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SYNERGISTIC COMBINATION OF A SUBSTANCE WITH GASTRIC ACID SECRETION INHIBITING EFFECT AND AN ACID DEGRADABLE ANTIBIOTIC

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SYNERGISTIC COMBINATION OF A SUBSTANCE WITH GASTRIC ACID SECRETION INHIBITING EFFECT AND AN ACID DEGRADABLE ANTIBIOTIC

Field of the Invention

The present invention relates to a combination of a substance with inhibiting effect on the gastric acid secretion, thus a substance which increases the intragastric pH e.g. proton pump inhibitors, histamin-H_2-blockers and one or more antibacterial compounds which are acid degradable.

Background of the Invention

In the treatment of the peptic ulcer disease current therapy aims at reducing the gastric acid secretion, thus resulting in a recess of the injuries in the gastro-intestinal tract. Inhibitors of the gastric acid secretion, proton pump inhibitors in particular, induce a rapid relief of pain and other symptoms associated with the ulcer disease. However, relapses of the disease is a documented fact. Since gastric antisecretory therapy only leads to reduction of the major tissue irritating factor, gastric acid, the plausible cause of the disease, Helicobacter pylori, remains mainly unaffected. (Helicobacter pylori was earlier named Campylobacter pylori.)

Helicobacter pylori is affected by certain antibiotic compounds e.g. macrolides and penicillins as has been shown in vitro and in vivo. However, these products are degraded into nonantibacterial metabolites in the

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presence of gastric acid, which drastically reduces their antibacterial efficacy.

In view of the widespread use of antimicrobial pharmaceuticals in the treatment of infectious diseases or for other purposes and the consequent emergence of drug-resistant strains, increased incidence of microbial substitution due to disturbance of the normal bacterial flora, changes in profile of infectious diseases, etc., there has been a constant demand for the development of new antimicrobial agents or combinations thereof.

Prior art

Proton inhibitors e.g. omeprazole and its pharmaceutically acceptable salts, which are used in accordance with the invention, are known compounds, e.g. from EP 5129 and EP 124495 and can be produced by known processes. From US 5093342 it is also known that omeprazole can be used in the treatment of Helicobacter infections. Further it has earlier been proposed in WO 92/04898 to use a specific antibiotic, amoxycillin, which is stabile in gastric acid, in combination with omeprazole in the treatment of duodenal ulcers. No specific test data are included in said document.

From e.g. Science, March 22, 1946, p. 359-361 it is known that if acid degradable penicillins are administered orally they will be destroyed by the acid content in the stomach.

Further it is described in Eur. J. Clin. Microbiol. Infect. Dis, August 1988, p. 566-569 that some acid degradable antibiotics are active in vitro against Helicobacter pylori.

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Outline of the invention

It has now unexpectedly been found that a combination of a substance with inhibiting effect on the gastric acid secretion, thus a substance which increases the intragastric pH e.g. proton pump inhibitors, histamin-H_2-blockers and one or more antibacterial compounds which is acid degradable give high plasma concentration of the antibiotic following oral administration.

By reducing the acidity in the stomach it is possible to markedly increase the bioavailability of acid-degradable antibiotics thus leaving more of a given dose of the compound available for local antibacterial effect as well as for absorption. Selection of narrow-spectrum antibiotics e.g. benzylpenicillin is favourable since such antibiotics have few side-effects. Due to known physico-chemical properties in general of weak bases like for instance omeprazole, the selection of weak bases e.g. erythromycin favours an increased accumulation of the antibiotic in the stomach wall and gastric crypts where the microbs e.g. Helicobacter pylori resides.

Thus, by combining the components of the present invention synergism of the antibacterial effect of antibiotic compounds is achieved resulting in an improved therapeutic efficacy.

The new combination is especially directed to the treatment of gastropathies e.g. induced by Helicobacter pylori infections. Helicobacter pylori is a gram-negative spirilliform bacterium which colonises in the gastric mucosa. Treatment with commonly used acid degradable antibiotics alone has given insufficient effect.

The combination of 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-

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2-pyridinyl)methyl]sulfinyl}-1H-benzimidazole (generic name: omeprazole) or pharmaceutically acceptable salts thereof and an acid degradable antibiotic give an especially high plasma concentration of the antibiotic following oral administration.

