal axis reflects the proportion of patients with UGI pain, and the vertical axis reflects the proportion of patients with unhealed ulcers; rather than proportions of patients without UGI pain and with healed ulcers. The (1,1) point therefore reflects where the patients are at baseline, and the (0,0) point reflects the ideal therapeutic goal of a treatment or dose by the final visit. For a broader discussion of bivariate plots, references [Peace & Tsai, 2009and Peace & Chen, 2010] may be seen.

Figure 5 is the bivariate plot of daytime UGI pain and lack of ulcer healing. Figure 6 is the bivariate plot of nighttime UGI pain and lack of ulcer healing. The fact that all dose groups do not begin at the (1,1) point is due to the fact that some patients had daytime UGI pain but not nighttime UGI pain and vice versa. Focusing on week 4 results, Figures 5 and 6 reflect a beautiful picture of dose response, both univariately and bivariately.

3.2 Final study analysis results

At the final study analysis, 168, 182, 165 and 188 patients [Young et al, 1989] were efficacy evaluatable, in the Placebo, 400 mg C, 800 mg C and 1600 mg C groups, respectively. The cumulative duodenal ulcer healing rates are summarized in Figure 7 by week of endoscopy and treatment group. The healing rates were: 17%, 16%, 15% and 21% at week 1; 30%, 40%, 42% and 48% at week 2; and 41%, 62%, 73% and 77%; for the Placebo, 400 mg C, 800 mg C and 1600 mg C groups respectively. At week 4: 800 mg C was effective ($P < 10^{-8}$) as compared to Placebo; 800 mg C was superior to 400 mg C (P = 0.023); and 1600 mg C provided no clinically significant greater benefit {$\delta = 0.04$: 90% CI on ratio of 1600 mg C/ 800 mg C = (0.96; 1.17)} than did 800 mg C. Therefore, the study demonstrated that 800 mg C was clinically optimal.
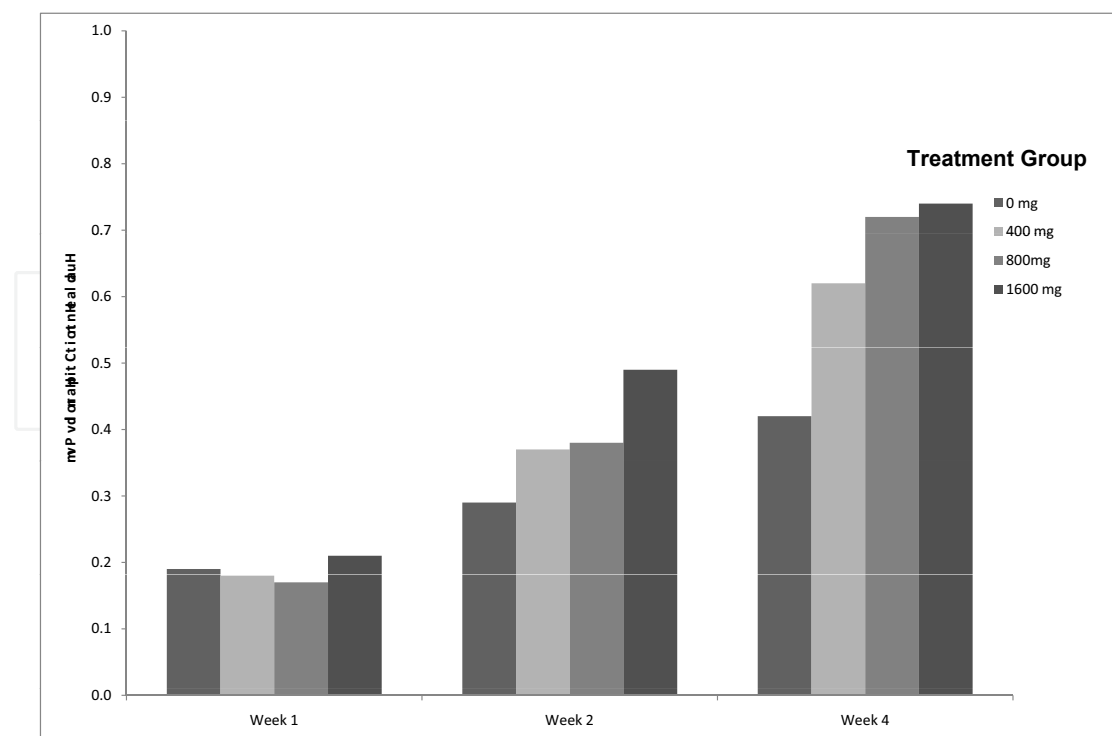

