Dose response relationships in clinical pharmacology
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"PHARMACOLOGICAL DOSE-RESPONSE CURVES IN GASTROINTESTINAL THERAPY"

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I. INTRODUCTION

Adequate and well controlled dose finding studies play a key role in the development of new drugs and in the evaluation of new indications for existing drugs. Hereby the range from the minimal effective dose to the maximal effective and well tolerated dose can be assessed and - as a conclusion - the optimal dose-range be defined. While careful clinical-pharmacological dose-response studies on a short term basis (single dose or infusion over several hours during one day) have been carried out in man already in the early seventies, this picture is less positive for clinical dose finding studies in gastrointestinal therapy. In fact only during the past few years different doses of an investigational drug have been compared within the same therapeutic trial.

Dose finding studies are carried out in patients with the specific disease during phase II and phase III of the clinical development. Meaningful pharmacodynamic studies can be performed also in healthy volunteers provided that a method with a high predictability for the desired therapeutic effect is available such as measurement of gastric acid secretion and its inhibition by a drug.

Dose finding studies which focus on the gastrointestinal tract can be carried out under two main aspects: First, to assess the therapeutic effect of a compound on the gastrointestinal tract (e. g. anti-ulcer drug). Second, under safety aspects, to evaluate the side effect of a drug on the gastrointestinal tract (e. g. gastric mucosal damage by non-steroidal anti-inflammatory drugs [NSAID]) and its prevention (e. g. by "cytoprotective" agents).

For the evaluation of new drugs in gastrointestinal therapy a number of methods are available which yield accurate and reproducible data. These methods are briefly described and examples for dose-response studies are given in the following sections.

II. ESOPHAGUS

Esophageal manometry

Esophageal manometry has become an established procedure for the drug evaluation in man. With this method the effect of drugs on smooth muscle in man can be investigated. Due to the direct accessibility of the esophagus the investigation is technically easy to perform and is well tolerated by the patient. For detailed description of this method we refer to the literature (Castell et al. 1987, Weihrauch 1981, 1988).

Esophageal manometry gives accurate and reproducible data of drug effects on lower esophageal sphincter pressure (LESP) and peristaltic contractions. Numerous dose finding studies have been performed in healthy volunteers as well as in patients. Since its value for drug studies has been well established during the past decade we propose the term "esophageal pharmacomanometry" for this method. Its usefulness for the evaluation of new drugs will further be increased by the fact that 24-hour ambulatory measurements with computer-assisted analysis will be available within short (Emde et al. 1988). With this technique an even more physiologic condition during the examination, a further reduction of possible irritation of the subject and quantitative analysis of the tracings will be available.

Dose-response studies have been carried out using esophageal pharmacomanometry for prokinetic and spasmolytic compounds. The prokinetic compounds which have been studied in healthy volunteers and in patients with gastroesophageal reflux disease are metoclopramide (Stanciu and Bennett, 1973, Cohen et al., 1976),

domperidone (Weihrauch et al, 1979) and cisapride (Gilbert et al., 1987). It could be shown that the lower esophageal sphincter pressure (LESP) is increased dose-dependently by rising intravenous doses of these drugs.

From the study of Stanciu and Bennett (Figure 1) a new pathophysiological conclusion could be drawn which was extremely important for the treatment of patients with reflux esophagitis: In patients with severe disease i.e. a significantly decreased lower esophageal sphincter pressure, metoclopramide increased only moderately the sphincter tonus while in patients with an intact function the increase was two to three-fold.

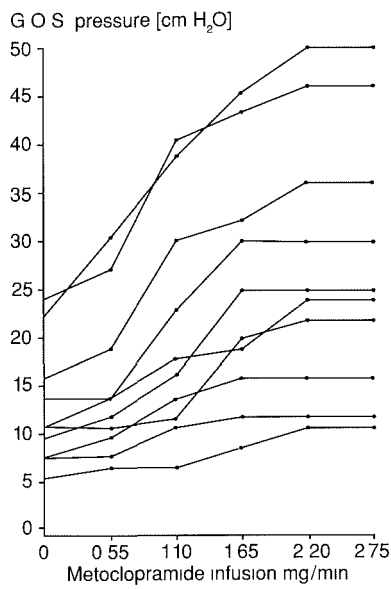

Fig. 1. Effect of rising intravenous doses of metoclopramide on lower esophageal sphincter pressure in reflux patients (Stanciu and Bennett, 1973).

