Papers

Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials

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Abstract

Objectives To determine the effectiveness of ranitidine and sucralfate in the prevention of stress ulcer in critical patients and to assess if these treatments affect the risk of nosocomial pneumonia.

Design Published studies retrieved through Medline and other databases. Five meta-analyses evaluated effectiveness in terms of bleeding rates (A: ranitidine v placebo; B: sucralfate v placebo) and infectious complications in terms of incidence of nosocomial pneumonia (C: ranitidine v placebo; D: sucralfate v placebo; E: ranitidine v sucralfate). Trial quality was determined with an empirical ad hoc procedure.

Main outcome measures Rates of clinically important gastrointestinal bleeding and nosocomial pneumonia (compared between the two study arms and expressed with odds ratios specific for individual studies and meta-analytic summary odds ratios).

Results Meta-analysis A (five studies) comprised 398 patients; meta-analysis C (three studies) comprised 311 patients; meta-analysis D (two studies) comprised 226 patients: and meta-analysis E (eight studies) comprised 1825 patients. Meta-analysis B was not carried out as the literature search selected only one clinical trial. In meta-analysis A ranitidine was found to have the same effectiveness as placebo (odds ratio of bleeding 0.72, 95% confidence interval 0.30 to 1.70, P = 0.46). In placebo controlled studies (meta-analyses C and D) ranitidine and sucralfate had no influence on the incidence of nosocomial pneumonia. In comparison with sucralfate, ranitidine significantly increased the incidence of nosocomial pneumonia (meta-analysis E: 1.35, 1.07 to 1.70, P = 0.012). The mean quality score in the four analyses (on a 0 to 10 scale) ranged from 5.6 in meta-analysis E to 6.6 in meta-analysis A.

Conclusions Ranitidine is ineffective in the prevention of gastrointestinal bleeding in patients in intensive care and might increase the risk of pneumonia. Studies on sucralfate do not provide conclusive results. These findings are based on small numbers of patients, and firm conclusions cannot presently be proposed.

Introduction

Ranitidine and sucralfate are widely used to prevent stress ulcers in patients admitted to intensive care units.[1] A meta-analysis published by Cook et al in 1996 showed that H_2 receptor antagonists (such as cimetidine and ranitidine together) are more effective than placebo for this clinical indication.[2] With regard to sucralfate, this meta-analysis found a small but significant reduction in overt bleeding but no effect on clinically important events. The meta-analysis did not resolve the question of an increased risk of nosocomial pneumonia related to the use of H_2 receptor antagonists.

Several arguments emphasise the need for up to date information on this issue. Firstly, ranitidine has become the main H_2 receptor antagonist used for prophylaxis for stress ulcers, and cimetidine has generally been abandoned[1]; secondly, new findings have been published on effectiveness and complications of ranitidine; and, thirdly, a meta-analytic comparison of ranitidine versus placebo has never been carried out, and as the comparison of sucralfate and placebo made by Cook et al gave no proof of the effectiveness of this drug, ranitidine and sucralfate might both be ineffective. Another problem is that the most recent randomised studies on this topic did not include a group with no prophylaxis and compared supposedly active treatments with one another.[3] [4]

We conducted a literature search to identify randomised trials, and we carried out a meta-analysis to update the results of Cook's study with regard to effectiveness and infectious complications.

Methods

Searching

Our Medline search covered the period from 1966 to 20 June 2000 and was based on four key words (stress, pneumonia, ranitidine, sucralfate) and on the extraction of studies published in English (see appendix). Randomised studies were identified by using the key words "randomized controlled trial" or "random" according to a validated literature search.[5]

This search was supplemented by examining the Iowa-IDIS system (Iowa Drug Information, Iowa University, United States) from 1966 to December

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Table 1 Results of Medline search and selection of randomised controlled trials in meta-analyses. Figures are numbers of trials

	Effectiveness of drug *v* placebo		Rate of pneumonia		
	Ranitidine (analysis A)	Sucralfate (analysis B)	Ranitidine v placebo (analysis C)	Sucralfate v placebo (analysis D)	Ranitidine v sucralfate (analysis E)
Identified and screened studies	51	46	59	35	11
Studies excluded	45*	42*	56*	33*	3*
Potentially relevant trials for inclusion	6	4	3	2	8
Studies excluded	1[24]†	3[16-18]†	0	0	0
Trials included	5[11-15]	1[11]	3[12 13 15]	2[17 18]	8[3 19-26]

*Studies were excluded because they did not compare treatment options considered by meta-analysis in question (A=16; B=18, C=12; D=14; E=1) or because objective of trial was not prophylaxis of stress ulcer (A=29; B=23, C=44; D=19; E=1) or because they duplicated study already included in meta-analysis question (A=0; B=1, C=0; D=0; E=1).
†Studies excluded because end point of bleeding did not meet definition of "clinically important bleeding" according to Cook et al.[2]

1999 and Drugdex (CD Rom Drugdex, vol 104, Micromedex, Englewood, Colorado, United States).