Fig. 7. Cumulative Proportion of Patients with Healed Ulcers by Week and Treatment Group (Final Study Results)

3.3 Other considerations

3.3.1 Bioequivalence trial of two-400 mg tablets and One-800 mg tablet

At the time the duodenal ulcer trial was conducted, there was no commercially available 800 mg C tablet. The commercially available 400 mg C tablet was used. Therefore a blood level trial that demonstrated bioequivalence [Randolph et al, 1986a] between a new 800 mg C tablet formulation (to be marketed) and two-400 mg C commercially available tablets had to be conducted with results available by the completion of the duodenal ulcer trial.

3.3.2 Cimetidine-by-drug interaction trials

Since C was widely prescribed (the prescription leader at the time), a change in dosage regimen, particularly a larger dose, required other trials involving the new 800 mg C regimen. We conducted specific Cimetidine-by-drug interaction trials exploring whether 800 mg C altered the circulating levels of other widely prescribed drugs. The drugs selected were Theophylline [Seaman et al, 1985; Randolph et al, 1986b; Randolph et al, 1986c] and Lidocaine [Frank et al, 1983] and Warfarin [Sax, et al, 1987].

3.3.3 Study in the elderly

At the time the duodenal ulcer trial was conducted, the FDA IND/ NDA rewrite was in progress, which among other specifics, stipulated that pharmaceutical companies should conduct studies in the elderly to explore whether doses of drugs posed a drug dose-by-age interaction. In addition, conducting clinical efficacy trials in the elderly was gaining sway. We actually developed a protocol for a small clinical trial comparing the 800 mg C to Placebo in elderly (age ≥ 65 years) patients with duodenal ulcers. The trial was to enroll 100 patients balanced across the 800 mg C and Placebo groups.

However, prior to starting the trial the author subset the final database for the trial described in this chapter and found it contained 101 elderly patients of which 19 were in the Placebo group and 23 in the 800 mg C group. Randomization in the large trial did not guarantee balance across treatment groups in this subset of elderly patients. Therefore the treatment groups were compared statistically in terms of baseline characteristics, and found to be comparable. Sixteen (16) of 23 (75.6%) elderly patients treated with 800 mg C experienced ulcer healing, as compared to 6 of 19 (32%) in the Placebo group {δ = 38%; 95% CI = (10.3%;75.6%)}. Since there was evidence in the original trial database that 800 mg C was effective in the elderly, there was no need to conduct a separate clinical efficacy trial in the elderly.

Results from the duodenal ulcer trial, the bioequivalence trial and the Cimetidine-by-drug interaction trials provided the primary data to support filing a supplemental new drug application (SNDA) to the FDA for the approval of C as a single 800 mg tablet taken at bedtime for the treatment of duodenal ulcers.

3.4 Innovative aspects of the clinical trial program

There are several aspects of this program that were rather innovative.

3.4.1 Interim analyses to drop placebo arms

Interim analyses plans that would allow dropping of the placebo arm after establishing efficacy of the doses, while allowing the dose arms to run to completion for dose discrimination, were developed.

3.4.2 Third party blinding during interim analyses

Interim analysis plans that safeguarded company personnel from knowing the identity of investigators, of patients and treatment groups were developed. These included: a. using an outside data management group who generated an analysis data set in which dummy treatment group labels, investigator id and patient id, while preserving the original randomization appeared; and b. having the outside data management group provide the blinded data set to the company statistician and to the FDA plus the file containing the IDs directly to the FDA.

3.4.3 Trial objectives as only three of six pairwise comparisons

The study objective was formulated as only 3 of six pairwise comparisons among the four dose groups while preserving the overall experiment wise Type I error across these three comparisons. The other 3 comparisons could be investigated, preferably using confidence intervals, but they should not invoke a Type I error penalty on the study objective.

3.4.4 Giving up information on center differences

Instead of using centers as a blocking factor in the primary analyses, the 12 classifications of smoking status-by-baseline ulcer size was used as the blocking factor due to small numbers of patients per treatment group per center and due to the prognostic importance of smoking status and baseline ulcer size.

3.4.5 Assessment of type of monitoring by treatment group

An assessment of differences in treatment effect between sites monitored by in-house personnel and those monitored by the CRO was conducted. There was no treatment-by-type of monitoring interaction, although the healing rates were generally lower among CRO monitored sites.