Recently it could be shown by esophageal pharmacomanometry that prostaglandin E_1 and E_2-analogues do not have a negative effect on esophageal motility as it was concluded from animal studies. On the contrary in man prostaglandin analogues even increase LESP in doses which are used for ulcer treatment (Baunack et al., 1988) (Figure 2). This result is of high importance for the treatment of peptic ulcer disease in regard to drug safety. Furthermore it qualifies these prostaglandins for studies in reflux esophagitis.

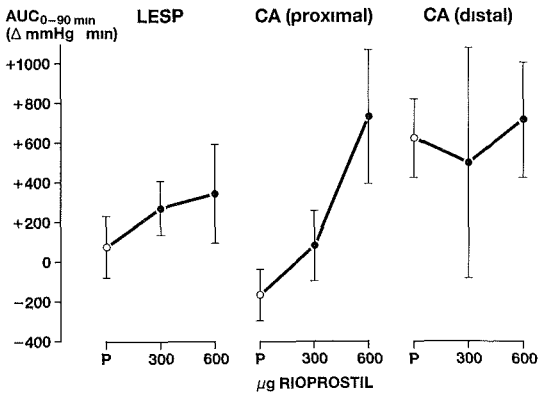

Fig. 2. Dose-related effect of 300 and 600μg of rioprostil p.o. compared to placebo on lower esophageal sphincter pressure (LESP) and contraction amplitudes (CA) of esophageal peristalsis (Baunack et al., 1988).

Spasmolytic agents: Esophageal pharmacomanometry has contributed significantly to the elucidation of the pathogenesis of primary esophageal motility disorders, e. g. diffuse esophageal spasm (DES) and achalasia as well as to their treatment. It could be shown that especially calcium-antagonists of the dihydropyridine type as nifedipine have a dose-dependent effect on esophageal motility in healthy volunteers (Baunack et al., 1985) and a positive therapeutic effect on esophageal spasms in achalasia and DES (Weihrauch, 1984).

Endoscopy

Endoscopic examinations are of great importance for dose-response studies for reflux esophagitis. As stated above only recently such studies with comparison of different doses have become available. For the quantitative assessment of therapeutic improvement by scoring a system for the severity of the lesions is used. Figure 3 shows the dose-dependent effect of cimetidine on the healing of reflux esophagitis.

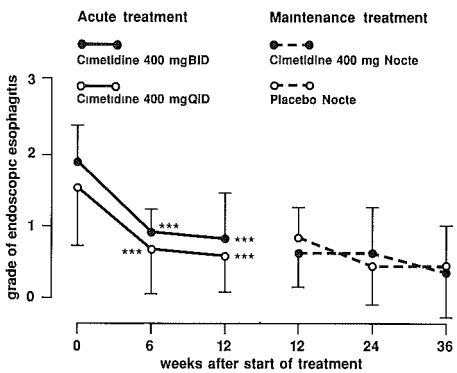

Fig. 3. Effect of different dose-regimens of cimetidine on the healing of reflux esophagitis (Kaul et al., 1986).

pH-Metry

24-hour pH-metry for the assessment of gastroesophageal reflux and the effect of drugs is being increasingly used. Portable instruments and computer assisted evaluation has improved the value of the method significantly. For the assessment of the severity of the disease and its change by the treatment essentially the frequency and the duration of reflux episodes are analysed.

Bennett et al. (1983) could show that 1 and 2 g of cimetidine influenced significantly the number of reflux episodes but not the other variables as percent time < pH 5 and 4 and mean duration of reflux episodes.