The salt of omeprazole according to the invention is an alkaline pharmaceutically acceptable salt. Examples of such salts include inorganic salts, such as alkali metal salts, e.g. sodium salt, potassium salt etc., alkaline earth metal salts, e.g. calcium salt, magnesium salt etc., ammonium salt, organic salts such as organic amine salts, e.g. trimethylamine salt, triethylamine salt, pyridine salt, procaine acid, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, N-methylglucamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt, phenylethylbenzylamine salt, dibenzylethylenediamine salt.

Also other proton pump inhibitors, such as lansoprazole may be used according to the invention.
The antibiotic used in the combination should be of the kind, which has a bioavailability which may be improved due to elevation of intragastric pH. It should also be an antimicrobial compound with a very narrow spectrum e.g. benzylpenicillin.

Other examples are acid degradable and acid semi-stabile macrolides e.g. erythromycin base and clarithromycin (Nakagawa et al., Chem. Pharm. Bull., 1992, 40, 725-28). Further examples are antibiotics and/or salts thereof which are pharmaceutically enginered for acid protection like for instance enteric coating (e.g. Ery-Max®).

The antibacterial activity against Helicobacter pylori as

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indicated by MIC-values of macrolides is drastically decreased with increased pH of the medium in vitro (Melanoski et al., ICAAC, 1992, abstract 713, p 229).

The combination according to the present invention can be produced in one pharmaceutical formulation comprising both active ingredients or in two separate tablets or capsules, powder, mixture, effervescence tablets or solution.

The active ingredients according to the invention are administered in the form of a pharmaceutical preparation containing the active ingredients as such (e.g. the free base in the case of erythromycin) or in the case of omeprazole also as a salt thereof in combination with a pharmaceutically acceptable carrier by the oral or parenteral route. The carrier mentioned above may be a solid, semi-solid or liquid diluent or a capsule. Compatible dosage forms include various types of tablets, capsules, granules, powders, oral liquids, injections and so on. The proportions of the active ingredient in the total composition is generally 0.1 to 100 weight percent and preferably 0.1 to 95 weight precent.

In the manufacture of a pharmaceutical preparation for oral administration, the active ingredient can be formulated with a solid particulate carrier such as lactose, sucrose, sorbitol, mannitol, starch, amylopectin, a cellulose derivative or gelatin, and a lubricating agent such as magnesium stearate, calcium stearate or polyethylene glycol wax may be further incorporated. The resulting composition is then compressed into tablets. Coated tablets or dragees can be manufactured by coating the core tablets, thus prepared, with a thick sugar solution containing gum arabic, gelatin, talc, titanium dioxide, etc. or a lacquer

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prepared using a volatile organic solvent or solvent mixture.

Soft gelatin capsules can be manufactured by filling a composition comprising the active ingredient and a known vegetable oil into capsules. Hard gelatin capsules can be manufactured by filling into capsules the granules or pellets each comprising the active ingredient and a solid particulate carrier such as lactose, sucrose, sorbitol, mannitol, potato starch, corn starch, amylopectin, a cellulose derivative or gelatin.

The dosage of omeprazole or a salt thereof and the antibiotic depends on individual needs (for example, the patient's condition, body weight, age, sex, etc.) as well as on the method of administration. Generally speaking, the oral dosage may range from 1 to 200 mg of omeprazole per day and up to 10 g of acid degradable antibiotic per adult human. Each may be administered in one to a few divided doses.

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Pharmacological tests

Benzylpenicillin was administered alone to eight healthy volunteers and in combination with omeprazole and the plasma concentration was measured. When benzylpenicillin was administered alone the plasma concentrations were insufficient for a therapeutical effect (Table 1). When benzylpenicillin was combined with omeprazole therapeutical useful plasma concentrations were reached (Table 2). Similar results were obtained after oral administration of erythromycin lactobionate prior and after omeprazole induced reduction of acid secretion in man (Tables 3 and 4). Semidegradable macrolides, e.g. Ery-Max® and clarithromycin are absorbed to a certain

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extent (Tables 5 and 7). However, after administration of an acid secretion inhibitor, omeprazole, a marked increase of the bioavailability of the macrolides is shown as indicated by the difference in C_{max} and AUC in healthy volunteers (Tables 6 and 8). Compare also Fig. 1 and Fig. 2 showing the accurate plasma concentrations of Ery-Max® and clarithromycin with and without omeprazole. The high plasma concentrations of the antibiotics after reduction of the gastric acid secretion is evidence for a great reduction of the degradation in the stomach of the antibiotics used. This results in an increased amount of the active antibiotic in the gastric lumen, thus resulting in increased local antimicrobial effect. It also leads to a larger amount of the antibiotic available for absorption, thus resulting in increased plasma and tissue levels of the antibiotic (increased bioavailability). The best mode of carrying out the invention at present is to combine omeprazole with erythromycin.