3.4.6 Association between ulcer healing and smoking status and ulcer size

The duodenal ulcer trial definitively established for the first time negative correlations between ulcer healing and smoking and ulcer healing and baseline ulcer size. Effectiveness estimates of ulcer healing were adjusted for smoking status and baseline ulcer size.

3.4.7 Utilization of bivariate graphical methods

The duodenal ulcer trial was the first to utilize bivariate plots to profile ulcer healing and UGI pain relief jointly. The plots illustrated strong dose response in terms of ulcer healing and UGI pain relief separately and jointly.

3.4.8 Establishing effectiveness based on a subset analysis

Efficacy of the 800 mg C dose was established in the elderly based on a subset analysis. The trial entered a large enough elderly population to demonstrate that 800mg C was effective in elderly. That's a plus for conducting a trial larger than necessary to establish the effectiveness of each dose.

3.4.9 Maximum use of patients screened with UGI Pain

The focus of this manuscript has been to review features of the land mark, dose comparison trial of once nightly C in the treatment of duodenal ulcer. This trial was one of three clinical

trials comprising a major clinical trial program. Each center conducted three protocols: the one discussed in duodenal ulcer, but also one in gastric ulcer and one in dyspepsia.

Patients were recruited on the basis of having experienced ulcer like symptoms including epigastric UGI pain. Those who satisfied general entry criteria and who gave consent were endoscoped. If duodenal ulcer (DU) was confirmed, they entered the DU trial. If gastric ulcer (GU) was confirmed, they entered a GU trial, and if there was no DU or GU, they entered a dyspepsia trial. This latter protocol provided a rather stringent definition of dyspepsia: Ulcer like symptoms including epigastric UGI pain not explained by the presence of DU or GU. This concurrent protocol method maximized the utility of the advertisement effort to get patients to the clinic who were experiencing ulcer like symptoms.

4. Conclusions

The SNDA clinical trial program that led to approval of clinically optimal dosing of the first H2-receptor antagonist: Cimetidine, in the treatment of duodenal ulcers has been reviewed in detail as a case study. The program included a landmark clinical trial that not only definitively established 800 mg C hs for 4 weeks as the clinically optimal dosing regimen, but also was the first to definitively establish negative associations between ulcer healing and smoking status and ulcer size, as well as the first trial to establish bivariate dose response in terms of ulcer healing and relief of UGI pain. Clinical optimality of 800 mg C hs was defined as 800 mg C being effective as compared to placebo; 800 mg C being more effective than 400 mg C; and 1600 mg C not being more effective than 800 mg C.

In addition, to make maximal use of patients screened, the program included clinical trials of the 800 mg C regimen in dyspepsia and in gastric ulcers. Further, the program also included drug interaction trials of the 800 mg C dose with widely used drugs and a bioequivalence trial of a new 800 mg C tablet compared to two, 400 mg tablets of the commercially available formulation. The bioequivalence trial was required as the clinical trial in DU was conducted using the commercially available 400 mg tablet at the time of study conduct.

Since the development of Cimetidine and other H$_2$-receptor antagonists: Ranitidine (Glaxo), Famotidine (Merck) and Zinatidine (Lilly), and the proton pump inhibitors (e.g. Prilosec and Prevacid) more is known about the causes of ulcers in the duodenum and stomach. It is now widely held that duodenal and gastric ulcers are caused by chronic use of NSAIDS: non-steroidal, anti-inflammatory medications (that decrease endogenous prostaglandin production), and by interference with the protective gastric mucosal layer from *Helicobacter pylori* infection [Thompson et al, 2010]. Current treatment consists of a combination of two antibiotics (clarithromycin and either amoxicillin or a nitroimidazole), and a proton pump inhibitor with the primary aim of eradicating H. Pylori infection [Gisbert et al, 2003]. Bismuth-based regimens are also used for second-line rescue therapy.

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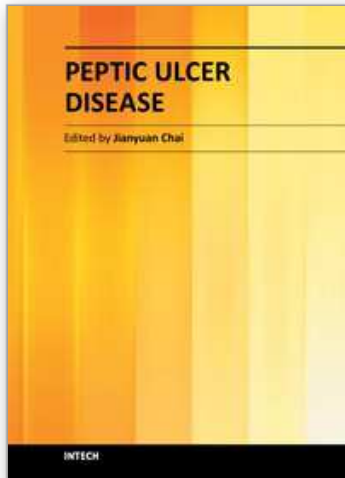
Peptic Ulcer Disease

Edited by Dr. Jianyuan Chai

Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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