Scintiscan

The results of this method correlate well with esophageal manometry. Due to the fact, however, that radio-labelled material has to be applied its suitability for the assessment of drug effects is limited.

III. STOMACH

Gastric secretion measurement

Measurement of gastric secretion and the effect of drugs on acid output is a good example for the high value of phase I dose finding studies in healthy volunteers for the anticipated optimal therapeutic dose in patients of phase II and phase III therapeutic trials. The methods for gastric acid secretion analysis and meal-stimulated acid secretion including quantitative 24-hour measurements are well established, accurate and reproducible.

Figure 4 shows the dose-dependent effect of rioprostil on pentagastrin stimulated acid secretion in (Demol et al., 1985) comparision to placebo. Under more physiological conditions the effect of the same compound on meal stimulated acid secretion is shown (Singer et al., 1985, Schulte et al, 1987, Feldman et al., 1988).

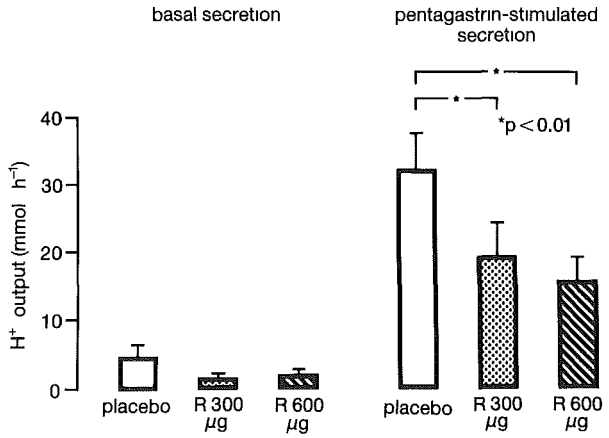

Fig. 4. Effect of rioprostil on the pentagastrin-stimulated secretion (Demol et al., 1985).

Long term monitoring of gastric pH : pH-Metrie

Prolonged measurements of gastric acidity are well suited for the evaluation of gastric antisecretory drugs. Until recently this long monitoring was done by intubation and aspiration. However, this implies repeated sampling procedures which are inconvenient and uncomfortable for the subjects. Nocturnal sampling, especially when acid secretion is inhibited by drug intake, is often impossible due to low intragastric volumes (Levin et al., 1948).

The recent development of stable, miniaturized glass electrodes and digital processing facilities has enabled the long-term reliable, safe and comfortable monitoring of intragastric pH in volunteers or patients (Fimmel et al., 1985).

The technique is very well suited for assessing the effect of antisecretory drugs on night secretion. With this technique it was shown, for example that a regimen of two doses of 300 mg of ranitidine did not lead to longer-lasting inhibition of gastric pH than two doses of 150 mg (Walt et al., 1981).
This method provides precise pH-threshold 24-h curves which give a precise indication of % reading of pH above 4 (considered as necessary for the ulcer healing) and so provide a more rational basis to compare the efficacy of different drugs.

Endoscopy (Ulcer studies)

Endoscopy is an objective way of diagnosing peptic ulcer and its healing. However, the appreciation of the size of the ulcer can vary greatly from one investigator to another. This is why the only reliable endpoint for clinical efficacy is the complete disappearance of the ulcer with or without a scar.

It is important to realize that there is a strict correlation between ulcer healing rates and the potency of a drug to suppress acid secretion. Better dose-response curves can be obtained when additionally to baseline and 4 weeks endoscopies an examination is also performed after 2 weeks.

Out of tens of large double-blind trials in patients with peptic ulcer very few have been real dose finding studies. The reason for that is that investigators use strong antisecretory doses in the first trials and then progressively reduce the dosage in successive trials.

For example 80 mg ranitidine decreases the H^+ secretion by 70 % in healthy volunteers but the usual doses applied in patients during trials are 150 mg bid or 300 mg od. Concerning famotidine, the dose of 20 mg inhibits the pentagastrine stimulated secretion by already 90 % : this explains why Gitlen et al. (1985) found no difference in the 8-weeks healing rate in DU patients when comparing 20 mg bid, 40 mg bid and 40 mg od (82, 82 and 83 % respectively).