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Concentration in plasma of benzylpenicillin after oral administration Dose 1.0 g.

Table 1 (without omeprazole)

Person number	Plasma concentration mg/L									Cmax mg/L	AUC H.mg /L
	15′	30′	45′	1 h	1.5 h	2 h	3 h	4 h	6 h		
1	0.24	0.50	0.54	0.41	0.22	0.135	0.074	<0.02	<0.02	0.54	0.81
2	0.53	1.60	1.47	1.24	0.52	0.30	0.14	0.063	<0.02	1.60	2.06
3	0.23	0.51	0.45	0.37	0.21	0.11	0.051	0.016	<0.02	0.51	0.69
4	0.076	0.23	0.20	0.15	0.084	0.053	0.044	0.023	<0.02	0.23	0.38
5	0.26	0.50	0.41	0.40	0.28	0.17	0.071	0.042	<0.02	0.50	0.84
6	0.33	0.37	0.26	0.20	0.099	0.051	0.038	<0.02	<0.02	0.37	0.48
7	0.17	0.26	0.23	0.17	0.14	0.075	0.027	<0.02	<0.02	0.26	0.39
8	0.104	0.125	0.124	0.121	0.062	0.050	0.021	<0.02	<0.02	0.125	0.24
Mean value	0.24	0.51	0.46	0.38	0.20	0.118	0.058	<0.03	<0.02	0.52	0.74
± S.D.										0.46	0.58

Cmax:tdep=4.163 P<0.01

AUC:tdep=5.553 P<0.001

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Concentration in plasma of benzylpenicillin after oral administration Dose 1.0 g.

Table 2 (with omeprazole)

Person number	Plasma concentration mg/L									Cmax mg/L	AUC H.mg/L
	15′	30′	45′	1 h	1.5 h	2 h	3 h	4 h	6 h		
1	0.89	2.98	3.25	3.41	3.74	2.79	0.89	0.70	0.25	3.74	9.54
2	0.73	2.80	5.51	5.74	2.26	1.62	0.84	0.76	0.28	5.74	9.52
3	1.40	6.24	9.85	9.75	6.59	1.67	0.53	0.30	0.061	9.85	13.20
4	0.11	0.72	1.22	3.05	7.57	5.59	2.94	0.45	0.094	7.57	12.80
5	0.64	2.48	2.45	2.10	1.95	1.10	0.46	0.25	0.054	2.48	4.82
6	1.24	3.22	3.65	3.57	1.42	0.84	0.55	0.33	0.074	3.65	5.78
7	0.33	0.83	1.43	1.52	1.17	0.87	0.45	0.21	0.074	1.52	3.34
8	0.62	1.37	2.31	2.35	2.54	1.37	0.48	0.23	0.041	2.54	5.00
Mean value	0.745	2.58	3.71	3.94	3.41	1.98	0.89	0.40	0.116	4.64	8.00
± S.D.										2.87	3.79

Cmax:tdep=4.163 P<0.01

AUC:tdep=5.553 P<0.001

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Concentration in plasma of erythromycin lactobionate after oral administration. Dose 1.0 g.

Table 3 1(2) Without preceding omeprazole treatment

Subject number	Serum levels in mg/L at indicated times									
	0	15′	30′	45′	1 h	1.5 h	2 h	3 h	4 h	6 h
1	<0.015	0.015	0.15	0.29	0.28	0.20	0.18	0.13	0.091	0.047
2	<0.015	0.26	0.33	0.30	0.25	0.25	0.18	0.15	0.16	0.070
3	<0.015	0.042	0.22	0.21	0.24	0.14	0.13	0.12	0.86	0.049
4	<0.015	0.032	0.042	0.030	0.039	0.078	0.084	0.076	0.072	0.046
5	<0.015	0.023	0.13	0.16	0.16	0.15	0.14	0.12	0.082	0.051
6	<0.015	0.068	0.12	0.094	0.11	0.098	0.077	0.074	0.059	0.034
7	<0.015	0.57	0.98	0.75	0.68	0.43	0.37	0.32	0.27	0.088
8	<0.015	0.071	0.27	0.33	0.23	0.16	0.16	0.12	0.095	0.044
Mean value	<0.015	0.135	0.28	0.27	0.25	0.18	0.165	0.14	0.11	0.054
± S.D.		±0.193	±0.30	±0.22	±0.19	±0.11	±0.092	±0.078	±0.070	±0.017

