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Influence of ulcer healing agents on ulcer relapse after discontinuation of acute treatment: a pooled estimate of controlled clinical trials

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SUMMARY Whether or not the incidence of ulcer relapse varies according to the drug used to produce initial healing is a controversial matter. We tackled this problem using data from 15 eligible trials from 25 published controlled trials in patients followed up for six to 12 months. Pooled estimates of differences in ulcer relapse incidence between patients initially healed with H_2-antagonists and patients initially healed with non-H_2-antagonist drugs were calculated. The overall incidence of relapse in patients healed with comparator drugs is 11 percentage units lower at six and 12 months, than that observed in H_2-antagonist-healed patients. The confidence intervals are $\pm 8\%$ at six months and $\pm 7\%$ at 12 months. These data suggest the existence of a different effect on relapse incidence for the entire class of comparator drugs taken as a whole, compared with H_2-antagonists. On considering the non-H_2-antagonists singly, this conclusion holds good only in the case of tripotassium dicitrato bismuthate.

It is only in this decade that investigators have started to tackle the vexed question as to whether or not the incidence of ulcer relapse varies according to the drug used to produce initial healing. In other words, do the various mechanisms of action of ulcer healing agents have different effects on the likelihood of ulcer recurrence? For obvious reasons the healing agents used to date as controls in comparative studies against other anti-ulcer drugs have mainly been cimetidine and, to a lesser extent, ranitidine. Relatively few controlled comparative trials have been published on this subject: eight *versus* colloidal bismuth (tripotassium dicitrato bismuthate, TDB),[1–8] three *versus* sucralfate,[9–11] six *versus* antacids,[12–17] three *versus* carbenoxolone,[18–20] two *versus* pirenzepine,[21 22] two *versus* trithiozine,[23 24] and one *versus* doxepin.[25] The number of patients studied in each of these trials has usually been too small, however, for any of the trials, taken singly, to yield generally convincing results. Moreover, the different trial designs, the substantial variability of reporting styles and, sometimes, the poor quality of reporting, the uncertainty as to the representativity of the samples studied, and the conflicting results obtained make it difficult to define the impact of different anti-ulcer drugs on the incidence of relapse.

The aim of the present study, too, was to compare the relapse incidence observed in patients initially healed with H_2-antagonists and that observed in patients initially healed with other anti-ulcer agents. The method used, however, differs from that of traditional reviews, which tend to be all too liable to reviewer subjectivity, in that it is a method which, according to the principles of meta-analysis,[26 27] is based on a weighted pooled estimate of the results of the individual trials.

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Methods

SCANNING OF THE LITERATURE

Papers were retrieved by scanning of the literature (including abstracts) in the form of both computer aided (Medline, EMBASE, Pascal) and ordinary

informal searches. When data were insufficient, other details were solicited (and obtained in all cases but one) by correspondence with the authors.

SELECTION OF PAPERS

Data on incidence of relapse were taken from trials matching up to the following criteria: (1) comparator drug of specific, well proven anti-ulcer efficacy; (2) no fewer than 10 patients followed up after ulcer healing in at least one of the treatment groups; (3) follow up of at least six months' duration; (4) duodenal or prepyloric ulcer site (as assessed by endoscopy); (5) initial healing obtained with a single drug and not with a combination of anti-ulcer agents; (6) no maintenance treatment, even with placebo, in the posthealing follow up period; and (7) reports (whether full papers or abstracts) matching up to not less than six of the nine criteria proposed by Gardner *et al*[28] in the *British Medical Journal* regarding the optimal characteristics of a controlled trial.