For cimetidine, the best documented H_2-receptor-antagonist, only in 1986 a large multicenter, double-blind placebo-controlled dose finding study was published which clearly showed that in a total of 703 patients cimetidine given once at bedtime accelerates duodenal ulcer healing dose-dependently after 4 weeks (Braverman, 1986) (Figure 5).

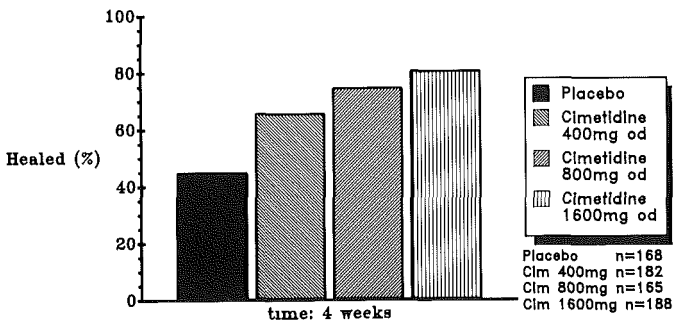

Fig. 5. Dose-dependent effect of cimetidine on 4-weeks healing rates of duodenal ulcer (redrawn from the data of Bravermann, 1986).

Another dose finding study compared different doses of enprostil with placebo at 2 and 4 weeks (Thompson, 1986).
Recently a specific blocker of the enzyme H^+ K^+-ATP ase (the gastric proton pump) in the parietal cell, omeprazole has been introduced in the therapy of peptic ulcer. This substance binds strongly for periods longer than 16 h which explains why the antisecretory effect persists a long time after the substance has disappeared from the blood stream. Moreover its antisecretory activity increases in a few days because omeprazole increases its own availability by inhibiting acid secretion (Prichard et al., 1985). These interesting characteristics explain why the antisecretory effect of omeprazole does not correlate with Cmax but with AUC in a non linear fashion (Sharma et al., 1984).

In a carefully designed dose finding study realized in 43 DU patients the administration of 20, 30, 40 or 60 mg/day induced a

healing in 90% more in the 4 groups (Brit. Coop. Study, 1984). This absence of dose-effect can be explained by the already strong inhibitory effect of 20 mg (more than 90 % in volunteers). However a linear correlation between the dose and response is observed between doses (10 to 60 mg/day) after 2 weeks of treatment (healing rates between 50 and 100 %).

Endoscopy (NSAID-lesion prevention studies)

Endoscopy is the best way to analyse the therapeutic and preventive effect of protective substances on lesions induced by non steroidal antiinflammatory drugs (NSAID). This model has been validated by several authors although different scores of lesions have been used (Lanza et al., 1980; Silverstein et al., 1980).

Several new prostaglandins have been tested prophylactically or therapeutically against the gastric lesions induced by acetylsalicylic acid (ASA). Gilbert et al. (1984) showed for a PGE_2 derivative clear dose-response between the dose of the prostaglandin and the proportion of volunteers with minimal or no gastro-duodenal lesion induced by 1.3 g of ASA.

By the endoscopic examination using a toxicity score a clear therapeutic (preventive) dose-response can be described (Tolman, et al.,1988)

Gastric emptying

This method requires application of a radio-labelled meal which limits its general use. Additionally vast interindividual variations narrow the value of this method. Therefore, its use for dose finding studies cannot be recommended. Possibly in the future gastric emptying assessment by sonography may reach the accuracy which is necessary to differentiate between doses.

A dose-response relationship could be demonstrated for cisapride (Baeyens et al., 1984).

Gastric potential difference (GPD)

Measurement of the gastric transmucosal potential difference (PD) is an easy and well tolerated technique. The GDP is a very sensitive index of the mucosal integrity.
A good correlation between the kinetic of the ASA-induced drop of PD and the percentage of damaged cells with light microscopy has been demonstrated in healthy volunteers by Baskin et al. (1976)

In volunteers we have used this technique to show a dose-dependent reduction of the area under the curve (AUC) of the PD by two doses of rioprostil of the drop following the ingestion of 0.5 g of ASA given together with rioprostil (Demol et al., 1986)

Vance et al. (1982) have demonstrated a linear correlation between the kinetic of bioavailability of ASA and the AUC of PD.