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Concentration in plasma of erythromycin lactobionate after oral administration. Dose 1.0 g.

Table 3 2(2) With preceeding omeprazole treatment

Subject number	Serum levels in mg/L at indicated times									
	0	15′	30′	45′	1 h	1.5 h	2 h	3 h	4 h	6 h
1	<0.015	2.9	7.5	7.6	7.2	4.9	4.0	3.1	3.5	1.4
2	<0.015	2.3	6.8	5.7	4.5	5.3	3.6	3.3	3.2	1.4
3	<0.015	2.7	12.7	10.9	7.8	6.0	5.3	4.5	4.0	2.4
4	<0.015	3.2	6.0	3.3	2.5	1.9	2.8	2.4	2.4	0.82
5	<0.015	0.25	2.8	6.4	4.8	3.0	2.5	2.0	2.8	1.2
6	<0.015	1.5	4.9	3.4	2.7	1.6	1.8	1.6	2.1	0.89
7	<0.015	6.3	9.8	9.3	6.2	5.3	4.6	4.6	3.9	1.8
8	<0.015	3.8	12.8	13.0	11.1	10.7	7.3	5.6	4.3	2.2
Mean value	<0.015	2.87	7.91	7.45	5.85	4.84	3.99	3.39	3.28	1.51
± S.D.		±1.77	±3.60	±3.46	±2.86	**±2.89**	±1.76	±1.40	±0.79	± 0.58

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Table 4

Kinetic data following oral administration(s) of erythromycin lactobionate to 8 healthy volunteers with and without co-administration of omeprazole. A cross over study.

Omeprazole	C_{max} mg/L mean ± SD	T_{max} h median	AUC H.mg/L 0-6 H
YES	8.38 ± 0.28	0.5	21.74 ± 8.64
NO	0.32 ± 0.28	0.75	0.83 ± 0.55

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Blood serum levels of erythromycin Ery-Max® following oral administration. Dose 500 mg.

Table 5 1(2) Without preceeding omeprazole treatment.

Subject number	Serum levels in mg/L at indicated times (min)									
	0	30 m	60 m	90 m	120 m	150 m	180 m	300 m	480 m	720 m
1	0.00	0.06	0.06	0.06	0.12	0.28	1.90	0.76	0.15	0.06
2	0.00	0.06	0.06	0.06	0.06	0.06	0.06	0.65	0.19	0.06
3	0.00	0.06	0.06	0.06	0.06	0.08	0.75	0.49	0.20	0.06
4	0.00	0.06	0.06	0.06	0.06	0.16	0.43	0.92	0.25	0.07
5	0.00	0.06	0.06	0.06	0.06	0.25	0.95	1.50	0.45	0.07
6	0.00	0.06	0.06	0.06	0.06	0.06	0.06	0.52	0.17	0.06
7	0.00	0.06	0.10	0.38	0.41	0.68	1.10	0.46	0.20	0.06
8	0.00	0.06	0.06	0.06	0.51	1.20	1.70	0.86	0.31	0.06
Mean	0.00	0.06	0.07	0.10	0.17	0.35	0.87	0.77	0.24	0.06
Sdev	0.00	0.00	0.01	0.11	0.18	0.40	0.69	0.34	0.10	0.01

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Blood serum levels of erythromycin Ery-Max® following oral administration. Dose 500 mg.

Table 5 2(2) Without preceeding omeprazole treatment.