STATISTICAL ANALYSIS

In assessing the clinical outcome of patients treated with the H_2-antagonist and of those treated with the comparator anti-ulcer agent in each of the selected trials, we considered the incidence of ulcer relapse six months and 12 months after healing, as reported by the authors. To evaluate the difference between drugs in each study in terms of incidence of relapse, we calculated the algebraic difference between the two relapse incidences and its 95% confidence interval based on a standard approximate method.[29]

All eligible studies were included in the meta-analysis. For the purposes of pooling the results of all trials, Cochran's weighted method[30] was applied to the difference between relapse incidences in each trial. Furthermore, studies were classified in terms of whether the relapse incidence observed in patients coming from H_2-antagonist treatment showed an above 10% difference compared with that observed in patients coming from comparator drug treatment. The results of this classification were compared with the theoretical result expected if between treatment differences were equal to 0 (two tailed sign test).[31]

Results

The 10 studies which were not eligible for our review on the basis of the exclusion criteria outlined above are listed in Table 1, while Table 2 gives the descriptive characteristics of the 15 eligible trials.

The following table (Table 3) gives the distribution of the trials classified according to whether the relapse incidences in the various treatment groups compared showed differences of more than 10%.

The Figure represents graphically, for each study, the difference between the relapse incidence in patients initially healed with the H_2-antagonist and that in the patients healed with the comparator drug, together with the respective 95% confidence interval. The overall difference between ulcer relapse incidences, together with the respective 95% confidence interval, has also been calculated for each class of comparator drugs regardless of dose.

Discussion

The number of trials figuring in this analysis is less than the total number retrievable from the literature.[1-25] We actually used only about half of the trials

Table 1 *Comparative trials excluded from meta-analysis for failing to match up to inclusion criteria adopted*

Investigator(s)	*Acute treatment*	*Reasons for non-eligibility*	*Exclusion criteria (see selection of papers)*
Vantrappen *et al*[3]	Cimetidine *v* TDB	Follow up restricted to 3 months	3
Bianchi Porro *et al*[5]	Cimetidine *v* TDB	Maintenance treatment with cimetidine 400 mg nocte in patients initially healed with cimetidine	6
Bianchi Porro *et al*[6]	Ranitidine *v* TDB	Maintenance treatment with placebo	6
Berstad *et al*[13]	Cimetidine + antacids *v* trimipramine + antacids	Initial healing induced with combination therapy	5
Ström *et al*[14]	Cimetidine *v* antacids + anticholinergics or placebo	Initial healing induced with combination of active drugs or placebo	5
Guslandi *et al*[18]	Cimetidine *v* carbenoxolone	Maintenance treatment with carbenoxolone and cimetidine and subsequent follow-up restricted to 3 months	6
			3
Solhang *et al*[11]	Cimetidine *v* sucralfate	Abstract with insufficient information	7
Tomassetti *et al*[24]	Cimetidine *v* trithiozine	Anti-ulcer efficacy unproven for trithiozine	1
Diaz[23]	Cimetidine *v* trithiozine		
Hoff *et al*[25]	Cimetidine *v* doxepin	Anti-ulcer efficacy not proven on an adequate scale for doxepin	1

Table 2 *Descriptive characteristics of duodenal ulcer relapse incidences associated with H_2-antagonists (cimetidine or ranitidine) and comparator anti-ulcer agents after discontinuation of acute treatment in eligible comparative trials*