Figure 6 shows the effect of different doses of rioprostil on GPD in volunteers with concomitant ingestion of ASA.

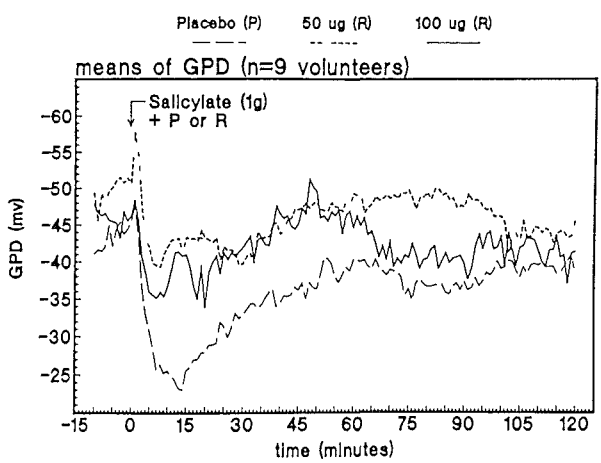

Fig. 6. Dose-dependent effect of rioprostil (R) on salicylate (S)-induced change of gastric potential difference (GPD) (Demol et al., 1986).

Fecal occult blood loss measurement

^{51}Cr-labelled red blood cells

The measurement of ^{51}Cr activity in the stool after i.v. application of ^{51}CR labelled red blood cells as a parameter for fecal occult blood loss in man is a sensitive and internationally well established method.

A dose-dependent protective effect of the PGE_1-analogue rioprostil on occult blood loss after high doses of ASA could be shown (Cohen et al., 1984).

IV. GALLBLADDER

For the evaluation of drug effects on gallbladder motility sonography is used. The total plane of the gallbladder and its changes after drug application are measured by planimetry. Experience is limited. However, first studies are promising (Hopman et al., 1985).

V. SMALL BOWEL

H_2-breath test is a very easy and useful method to measure the mouth - to - caecum transit time in volunteers or patients. However, its variability is high and is probably not reproducible enough to be used as a tool for pharmacological dose-response studies. To our knowledge no dose finding studies have been published using this method.

VI. LARGE BOWEL

Endoscopy

During the last decade two main tools for quantitative assessment of improvement of inflammatory bowel disease have become available: Fibre optic endoscopy and an improved scoring system

for inflammatory activity, the so called "activity index". Just recently a therapeutic dose-response study has been carried out (Schroder et al., 1987).

It could be shown that in comparison to placebo 1,6 g and 4,8 g of 5-ASA, respectively, influenced complete and partial healing of chronic ulcerative colitis dose-dependently (Figure 7).

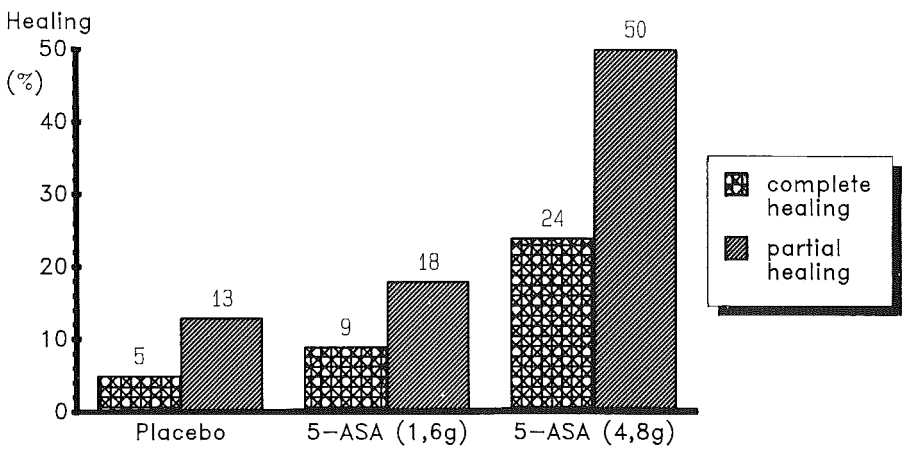

Fig. 7. Effect of oral 5-Aminosalicylic acid (5-ASA) therapy on mildly to moderately active ulcerative colitis (drawn from data of Schroder et al., 1987).

