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ORIGINAL REPORT

The Safety of Ranitidine Bismuth Citrate in Controlled Clinical Studies

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SUMMARY

Ranitidine bismuth citrate (PYLORID™, TRITEC®) is a novel drug which heals peptic ulcers and when co-prescribed with either clarithromycin or amoxycillin eradicates *Helicobacter pylori*. In controlled clinical studies it was well-tolerated when given alone or when co-prescribed with either antibiotic. Data from 20 clinical studies are reported in this analysis of safety with almost 5000 patients having received ranitidine bismuth citrate (200, 400, or 800 mg twice daily). The incidence of adverse events reported with this new drug, either alone or with an antibiotic, was not different from or lower than in patients given placebo and was independent of the dose of ranitidine bismuth citrate tested. Most commonly reported events (>1% of patients) were upper respiratory tract infection, constipation, diarrhoea, nausea and vomiting, dizziness, and headache, the latter being the only event reported by >2% of patients who received ranitidine bismuth citrate alone. Adverse events considered by the clinical investigator to be adverse reactions occurred with a similar frequency amongst patients given ranitidine bismuth citrate (8%), ranitidine hydrochloride (6%), or placebo (6%). The incidence of adverse reactions was greater when co-prescribed with amoxycillin (11%) or clarithromycin (20%) although it was not different from that noted with the antibiotics alone. Serious adverse events were reported in similar proportions of patients given placebo, ranitidine bismuth citrate alone or with an antibiotic, and ranitidine hydrochloride (range: <1–2%). The safety profile of ranitidine bismuth citrate was thus comparable to that of ranitidine hydrochloride (ZANTAC™), a drug with a well-established record of safety in clinical use.

KEY WORDS — ranitidine; bismuth; safety; controlled clinical trial; peptic ulcer; *Helicobacter pylori*

INTRODUCTION

Ranitidine bismuth citrate is a novel salt of ranitidine with a complex of bismuth and citrate which has unique chemical and physical properties.[1,2] It has the gastric antisecretory activity of ranitidine and the mucosal protective and anti-*Helicobacter* properties of bismuth.[1,3] Ranitidine bismuth citrate alone provides effective healing and symptom relief, both in duodenal ulcer disease[4,5] and gastric ulcer disease.[6] When co-prescribed with clarithromycin[7–10] or amoxycillin[11,12] it eradicates *H. pylori* and, as a consequence, reduces the risk of ulcer recurrence.

To assess the safety of ranitidine bismuth citrate, analyses of adverse events, laboratory data and physical findings were conducted for patients in the clinical development programme undertaken to register this new medicine.

CLINICAL EXPERIENCE

Safety data were collected from all studies conducted to support the clinical development programme. These comprised 20 clinical trials, including those in which ranitidine bismuth citrate was used alone (monotherapy) and in conjunction with an antibiotic (co-prescription studies), and a number of other studies.

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The *monotherapy* programme comprised four studies in patients with duodenal ulcer[4,5] and one in patients with gastric ulcer.[6] All studies with ranitidine bismuth citrate (200, 400 or 800 mg twice daily) were comparative with ranitidine hydrochloride (150 mg or 300 mg twice daily), a drug with an established safety profile.[13,14] Two studies also included placebo and bismuth citrate treatment arms. The duration of treatment in these clinical trials was 4–8 weeks. A total of 5605 patients from the monotherapy programme were included in the analysis of safety.

The *co-prescription* studies included a 2-week pilot study in *H. pylori*-positive patients who received ranitidine bismuth citrate 800 mg bd plus one or two of a number of different antibiotics.[15] In eight subsequent studies the efficacy and safety of ranitidine bismuth citrate in combination with either clarithromycin[7–10] or amoxycillin[11,12] was investigated. In these, patients were randomized to treatment with ranitidine bismuth citrate 400 mg twice daily or ranitidine bismuth citrate 400 mg or 800 mg twice daily plus antibiotic. In addition, four of the co-prescription studies were placebo-controlled and also had a treatment arm where patients received antibiotic alone. Treatment with ranitidine bismuth citrate was for 4 weeks with the antibiotic given during the first 2 weeks of the total 4-week treatment period. Included in the safety analysis were 1562 patients from this part of the clinical development programme.