		Healed %			*Patients followed up (n)*		*Incidence of relapse*	
Investigator(s)	*Acute treatment*	*Wk 4*	*Wk 6*	*Wk 8*	*6 months*	*12 months*	*6 months*	*12 months*
Martin *et al*[1]	Cimetidine	60·0	—	85·0	27	27	70·0	85·0
	TDB	66·0	—	89·0	30	28	13·0	39·0
Kang and Piper[2]	Cimetidine	—	96·0	—	18	16	44·0	75·0
	TDB	—	96·0	—	17	17	47·0	76·0
Shreeve *et al*[4]	Cimetidine	—	54·0	—	10	10	50·0	60·0
	TDB	—	75·0	—	15	15	33·0	47·0
Lee *et al*[7]	Ranitidine	81·0	—	97·0	54	54	74·0*	89·0
	TDB	90·0	—	97·0	53	53	41·0	62·0
Hamilton *et al*[8]	Cimetidine	—	74·0	—	19	18	43·0	78·0
	TDB	—	81·0	—	28	24	30·0	43·0
Marks *et al*[9]	Cimetidine	—	—	—	—	22	—	73·0
	Sucralfate	—	—	—	—	27	—	63·0
Hentschel *et al*[10]	Cimetidine	73·0	84·0	—	23	21	65·0	81·0
	Sucralfate	66·0	91·0	—	28	27	64·0	85·0
Schenk *et al*[19]	Cimetidine	—	70·0	80·0	10	10	50·0	58·0
	Carbenoxolone	—	50·0	55·0	4	4	25·0	25·0
Vincent-Brown *et al*[20]	Cimetidine	—	67·0	—	—	26	—	76·0
	Carbenoxolone	—	66·0	—	—	24	—	81·0
Hansky *et al*[12]	Cimetidine	—	—	—	18	—	95·0	—
	Antacids	—	—	—	13	—	69·0	—
Ippoliti *et al*[15]	Cimetidine	62·0	86·0	—	47	40	55·0	73·2
	Antacids	64·0	80·0	—	43	41	56·0	70·0
Hentschel *et al*[16]	Cimetidine	77·0	—	—	22	21	54·0	76·0
	Antacids	87·0	—	—	28	26	57·0	92·0
Bytzer *et al*[17]	Ranitidine	89·0	100·0	—	—	28	—	71·4
	Antacids	84·0	96·0	—	—	22	—	50·0
	Ranitidine†	54·0	69·0	—	—	17	—	47·6
	Antacids	68·0	79·0	—	—	22	—	50·0
Dzieniszewski *et al*[22]	Ranitidine	—	92·0	—	30	—	36·6	—
	Pirenzepine	—	75·0	—	22	—	50·0	—
Vezzadini *et al*[21]	Cimetidine	—	85·0	—	17	—	47·0	—
	Pirenzepine	—	79·0	—	14	—	28·0	—

*4 months, excluded from the analysis; †prepyloric ulcer.

available, partly on account of excessively short follow up periods or implementation of maintenance treatment after initial healing induced by combination therapy or by drugs of unproven, aspecific or inadequately documented anti-ulcer efficacy. If we judge the trials purely on the basis of the arithmetical values of relapse incidences, we find that the incidence of relapse in patients initially healed on H_2-antagonists is higher than that in patients on comparator drugs in seven of 11 studies at six months and in eight of 13 studies at 12 months. The probability of obtaining distributions of this type when there is no difference between the two classes of drug is strong ($2p>0{\cdot}50$ both at six months and 12 months, sign test).

If, on the other hand, we consider only above 10% differences in relapse incidence (Table 3), we observe that the six month relapse incidence in patients treated with H_2-antagonists is higher in six studies (as against one study in which it is lower and four in which incidences are equal, while the 12 month relapse incidence in H_2-antagonist treated patients is higher in six studies (as against two in which it is lower and five in which incidences are equal). The probability of such distributions occurring by chance is reduced ($2p=0{\cdot}12$ at six months and $2p=0{\cdot}29$ at 12 months, sign test). These results are insufficient to suggest that healing with H_2-antagonists has a different impact on posthealing ulcer relapse from that obtained with comparator drugs.

On making a pooled estimate, however, of the results of the trials analysed in this study (Figure) in terms of differences between relapse incidences, the overall incidence of relapse in the non-H_2-antagonist treated patients is 11 percentage units lower at both six and 12 months than that observed in the H_2-antagonist treated patients. The two confidence intervals do not include the zero, which may lead to the conclusion that there is enough evidence for the existence of different effects of H_2-antagonists and of the overall class of non-H_2-antagonists drugs on

Table 3 *Distribution of trials according to higher (>10%), equal (±10%) or lower (<10%) incidence of ulcer relapse in H_2-antagonist treated patients compared with that in comparator drug treated patients*