Conclusion

It is concluded that pharmacological dose-response studies in the treatment of gastrointestinal diseases have been carried out only during the past few years. Before, innumerable studies have been performed for example in peptic ulcer disease comparing one dose of the investigational drug with placebo and/or a standard drug. It is obvious that the recent change of the approach to the therapeutic evaluation of a new drug reflects also a strong impact of the requirements of the health authorities in different countries.

Various methods in clinical pharmacology with a high predictability make a first judgement on different therapeutic doses possible and should be used for new drug developments. Nevertheless therapeutic dose finding studies are ultimately necessary.

REFERENCES

Baeyens R, Reyntjens A, Verlinden M (1984)
Cisapride accelerates gastric emptying and mouth-to caecum transit of a barium meal.
Eur. J. Clin. Pharmacol. 27 (3) 315-318

Baskin WN, Ivey KJ, Krause WJ, Jeffrey GE, Gemmell RT (1976)
Aspirin-induced ultrastructural changes in human gastric mucosa. Correlation with potential difference.
Ann. Int. Med. 85, 299-303

Baunack AR, Demol P, Weihrauch TR (1985) Placebo-controlled comparison of the efficacy of the calcium antagonists Bay 1 8201 and nifedipine on the lower esophageal sphincter pressure (LESP) in volunteers. Gastroenterology 88 (5) 1319

Baunack AR, Froese G, Demol P, Wargenau M, Ruoff HJ, Weihrauch TR (1988) Effect of rioprostil, an oral prostaglandin E_1 (PGE_1) analogue, on lower esophageal sphincter pressure and on the motility of the distal esophagus in healthy volunteers.
Z. Gastroent. 26, 199-203

Bennett JR, Buckton G, Martin HD (1983) Cimetidine in gastro-oesophageal reflux. Digestion 26, 166-172

Braverman AJ (1986) Dose validation and study design criteria in current cimetidine studies. Clin. Ther. 8, Suppl. A, 49-56

British Cooperative Study (1984) Omeprazole in duodenal ulceration : acid inhibition, symptom relief, endoscopic healing and recurrence. Brit. Med. J. 289, 525-528

Castell DO, Richter JE, Boag Dalton C (1987) Esophageal motility testing. Elsevier, New York-Amsterdam-London, pp 35-78

Cohen A, Salzmann PM, Brady CL, Simon DM, McCormack GH (1984) Effect of rioprostil on aspirin induced gastrointestinal blood loss in normal volunteers. J. Clin. Pharmacol. 24, 401

Cohen S, Morris DW, Schoen HJ, DiMarino AJ (1976) The effect of oral and intravenous metoclopramide on human lower esophageal sphincter pressure. Gastroenterology 70, 484-487

Demol P, Wingender W, Weihrauch TR, Graefe KH (1985)
Inhibition of gastric secretion in man by rioprostil, a new synthetic methyl prostaglandin E_1.
Arzneim.-Forsch./Drug Res. 35, 839-843

Demol P, Schmitz HD, Weihrauch TR, Kuhlmann J (1986)
Prevention of the acetylsalicylic acid-induced changes of the gastric potential difference by the new synthetic prostaglandin E_1 analogue rioprostil.
Arzneim.-Forsch./Drug Res. 36 (II), 9, 1406-1408

Emde C, Bumm R, Kaufhold HJ, Hopert R, Bauerfeind P, Blum AL (1988) The 1st ambulatory esophageal pH-manometry device with continuous digital recording and automated-analysis-machine performance vs. human-experience. Gastroenterology 94, 114