Of the six other studies, one compared suppression and eradication of *H. pylori* with ranitidine bismuth citrate 800 mg twice daily or placebo given for 4 weeks to *H. pylori*-positive patients.[16] A second 4-week study examined the effect of giving twice daily ranitidine bismuth citrate 400 mg before or after food in patients with *H. pylori* infection.[17] Two comparative studies were of ranitidine bismuth citrate 800 mg and ranitidine hydrochloride 150 mg, both given twice daily, for treatment of non-steroidal anti-inflammatory drug (NSAID)-associated gastric or duodenal ulceration or severe erosions. Finally, two studies were of prevention of NSAID-associated ulcer in which patients were randomized to receive twice daily doses of ranitidine bismuth citrate 400 mg, ranitidine hydrochloride 150 mg, bismuth citrate, or placebo. In all four studies patients continued to take NSAIDs. Studies of healing of NSAID-associated ulcer were of 4 to 12 weeks' duration; both studies of prevention involved treatment with ranitidine bismuth citrate for 12 weeks. These six additional studies contributed 1903 patients to the analysis of safety, 1623 of whom participated in the NSAID studies.

Definitions

An *adverse event* was defined as any untoward clinical happening experienced by a patient in association with the study drug treatment, irrespective of whether or not the clinical investigator considered the event to be causally related to treatment. The investigator assessed the causal relationship to the study drug for each event using the following categories: almost certainly, probably, possibly, unlikely or unrelated to treatment.

A *serious adverse event* was defined as any event which was fatal, life-threatening, disabling or incapacitating, which resulted in or prolonged hospitalization, any congenital anomaly, cancer or overdose. Investigators were asked to provide an opinion of what caused the event: the study drug, lack of efficacy, withdrawal of study drug, concurrent medication, concurrent disorder, or another specified cause.

An *adverse reaction* was defined as any adverse event that the clinical investigator regarded as possibly, probably, or almost certainly related to the study drug or had an unknown or missing causality.

Total clinical trial experience

The total safety population (i.e. patients in the study who received at least one dose of study medication) consisted of 9070 patients. Of these, 4985 received treatment with ranitidine bismuth citrate, equalling 340 patient-years' exposure to the drug. As previously mentioned, four of the studies included patients who continued to receive NSAIDs. Since this confounds interpretation of the safety profile of ranitidine bismuth citrate alone, data from these studies are excluded from the analyses described in following four sections of the text relating to frequencies of events.

Adverse event rates

During treatment, the overall incidence of patients reporting adverse events was higher in those who received placebo than in those who received ranitidine bismuth citrate either alone or with an antibiotic with the exception only of when the drug was co-prescribed with clarithromycin 500 mg tds. The incidence of adverse events reported by

Table 1 — Adverse event rates

Treatment	Proportion of patients reporting adverse event(s) (%)
Placebo	33
Placebo + NSAID	56
Ranitidine hydrochloride — 150 mg bd, 300 mg bd	24
Ranitidine hydrochloride — 150 mg bd + NSAID	49
Ranitidine bismuth citrate — 200 mg bd	19
— 400 mg bd	25
— 800 mg bd	16
Ranitidine bismuth citrate — 400 mg bd, 800 mg bd + NSAID	56
Ranitidine bismuth citrate — 400 mg bd + amoxycillin 500 mg qds	26
— 800 mg bd + amoxycillin 500 mg qds	20
— 400 mg bd + clarithromycin 250 mg qds	29
— 800 mg bd + clarithromycin 250 mg qds	28
— 400 mg bd + clarithromycin 500 mg tds	39

patients who received ranitidine bismuth citrate alone was comparable to the incidence with ranitidine hydrochloride, and there was no evidence of a dose-related effect (Table 1). The incidence of adverse events by body system is shown in Fig. 1. The most commonly reported adverse events were upper respiratory tract infection, constipation, diarrhoea, nausea and vomiting, dizziness, and headache (Table 2). Diarrhoea was more commonly reported by patients who received the drug with amoxycillin (7%) or clarithromycin (8%) but, in patients who received placebo alone, this was reported at a similar incidence. Disturbance of taste was reported by some patients who received clarithromycin alone (11%) or co-prescribed with ranitidine bismuth citrate (6%).