Subject number	AUC levels at indicated times (min)										
	0	30 m	60 m	90 m	120 m	150 m	180 m	300 m	480 m	720 m	Tot AUC
1	0	0.015	0.03	0.03	0.045	0.1	0.545	2.66	1.365	0.42	5.21
2	0	0.015	0.03	0.03	0.03	0.03	0.03	0.71	1.26	0.5	2.635
3	0	0.015	0.03	0.03	0.03	0.036	0.208	1.24	1.035	0.52	3.144
4	0	0.015	0.03	0.03	0.03	0.055	0.148	1.35	1.755	0.646	4.059
5	0	0.015	0.03	0.03	0.03	0.078	0.3	2.45	2.925	1.036	6.894
6	0	0.015	0.03	0.03	0.03	0.03	0.03	0.58	1.035	0.46	2.24
7	0	0.015	0.04	0.12	0.198	0.273	0.445	1.56	0.99	0.52	4.16
8	0	0.015	0.03	0.03	0.143	0.428	0.725	2.56	1.755	0.74	6.425
Mean	0	0.015	0.031	0.041	0.067	0.129	0.304	1.639	1.515	0.605	
Sdev	0	0.015	0.004	0.032	0.066	0.145	0.25	0.827	0.647	0.202	

AUC: 4.34 ± 1.7

C_{max}: 1.005

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Blood serum levels of erythromycin Ery-Max® following oral administration. Dose 250 mg.

Table 6 1 (2) With preceeding omeprazole treatment.

Subject number	Serum levels in mg/L at indicated times (min)									
	0	30 m	60 m	90 m	120 m	150 m	180 m	300 m	480 m	720 m
1	0.00	0.06	0.54	3.2	2.4	2.3	1.9	0.79	0.22	0.06
2	0.00	0.06	0.06	0.1	0.69	2.1	1.7	0.54	0.14	0.06
3	0.00	0.06	0.29	1.2	2.5	2.5	1.4	0.75	0.23	0.06
4	0.00	0.06	0.06	0.094	0.84	0.74	0.37	1.3	0.45	0.081
5	0.00	0.06	0.06	0.059	0.58	1.5	1.7	1.6	0.5	0.084
6	0.00	0.06	0.068	0.49	1.2	0.86	0.68	0.48	0.14	0.06
7	0.00	0.06	0.057	1.1	1.3	2	2.1	0.87	0.27	0.087
8	0.00	0.06	0.48	1.4	1.9	1.6	1.7	1	0.28	0.084
Mean	0.00	0.06	0.20	0.96	1.43	1.7	1.44	0.92	0.28	0.07
Sdev	0.00	0.00	0.21	1.06	0.76	0.65	0.61	0.38	0.13	0.01

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Blood serum levels of erythromycin Ery-Max® following oral administration. Dose 250 mg.

Table 6 2(2) With preceeding omeprazole treatment.

Subject number	AUC levels at indicated times (min)										
	0	30 m	60 m	90 m	120 m	150 m	180 m	300 m	480 m	720 m	Tot AUC
1	0.00	0.015	0.15	0.935	1.4	1.175	1.05	2.69	1.515	0.56	9.49
2	0.00	0.015	0.03	0.04	0.198	0.698	0.95	2.24	1.02	0.4	5.59
3	0.00	0.015	0.088	0.373	0.925	1.25	0.975	2.15	1.47	0.58	7.825
4	0.00	0.015	0.03	0.039	0.234	0.395	0.278	1.67	2.625	1.062	6.347
5	0.00	0.015	0.03	0.03	0.16	0.52	0.8	3.3	3.15	1.168	9.173
6	0.00	0.015	0.032	0.14	0.423	0.515	0.385	1.16	0.93	0.4	3.999
7	0.00	0.015	0.029	0.289	0.6	0.825	1.025	2.97	1.71	0.714	8.187
8	0.00	0.015	0.0135	0.47	0.825	0.875	0.825	2.7	1.92	0.728	8.493
Mean	0.00	0.015	0.065	0.289	0.595	0.782	0.786	2.36	1.793	0.702	
Sdev	0.00	0.00	0.052	0.31	0.434	0.312	0.295	0.703	0.764	0.284	

AUC: 7.38 ± 1.9

C_{max}: 1.94

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Blood serum levels of clarithromycin following oral administration. Dose 250 mg.

Table 7 1(2) Without preceeding omeprazole treatment.