Comparator drug	6 months			12 months		
	>10%	±10%	<10%	>10%	±10%	<10%
TDB	Martin *et al*[1] Shreeve *et al*[4] Hamilton *et al*[8]	Kang and Piper[2]		Martin *et al*[1] Shreeve *et al*[4] Hamilton *et al*[8] Lee *et al*[7]	Kang and Piper[2]	
Sucralfate		Hentschel *et al*[10]			Hentschel *et al*[10] Marks *et al*[9]	
Antacids	Hansky *et al*[12]	Ippoliti *et al*[15] Hentschel *et al*[16]		Bytzer *et al*[17]	Ippoliti *et al*[15]	Hentschel *et al*[16] Bytzer *et al*[17]*
Carbenoxolone	Schenk *et al*[19]			Schenk *et al*[19]	Vincent-Brown *et al*[20]	
Pirenzepine	Vezzadini *et al*[21] Sign test: 2p=0·12		Dzieniszewski *et al*[23]	Sign test: 2p=0·29		

*prepyloric ulcer.

relapse incidences. On considering the individual drugs in the non-H_2-antagonist group, however, this conclusion appears to hold good only in the case of TDB. The mean difference between relapse incidence in patients with ulcers initially healed on TDB and that in patients with ulcers initially healed on H_2-antagonists is 26 percentage units at six months and 27 percentage units at 12 months, and neither of the two 95% confidence intervals includes the zero (Figure). With all the other drug classes, the differences are lower and the respective confidence intervals include the zero. The pooled estimate of the trials, therefore, suggests a lower incidence of ulcer relapse, both at six and 12 months, in patients initially healed with TDB as compared with those healed with H_2-antagonists. Insufficient evidence is available, however, for a differential effect on ulcer relapse of the other non-H_2-antagonist ulcer healing agents, such as sucralfate, carbenoxolone, antacids and pirenzepine.

The reasons for the lower incidence of duodenal ulcer relapse after healing with TDB are not clear. As TDB does not block gastric acid secretion, it does not cause a rise in serum gastrin concentrations and increased parietal cell mass with secondary rebound hypersecretion of the type described in H_2-blocker treated patients in a number of reports.[32-35] Nevertheless, clinically important rebound secretion after discontinuation of either short or longterm treatment has been ruled out after both cimetidine[36-40] and ranitidine,[41-43] regardless of any increase in serum gastrin concentrations during treatment and regardless of whether or not an alteration of H_2-receptor sensitivity is operating, as reported by some investigators.[44] Moreover, other non-antisecretory drugs, particularly sucralfate, whose mechanism of action strongly resembles that of TDB, are not characterised by a lower incidence of relapse after discontinuation of treatment than is observed in patients initially treated with H_2-antagonists. In view of the randomisation of treatment in the selected trials, any possibility that ulcers of the TDB treated patients were more benign initially and thus less prone to relapse can probably be ruled out.

A bactericidal activity against *Campylobacter pyloridis*, a microorganism frequently found in patients with gastroduodenal inflammatory and/or peptic lesions,[45] has been described for TDB, but not for cimetidine, carbenoxolone, sucralfate or antacids.[46]

It has also been suggested[47] that the superior re-epithelialisation induced by TDB may be hypothetically related to the fact that the gastric epithelium continues, for some time, to receive a beneficial effect from the drug, which is progressively released after partial accumulation in the body. In support of such a hypothesis may be findings of a urinary excretion of bismuth nine times greater than normal as many as two weeks after discontinuing acute treatment.[48] It is hard to imagine, however, an accumulation of TDB sufficient to guarantee its persistent release and thus an epithelial protective capability of the drug over six or 12 months; this would imply a significant absorption of TDB, which so far is unproven.