Adverse reactions

Adverse events, assessed blind by the investigator, were assigned as adverse reactions at a similar frequency for placebo, ranitidine bismuth citrate

Table 2 — Most commonly reported adverse events with ranitidine bismuth citrate (% of patients)

Adverse event	Placebo ($n = 502$)	Ranitidine bismuth citrate ($n = 3548$)	Ranitidine hydrochloride ($n = 1740$)	RBC + amoxycillin ($n = 372$)	RBC + clarithromycin ($n = 348$)	Amoxycillin ($n = 61$)	Clarithromycin ($n = 120$)
Headache	8.0	4.5	6.0	5.6	6.9	3.3	7.5
Diarrhoea	4.6	1.9	2.0	7.0	8.0	3.3	7.5
Constipation	1.8	1.5	0.6	0	0.3	0	0
Nausea and vomiting	3.4	1.5	1.1	3.0	3.2	0	1.7
Dizziness	0.8	1.5	1.0	0.8	1.1	3.3	2.5
Upper respiratory tract infection	1.6	1.3	1.5	1.6	0.9	0	1.7

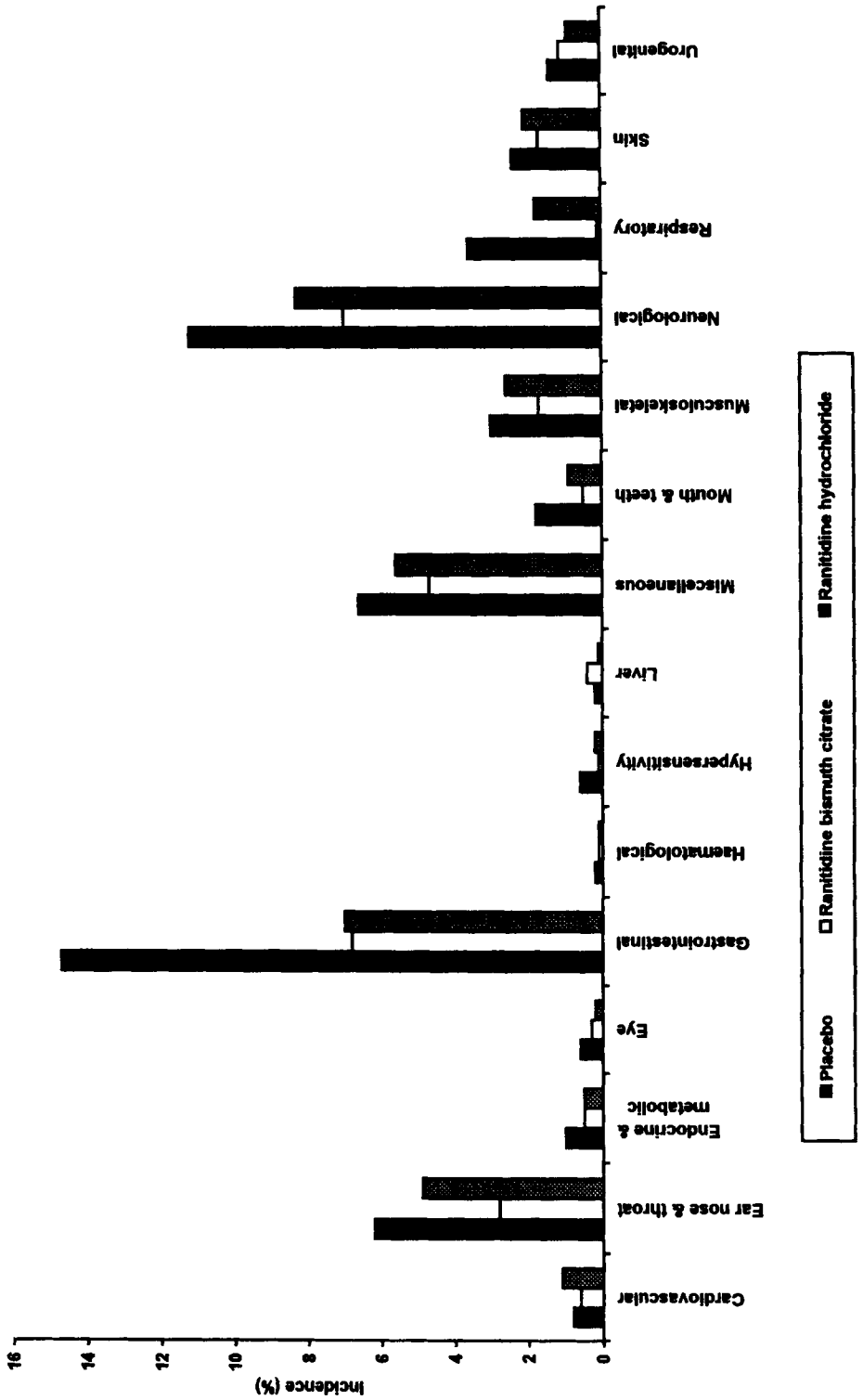

Fig. 1 — Incidence of adverse events by body system

alone, and ranitidine hydrochloride (Table 3). There was no evidence of a dose-related effect of ranitidine bismuth citrate and no individual adverse reaction was reported by more than 2% of patients who received it. The incidence of adverse reactions was higher when the drug was co-prescribed with amoxycillin or clarithromycin. This is accounted for by diarrhoea which was assessed as drug-related in 6% of patients