Feldman M, Richardson CT (1988) Effect of placebo on meal-stimulated gastric acid secretion and serum gastrin concentration. Studies in healthy volunteers and duodenal ulcer patients. Dig. Dis. Sci. 33 (2), 152-156

Fimmel CJ, Etienne A, Cilluffo T, von Ritter C, Gasser T, Rey JP, Caradonna-Moscatelli P, Sabbatini F, Pace F, Buhler HW, Bauerfeind P, Blum AL (1985) Long-term ambulatory gastric pH monitoring: validation of a new method and effect of H_2-antagonists. Gastroenterology 88 (6) 1842-1851

Gilbert DA, Surawicz CM, Silverstein FE, Weinberg CR, Saunders DR, Feld AD, Sanford RL, Bergman D, Washington P (1984) Prevention of acute aspirin-induced gastric mucosal injury by 15-R-15 methyl prostaglandin E_2: an endoscopic study. Gastroenterology 86 (2) 339-345

Gilbert RJ, Dodds WJ, Kahrilas PJ, Hogan WJ, Lipman S (1987) Effect of cisapride, a new prokinetic agent, on esophageal motor function. Dig. Dis. Sci., Vol. 32, No. 12, 1331-1336

Gitlin N, Mucullough AJ, Smith JL (1985) Multiclinic double-blind dose ranging study evaluating the efficacy and safety of famotidine in the healing of active duodenal ulcer as compared to placebo. Americ. J. Gastroent. 80, 840

Hopman WPM, Kerstens PJSM, Jansen JBMJ, Rosenbusch G, Lamers CBHW (1985) Effect of graded physiologic doses of cholecystokinin on gallbladder contraction measured by ultrasonography. Gastroenterology 89, 1242-1247

Kaul B, Petersen H, Erichsen H, Myrvold HE, Grette K, Halvorsen T, Fjosne U (1986) Gastroesophageal reflux disease. Scand. J. Gastroent. 21, 139-145

Lanza FL, Royer GL, Nelson BS (1980) Endoscopic evaluation of the effects of aspirin, buffered aspirin and enteric-coated aspirin on gastric duodenal mucosa. N. Engl. J. Med. 303, 136-138

Levin E, Kirsner JB, Palmer WL, Butler C (1948) The variability and periodicity of the nocturnal gastric secretion in normal individuals. Gastroenterology 10, 939-951

Prichard PJ, Yeomans ND, Mihaly GW, Jones DB, Buckle PJ, Smallwood RA, Louis WJ (1985) Omeprazole: a study of its inhibition of gastric pH and oral pharmacokinetics after morning or evening dosage. Gastroenterology 88 (1 Pt 1), 64-69

Schulte K, Singer MV, Eysselein V, Demol P, Goebell H (1987) Effect of rioprostil, a synthetic prostaglandin E_1 on meal-stimulated gastric acid secretion and plasma gastrin levels in humans. Digestion 36, 162 - 167

Sharma BK, Walt RP, Pounder RE, Gomes M de F., Wood EC, Logan EH (1984) Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. GUT 25, 957-964

Schroder KW, Tremaine WJ, Ilstrup DM (1987) Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N. Engl. J. Med. 317, 1625-1629

Silverstein FE, Gilbert DA, Surawicz CS, Ring CE, Feld AD, Sanford RL, Saunders DR (1980) Prostaglandin E_2 (PGE_2) cytoprotection in aspirin-induced gastric mucosal injury - an endoscopic study. Am. J. Gastroent. 74, 93

Singer MV, Schulte H, Demol P, Eysselein V, Goebell H (1985) Dose response effects of rioprostil, a new synthetic methyl prostaglandin E_1 on gastric acid secretion and release of gastrin in humans. Gastroenterology 88, 1588

Stanciu C, Bennett JR (1973) Metoclopramide in gastrooesophageal reflux. GUT 14, 275-279