Subject number	Serum levels in mg/L at indicated times (min)									
	0	30 m	60 m	90 m	120 m	150 m	180 m	360 m	660 m	840 m
1	0.00	0.11	0.97	0.92	1.1	1.5	1.2	0.96	0.41	0.26
2	0.00	0.12	0.15	0.24	0.28	0.36	0.47	0.53	0.18	0.14
3	0.00	0.06	0.11	0.092	0.11	0.12	0.17	0.55	0.2	0.12
4	0.00	0.06	0.06	0.044	0.099	0.13	0.15	0.48	0.23	0.13
5	0.00	0.06	0.06	0.062	0.064	0.13	0.18	0.54	0.2	0.16
6	0.00	0.07	0.13	0.2	0.3	0.37	0.45	0.23	0.14	0.082
7	0.00	0.12	0.26	0.27	0.46	0.81	0.78	0.64	0.2	0.12
8	0.00	0.06	0.31	0.38	0.41	0.55	0.57	0.64	0.27	0.16
Mean	0.00	0.08	0.26	0.28	0.35	0.50	0.50	0.57	0.23	0.15
Sdev	0.00	0.03	0.30	0.28	0.34	0.47	0.36	0.20	0.08	0.05

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Blood serum levels of clarithromycin following oral administration. Dose 250 mg.

Table 7 2(2) Without preceeding omeprazole treatment.

Subject number	AUC levels at indicated times (min)										
	0	30 m	60 m	90 m	120 m	150 m	180 m	360 m	660 m	840 m	Tot AUC
1	0.00	0.028	0.27	0.473	0.505	0.65	0.675	2.16	4.11	1.005	9.875
2	0.00	0.03	0.068	0.098	0.13	0.16	0.208	1	2.13	0.48	4.303
3	0.00	0.015	0.043	0.051	0.051	0.058	0.073	0.72	2.25	0.48	3.739
4	0.00	0.015	0.03	0.026	0.036	0.057	0.07	0.63	2.13	0.54	3.534
5	0.00	0.015	0.03	0.031	0.032	0.049	0.078	0.72	2.22	0.54	3.713
6	0.00	0.018	0.05	0.083	0.125	0.168	0.205	0.68	1.11	0.333	2.771
7	0.00	0.03	0.095	0.133	0.183	0.318	0.398	1.42	2.52	0.48	5.575
8	0.00	0.015	0.093	0.173	0.198	0.24	0.28	1.21	2.73	0.645	5.583
Mean	0.00	0.021	0.085	0.133	0.157	0.212	0.248	1.068	2.4	0.563	
Sdev	0.00	0.007	0.079	0.146	0.154	0.201	0.207	0.525	0.838	0.199	

AUC: 4.88 ± 2.24

C_{max}: 0.68

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Blood serum levels of clarithromycin following oral administration. Dose 250 mg.

Table 8 1(2) With preceeding omeprazole treatment.

Subject number	Serum levels in mg/L at indicated times (min)									
	0	30 m	60 m	90 m	120 m	150 m	180 m	360 m	660 m	840 m
1	0.00	1.9	2.3	2.2	1.7	1.7	1.7	0.86	0.37	0.28
2	0.00	0.078	3	1.9	1.9	1.9	1.7	0.78	0.34	0.16
3	0.00	0.6	1.6	1.3	1.1	1.1	1.05	0.68	0.23	0.14
4	0.00	0.06	1.2	1.3	1.2	1.03	1.1	0.68	0.39	0.2
5	0.00	0.096	2.1	1.6	1.3	1.1	1.1	0.77	0.27	0.18
6	0.00	0.21	1.2	1.8	1.6	1	1.5	0.67	0.22	0.13
7	0.00	0.12	0.99	1.1	0.9	0.89	1.07	0.61	0.22	0.16
8	0.00	1.07	2.2	2	2	1.7	1.8	0.92	0.38	0.24
Mean	0.00	0.52	1.82	1.65	1.46	1.30	1.38	0.75	0.30	0.19
Sdev	0.00	0.66	0.69	0.39	0.40	0.39	0.33	0.11	0.08	0.05

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Blood serum levels of clarithromycin following oral administration. Dose 250 mg.

Table 8 2(2) With preceeding omeprazole treatment.