who received ranitidine bismuth citrate with amoxycillin or clarithromycin, and disturbance of taste with clarithromycin (ranitidine bismuth citrate with clarithromycin — 6%, clarithromycin alone — 11%).

Table 3 — Incidence of adverse reactions as assessed by the clinical investigator

Treatment	Incidence of adverse reactions (%)
Placebo	6
Ranitidine hydrochloride — 150 mg bd, 300 mg bd	6
Ranitidine bismuth citrate	
— 200 mg bd	9
— 400 mg bd	8
— 800 mg bd	7
Ranitidine bismuth citrate	
— + amoxycillin	11
— + clarithromycin	20

Withdrawals due to adverse events

The number of patients withdrawn from studies due to an adverse event was low and similar with ranitidine bismuth citrate 200 mg bd (4.6%), 400 mg bd (3.0%) and 800 mg bd (3.9%), ranitidine hydrochloride (3.0%), and placebo (2.4%). There was no dose-related effect in patients who received ranitidine bismuth citrate alone. The frequency of withdrawals was similar in patients who received amoxycillin (4%) or clarithromycin (3%) co-prescribed with ranitidine bismuth citrate 400 mg bd or 800 mg bd. Collectively, gastrointestinal adverse events most commonly led to withdrawal, but due to the low incidence, there was no clear evidence that any one particular adverse event led to withdrawal.