The difference in incidence of ulcer relapse has also been ascribed not to the beneficial action of TDB, but to an adverse effect of H_2-antagonists.[49,50] The lack of convincing evidence for early relapse in H_2-antagonist treated patients and the fact that, with the sole exception of TDB, no difference can be detected between ulcer relapse after H_2-antagonists

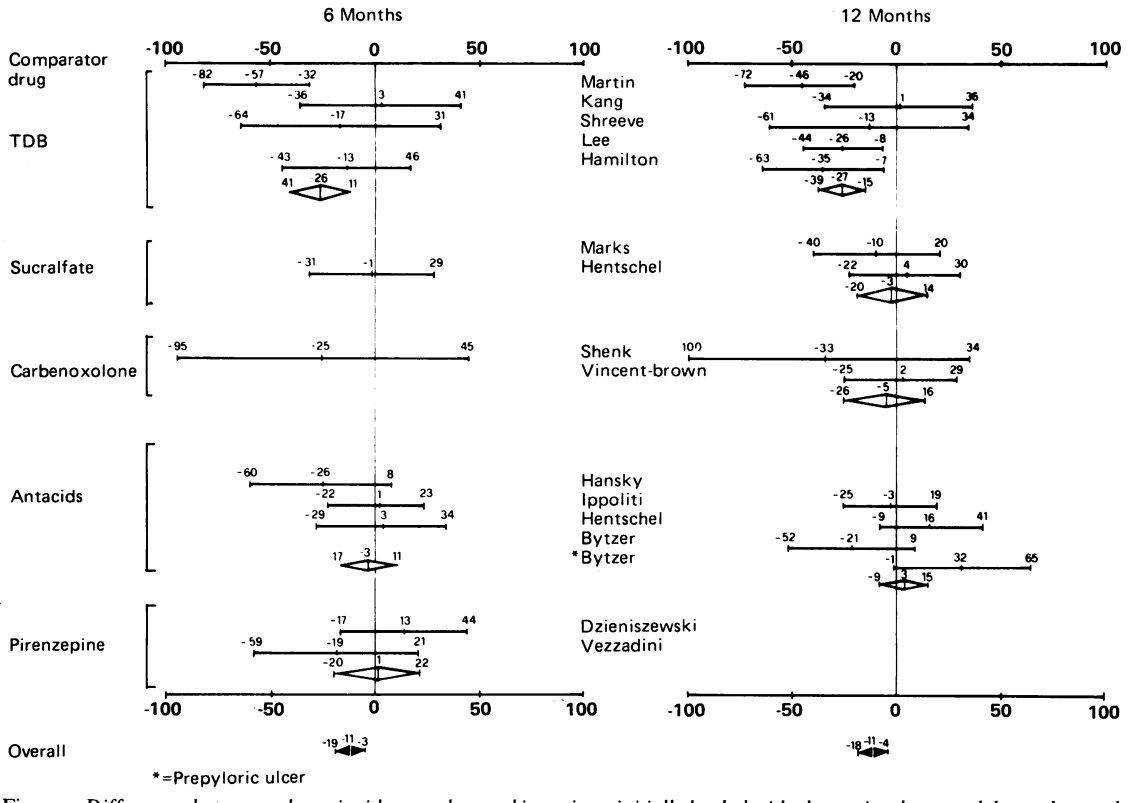

Figure *Differences between relapse incidences observed in patients initially healed with alternative drugs and those observed in patients healed with H_2-antagonists, together with 95% confidence interval. Numbers at centres of lines or diamonds denote differences; those at end points are confidence limits.*

and non-H_2-antagonists, suggest that any very broad ranging conclusions in this regard are either unfounded or excessively premature.

In conclusion, the meta-analysis we have carried out in this review leads us to assume, then, that there is sufficient evidence to suggest that patients initially healed on TDB are less prone to ulcer relapse than patients treated with H_2-antagonists, though the reasons for this have not been satisfactorily clarified.

Finally, we should stress that we do not agree with those who, on the basis of different relapse incidences in patients initially healed with H_2-antagonists or TDB, advocate changes in anti-ulcer drug prescribing policies.[49,50] While it is undoubtedly true that the institution of maintenance therapy after initial ulcer healing costs more than doing nothing at all, it is equally true to say that, during maintenance treatment, only 20–30%, and not 80–90%, of patients with duodenal ulcer suffer relapses[51] and that prevention of ulcer recurrence may prove even more effective with the use of more potent H_2-antagonists.[52,53]

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