Subject number	AUC levels at indicated times (min)										
	0	30 m	60 m	90 m	120 m	150 m	180 m	360 m	660 m	840 m	Tot AUC
1	0.00	0.475	1.05	1.125	0.975	0.85	0.85	2.56	3.69	0.975	12.55
2	0.00	0.02	0.77	1.225	0.95	0.95	0.9	2.48	3.36	0.75	11.4
3	0.00	0.15	0.55	0.725	0.6	0.55	0.538	1.73	2.73	0.555	8.128
4	0.00	0.015	0.315	0.625	0.625	0.558	0.533	1.78	3.21	0.885	8.545
5	0.00	0.024	0.549	0.925	0.725	0.6	0.55	1.87	3.12	0.675	9.038
6	0.00	0.053	0.353	0.75	0.85	0.65	0.625	2.17	2.67	0.525	8.645
7	0.00	0.03	0.278	0.523	0.5	0.448	0.49	1.68	2.49	0.57	7.008
8	0.00	0.268	0.818	1.05	1	0.925	0.875	2.72	3.9	0.93	12.49
Mean	0.00	0.129	0.585	0.868	0.778	0.691	0.67	2.124	3.146	0.733	
Sdev	0.00	0.165	0.275	0.251	0.192	0.191	0.174	0.416	0.499	0.18	

AUC: 9.7 ± 2.1

C_{max}: 1.9

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Discussion

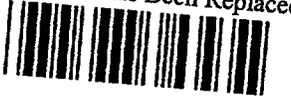
The advantage of the present combination of a compound that increases the intragastric pH, such as omeprazole and an acid degradable antibiotic, is that the bioavailability of the antibiotic will increase resulting in sufficient plasma levels for therapeutic effects. Another advantage is that there will be increased amounts of the acid degradable antibiotic in the gastric lumen.

Benzylpenicillin is interesting because it has a very narrow spectrum and therefore exerts a very limited effect on the normal intestinal flora.

By reducing the gastric acid secretion or acid neutralisation in the stomach the pH increases. Due to the less acidic millieu the orally administered acid degradable antibiotic will be less catabolized and thus locally exerting its antimicrobial effect. Another advantage is that increased amounts of the antibiotic will pass into the small intestine where it will be absorbed in biologically active form. Increasing the intragastric pH is also favourable for antibiotic efficacy as shown in vitro. If the pH of the medium where Helicobacter pylori is grown in vitro is reduced varying degrees below pH 7 the antibacterial properties rapidly decrease.

Those antibiotics which are weak bases e.g. macrolides will be excreted via the stomach wall due to its physico-chemical properties in congruence with other known weak bases i.e. nicotine, aminopurine and omeprazole (Larsson et al., Scand. J. Gastroenterol., 1983, 85, 900-7). Thus, the antibiotic weak base will be biologically concentrated in the stomach wall, where the bacterias (e.g. Helicobacter pylori) reside.

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CLAIMS

1. The combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH and an acid degradable antibacterial compound.

2. The combination according to claim 1 wherein the substance with inhibiting effect on the gastric acid is a proton pump inhibitor.

3. The combination according to claim 2 wherein the proton pump inhibitor is 5-methoxy-2-{[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof.

* C L M S *

4. The combination according to claim 1 with effect on gastritis and peptic ulcer caused by microbes.

5. The combination according to claim 1 with effect on gastritis and peptic ulcer caused by Helicobacter pylori.

6. The combination according to claim 1 characterized in that the acid degradable antibacterial compound is benzyl-penicillin.

7. The combination according to claim 1 characterized in that the acid degradable antibacterial compound is weak base antibiotics.

8. The combination according to claim 7 characterized in that the weak base antibiotic is erythromycin base.

9. The combination according to claim 7 characterized in that the antibiotic is clarithromycin.

10. Use of the combination according to claim 1 for the manufacture of a medicament for the treatment of gastritis and peptic ulcer caused by Helicobacter pylori.

11. A method for the treatment of gastritis and peptic

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ulcer caused by Helicobacter pylori comprising oral administering to a patient suffering therefrom a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH together with an amount of an acid degradable antibacterial compound sufficient for the treatment of said infection.

12. A pharmaceutical preparation for use in the treatment of gastritis and peptic ulcer caused by Helicobacter pylori infections wherein the active ingredients are a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH and an acid degradable antibacterial compound.

13. A process for the preparation of a combination according to claim 1 whereby a substance with inhibiting effect on the gastric acid secretion, which increases the intragastric pH is incorporated into the same preparation as an acid degredable antibacterial compound.

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* C L M S *