Serious adverse events

The incidence of serious adverse events was similar in those who received placebo (1.6%), ranitidine bismuth citrate (1.2%), ranitidine bismuth citrate with amoxycillin (0.5%) or with clarithromycin (0.6%), or ranitidine hydrochloride (1.2%). No individual event was reported in more than 1% of patients in any treatment group, and given this low incidence, no clear pattern could be identified. The most frequently experienced serious adverse events were gastrointestinal disorders. These were of a diverse nature reported in a similar incidence in all treatment groups and not unexpected for the study population. Only nine patients who received ranitidine bismuth citrate had a serious adverse event assessed as drug-related. Of these, three patients who received ranitidine bismuth citrate alone reported itching or rash. One patient with a history of allergy to erythromycin experienced anaphylactic shock when given ranitidine bismuth citrate 400 mg bd plus clarithromycin 500 mg tds. Two patients had elevated plasma transaminase concentrations (AST and ALT), one patient had received ranitidine bismuth citrate 800 mg bd, the other ranitidine bismuth citrate 400 mg bd plus amoxycillin 500 mg qds. One event, described as unusual behaviour, occurred in a patient with a history of personality disorder during treatment with ranitidine bismuth citrate 800 mg bd. Diabetic ketosis was reported in one patient who was taking ranitidine bismuth citrate 800 mg bd. One patient receiving ranitidine bismuth citrate 200 mg bd reported dizziness which resolved on withdrawal of the drug.

Deaths. Fourteen died during the course of the clinical programme, which in the case of the co-prescription studies included a 6-month post-treatment follow-up period. Seven received ranitidine bismuth citrate (three in monotherapy studies, two in co-prescription studies, two in NSAID studies), five received ranitidine hydrochloride, one received placebo, and one received bismuth citrate. None of the deaths was assessed as drug-related.

Only two patients died during treatment with ranitidine bismuth citrate; one due to an acute myocardial infarction and the other due to accidental drowning. Post-treatment, three of the five patients who died did so a substantial period after the last dose of ranitidine bismuth citrate and were unlikely to be associated with treatment. Three of these patients died due to cardiovascular disease, one due to respiratory failure, and the fifth due to an overdose of a non-study drug.

Of the five patients who received ranitidine hydrochloride, two died during treatment (one due to cardiac arrest and the other due to respiratory insufficiency) and three died post-treatment (one due to liver cancer, one due to cardiovascular collapse and the other due to heart failure).

Demographic variables

Age. In the total safety population, 7558 patients were <65 years old and 1512 patients were $\geqslant 65$ years old. Sub-analyses showed that during treatment with ranitidine bismuth citrate alone, there was little difference in the overall incidence of adverse events reported by younger (26%) compared with older patients (29%). The incidence of adverse events was higher in the older population who received ranitidine bismuth citrate co-prescribed with amoxycillin (36% versus 23%). In contrast, it was higher in the younger population who received co-prescription with clarithromycin (33% versus 28%). Therefore, there was no apparent overall effect of age on the adverse event profile.

Gender. The total safety population included 5642 male patients and 3428 female patients. There was evidence that more female than male patients reported adverse events whilst receiving placebo, ranitidine hydrochloride, and ranitidine bismuth citrate alone or co-prescribed with an antibiotic. The incidence of adverse events reported by female patients was approximately 10% higher than that reported by male patients. This was apparent during treatment, with reports of arthralgia and headache, and post-treatment, gynaecological adverse events. There was no apparent difference in other individual adverse events between male and female patients.

Laboratory data

Routine haematology and biochemistry were carried out on entry to a clinical study, and at each visit during the study. The result obtained for each test parameter was compared with a pre-defined set of laboratory threshold ranges which lie outside the normal range and represent a change of potential clinical significance.

The incidence of laboratory values falling outside the threshold range was similar in patients who received ranitidine bismuth citrate alone and ranitidine hydrochloride, but lower with placebo. There was no evidence of a dose-related effect of ranitidine bismuth citrate on individual parameters and there was no evidence of a detrimental effect when ranitidine bismuth citrate 400 mg bd was co-prescribed with amoxycillin 500 mg qds or clarithromycin 500 mg tds. The incidence of changes in laboratory values was slightly higher when ranitidine bismuth citrate 400 mg bd was co-prescribed with clarithromycin 250 mg qds and when ranitidine bismuth citrate 800 mg bd was co-prescribed with clarithromycin 250 mg qds or amoxycillin 500 mg qds.