Thomson ABR (1986) Treatment of duodenal ulcer with enprostil, a synthetic prostaglandin E_2 analogue. Am. J. Med. Vol. 81, 59-63

Tolman KG, Detweiler MK, Harrison CA, Rollins DE, Simon DA, Brady C, McCormack GH, Bryant EC (1988) Effect of rioprostil on aspirin-induced gastrointestinal mucosal changes in normal volunteers. J. Clin. Pharmacol. 28, 76-80

Vance J, Luecker PW, Tilling W, Procaccini R, Wetzelsberger N (1982) The transmural gastric potential difference in combination with pharmacokinetic profiles. A new approach to combine kinetic and dynamic properties of compounds. Meth. Find. Exp. Cl. Ph. 4, (7) 533-538

Walt RP, Male PJ, Rawlings J, Hunt RH, Milton-Thompson GJ, Misiewicz JJ (1981) Comparison of the effects of ranitidine, cimetidine and placebo on the 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer. GUT 22 (1) 49-54

Weihrauch TR, Forster CF, Krieglstein J (1979) Evaluation of the effect of domperidone on human oesophageal and gastroduodenal motility by intraluminal manometry. Portgrad. Med. J. 55 (Suppl. 1), 7-10

Weihrauch TR (1981) Esophageal manometry. Methods and clinical practice. Urban & Schwarzenberg, Baltimore-Munich

Weihrauch TR (1984) Diagnosis and treatment of oesophageal motor disorders. Scand. J. Gastroenterol. Suppl. 19/106, 124-133

Weihrauch TR (1988) Esophageal manometry. In: Webster JG (ed.), Encyclopedia of medical devices and instrumentation. Wiley & Sons, New York, pp 1236-1245

Discussion - Pharmacological dose-response curves in gastrointestinal therapy

E. Perucca

When discussing dose-response relationships in the case of inhibitors of gastric acid secretion, the time factor should always be taken into account. Studies with H_2 antagonists may show no difference between two doses at 4 or 8 weeks, but there may be a difference at an earlier time. Do you recommend exploring the effects before 4 weeks of treatment?

T.R. Weihrauch

One tends to limit the number of explorations since endoscopies are rather unpleasant, and a study at 4 weeks is almost an standard procedure. However, with the development of the highly effective proton pump inhibitors earlier times of exploration may be considered. Perhaps an endoscopy at 2 weeks, followed by another at 4 weeks in those patients that have not healed, would be a suitable recommendation in this case.

F. García Alonso

Have you been able to correlate the rate of healing with the achieved values of gastric pH? In my experience this is not the case with drugs such as omeprazole.

T.R. Weihrauch

Healing rates correlate directly with the degree of acid secretion inhibition. This is observed in the range of 60-100% inhibition. Omeprazole tends to produce maximal inhibition and therefore the correlation may not be so apparent.

P. Simon

The likelihood of finding statistically significant differences in dose-ranging studies obviously depends on the number of patients in each group. Shall we enormously increase the number of patients in these studies or can we find something else in terms of appreciation of statistical equivalence?

L.F. Prescott

When considering rates of ulcer healing and percentage inhibition of acid secretion one cannot forget that it may be better for the patient, in the long run, to have his ulcer healed a little less quickly, but more completely. In other words, what is the important end point? Is it the ideal to have the ulcer healed in one day? Is that what we should be looking for, or what is the best efficacy profile for this type of drug? What do we want? Do we know?

T.R. Weihrauch

The end point of efficacy is really the healing of the ulcer, so that is what we are really aiming at. Although complications and even symptoms may not always strictly correlate with the presence or absence of an ulcer, we want to heal the ulcers.

B.P. du Souich

These last years there have been many papers dealing with ulcer recurrence. Do we just want to heal something quickly or are we also interested in trying to avoid also the recurrence?

T.R. Weihrauch

Your are quite right. Healing is one thing and recurrence is a different issue and there are many things to consider. Prevention of recurrence is quite a different issue from ulcer healing and many results published are contradictory. Dose-response studies are truly needed in this field.