Use in renal and hepatic impairment

Renal impairment. One hundred and thirty-eight patients were identified as having some degree of renal impairment on entry to the study, defined by raised pre-study urea and/or creatinine (urea, $>1.25\times$ upper limit of normal; creatinine, $>1.30\times$ upper limit of normal). There was an uneven spread of these patients between the different treatment groups and therefore the value of comparisons is limited. Adverse events were reported in a similar incidence with ranitidine bismuth citrate (20%) and ranitidine hydrochloride (24%) and there was no evidence of an increased frequency of events in patients who received ranitidine bismuth citrate with either amoxycillin (20%) or clarithromycin (29%). Consistent with that reported in the total safety population the majority of adverse events during treatment were gastrointestinal, the incidence being similar with ranitidine bismuth citrate (12%) or ranitidine hydrochloride (10%).

A change in laboratory values for patients with renal impairment was defined as a change from normal pre-treatment values to outside the threshold range during treatment, or, a pre-treatment value above threshold which worsened during treatment.

The overall incidence of changes in laboratory values (all standard biochemical and haematological determinations) was similar in patients who received ranitidine bismuth citrate (63%) and those who received ranitidine hydrochloride (57%). There was no evidence of an increase in the frequency of changes in laboratory values in patients who received ranitidine bismuth citrate with an antibiotic.

Hepatic impairment. This was defined by a raised pre-study value in at least one of the following; bilirubin (> 1.5 × upper limit of normal), alkaline phosphatase (> 1.25 × upper limit of normal), AST (> 2 × upper limit of normal), ALT (> 2 × upper limit of normal), or GGT (> 2 × upper limit of normal).

Four hundred and sixty-one patients were included in this population. The majority received ranitidine bismuth citrate (224 patients) or ranitidine hydrochloride (100 patients), therefore limiting the value of comparisons between all treatment groups.

Adverse events were reported in a similar incidence with ranitidine bismuth citrate (28%), ranitidine hydrochloride (23%) and placebo (30%). In patients who received the drug with amoxycillin or with clarithromycin the frequency of events was 11% and 20% respectively. As in the total safety population during treatment, gastrointestinal disorders, headache, and miscellaneous disorders (e.g. disturbance of taste) were reported in a similar incidence by patients who received ranitidine bismuth citrate or ranitidine hydrochloride. The incidence of changes in laboratory data was greater in this population compared with the total clinical population, although there was a similar pattern.

Other safety evaluations

Discoloured tongue and dark stools. Discolouration of the tongue and darkening of stools (due to the formation of bismuth sulphide in the gut) are recognized effects associated with bismuth-containing drugs. Pre-treatment the incidence of discoloured tongue was low and similar in all treatment groups (range: < 1–2%). As expected, the incidence during treatment was higher in patients who received ranitidine bismuth citrate (range: 6–13%) than in any other treatment group, although there was no dose-related effect. Post-treatment, the incidence returned to pre-treatment levels or less in all treatment groups (range: < 1–2%).

Dark stools were reported before treatment in a similar incidence in all treatment groups (range: 1–9%). The incidence during treatment, not unexpectedly, was substantially higher in patients who received ranitidine bismuth citrate (range: 78–88%) compared with other treatment groups. There was a dose-related trend. Post-treatment the incidence of dark stools returned to pre-treatment levels or lower in all groups (range: 2–6%).

PREGNANCY

Eleven patients in the clinical development programme became pregnant — six received ranitidine bismuth citrate. Of these, four had a normal pregnancy with a healthy neonate, and one had a voluntary and uneventful termination. The sixth patient, who had received ranitidine bismuth citrate 800 mg bd for 4 weeks during the first trimester gave birth to a child with polydactyly (five fingers on the right hand). The child was otherwise healthy without other congenital abnormality. There was neither a maternal nor a paternal history of congenital abnormalities although two of three previous pregnancies had resulted in unexplained spontaneous abortion. Experience with ranitidine hydrochloride in pregnancy is limited, but it is not known to cause congenital abnormality. Similarly, little is known about the safety of bismuth salts in pregnancy although anecdotal reports of exposure failed to identify any evidence of toxicity.[18–20]

TROUGH PLASMA BISMUTH CONCENTRATIONS

As part of the clinical development of ranitidine bismuth citrate, blood samples were collected in nine studies to monitor trough plasma bismuth concentrations (i.e. concentrations approximately 12 h after dosing).

Plasma bismuth concentrations were determined in over 2100 patients who received ranitidine bismuth citrate alone or with an antibiotic.[21] The median plasma bismuth concentration in patients treated for 4 weeks with ranitidine bismuth citrate 400 mg twice daily was 2 ng/ml (95th percentile: 8 ng/ml, range from below quantification limit (0.2 ng/ml) to 84 ng/ml). Plasma bismuth concentrations and urinary excretion of bismuth returned to pre-dosing levels within 3 months of completing a 4- or 8-week course of treatment with ranitidine bismuth citrate.

Similar plasma bismuth concentrations after 4 weeks' treatment with ranitidine bismuth citrate 400 mg twice daily were found in male and female subjects. There was a tendency for higher concentrations when ranitidine bismuth citrate 400 mg twice daily was co-prescribed with clarithromycin

(median, 95th percentile; range: 6 ng/ml, 39 ng/ml, up to 91 ng/ml).

The systemic pharmacokinetics of ranitidine and bismuth during 28 days' dosing with high-dose ranitidine bismuth citrate have also been studied in healthy volunteers.[22] After multiple doses of ranitidine bismuth citrate 800 mg bd, bismuth concentrations in plasma approached steady state within 14–28 days. Bismuth absorption from ranitidine bismuth citrate was limited (less than 0.5% of the amount taken) and peak plasma bismuth concentrations did not exceed 19 ng/ml in any subject. Bismuth was measurable in minute concentrations in plasma for up to 5 months after dosing.

CONCLUSIONS

The management of peptic ulcer disease has undergone considerable change with the recognition that eradication of *H. pylori* infection markedly reduces ulcer recurrence. Early studies of eradication of *H. pylori* were predominantly of treatment regimens including a bismuth salt plus two antibiotics. Bismuth-containing compounds were used because of their known ulcer-healing and antibacterial properties. Combinations of colloidal bismuth subcitrate with, for example, metronidazole and tetracyline consistently provided high *H. pylori* eradication rates. Such triple therapies are, however, associated with poor patient compliance due to complex dosing regimens and frequent adverse drug reactions.

Ranitidine bismuth citrate is a new drug developed specifically for use in *H. pylori* eradication. It is a novel compound which provides the anti-*H. pylori* properties of bismuth and the gastric acid suppression associated with ranitidine. When co-prescribed with certain antibiotics, e.g. clarithromycin, it both heals duodenal ulcers and eradicates *H. pylori*.[7–12]

Historically, concern over the safety of bismuth-containing compounds has been focused primarily on the possibility of neurotoxicity. The unexplained 'epidemics' of the 1970s in France and Australia, where ingestion of bismuth subnitrate or bismuth subgallate was associated with neurotoxicity, have been reviewed extensively.[e.g. 23–27] In general, neurological symptoms were associated with prolonged use of excessively high oral doses of these salts of bismuth. Other adverse effects associated with bismuth intoxication include renal failure and disorders of the bones and joints.[23]

During the clinical development of ranitidine bismuth citrate no evidence of bismuth toxicity was noted. Indeed, the safety profile of ranitidine bismuth citrate was comparable to that of placebo and of ranitidine hydrochloride. There were no dose-related effects seen on adverse event or laboratory data. There was also no overall effect on the incidence of adverse events reported with ranitidine bismuth citrate co-prescribed with amoxycillin or clarithromycin although a slight increase in the frequency of events considered by the clinical investigator to be related to treatment was found. The only effects identified as clearly associated with ranitidine bismuth citrate were dark stools and, less frequently, discolouration of the tongue, findings expected with compounds containing bismuth.

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