Selection

On the basis of the material produced by our search, we carried out five meta-analyses that evaluated data on effectiveness in terms of rates of bleeding (meta-analysis A: ranitidine *v* placebo; meta-analysis B: sucralfate *v* placebo) and data of infectious complications in terms of incidence of nosocomial pneumonia (meta-analysis C: ranitidine *v* placebo; meta-analysis D: sucralfate *v* placebo; meta-analysis E: ranitidine *v* sucralfate). We investigated the issue of effectiveness only in studies with a control group that received no prophylaxis, while the issue of infectious complications was also assessed from comparative trials of ranitidine versus sucralfate. Eligible studies were included in meta-analysis A or B if they met the following criteria: patients were admitted to an intensive care unit or were undergoing mechanical ventilation, or both; randomised design; assessment of gastrointestinal bleeding. We excluded studies in which gastrointestinal bleeding did not meet the definition of "clinically important bleeding" according to Cook et al.[2] In meta-analyses C, D, and E the inclusion criterion gastrointestinal bleeding was replaced by the assessment of pneumonia. The definitions of pneumonia adopted by the individual investigators were recorded but were not assumed to be an inclusion or exclusion criterion.

Data extraction

Data were extracted by one reviewer (MV) with a structured form and checked for accuracy by a second reviewer (ST). Differences were resolved by consensus.

Assessment of quality of trials

We assessed methodological quality of the trials using a procedure similar to that adopted by Cook et al.[2] Five items were evaluated for each trial (patient selection, patient characteristics, randomisation, blinding, definition of bleeding or of pneumonia). Methodological quality was graded for each of the five items on a scale of 0, 1, or 2 (maximum score = 10). Three observers independently assessed quality (AM, MV, MG). Differences were resolved by consensus.

Qualitative data synthesis

Descriptive data for each trial included characteristics of participants, details of intervention, and definition of outcomes. Our assessment of clinical heterogeneity was focused in particular on a comparison of the definitions of bleeding and pneumonia across the trials.

Quantitative data synthesis

With regard to the two end points, the odds ratio was used as the principal measure for comparing the treatment effect within each trial. The results specific for trials were combined through standard meta-analytic techniques[6-8] to produce the summary odds ratio together with an assessment of the statistical intertrial heterogeneity. The meta-analysis calculations were based both on a fixed effect model[6 7] and on a random effect model.[6 8] The 95% confidence intervals for the odds ratio of individual studies were computed according to Wolf[9] (or by the "rule of three"[10] when zeros were present). To avoid the problems of bias and instability associated with estimation of odds ratios, 0.5 was added to each cell of the fourfold tables in keeping with Cook et al.[2] Heterogeneity was assessed as previously described.[7]

Results

Table 1 shows the trial flow for the five meta-analyses. There were 398 patients in meta-analysis A (five studies), 54 in meta-analysis B (one study), 311 in meta-analysis C (three studies), 226 in meta-analysis D (two studies), and 1825 in meta-analysis E (eight studies). Table 2 shows descriptive data for all the trials included in our meta-analyses.

Effectiveness of ranitidine v placebo (meta-analysis A)—Our literature search identified five trials,[11-15] three of which had already been included by Cook et al.[11-13] The mean (SD) quality score for these trials was 6.6 (0.9). With respect to the end point of clinically important bleeding, this meta-analysis (table 3) failed to show any significant benefit of ranitidine (summary odds ratio 0.72, 95% confidence interval 0.30 to 1.70, P = 0.46 for fixed effect model; 0.95, 0.37 to 2.43, P = 0.92 for random effect model; χ^2 for heterogeneity 6.8, df 4, P = 0.15).

Effectiveness of sucralfate v placebo (meta-analysis B)—Our literature search found the same randomised trials that had already been examined by Cook et al (three trials[16-18] for the end point of overt bleeding and one trial[11] for the end point of clinically important gastrointestinal bleeding). Because our analysis considered the end point of clinically important bleeding, only one trial[11] met the inclusion criteria and so no meta-analysis was carried out. The quality score of the trial of Ruiz-Santana et al was 7.0. The results of the study by Cook et al remained unchanged (table 4) with no difference between sucralfate and placebo (1.26, 0.12 to 12.9, P = 0.70).

Table 2 Patient characteristics, details of interventions, outcomes, and methodological quality score for trials included in our meta-analyses

Trial	Meta-analysis	Setting	No of patients	Mean age (years)	Intervention	Control	Outcomes	Methodological quality score*
Ruiz-Santana et al, 1991[11]	A	ICU	49	R=39 P=39	Ranitidine 50 mg iv every 6 hours	Placebo	See table 3	7
Apte et al, 1992[12]	A	Medical ICU	34	R=27† P=26†	Ranitidine 50 mg iv every 6 hours	Placebo	See table 3	6
Metz et al, 1993[13]	A	ICU	167‡	R=35.4 P=32.5	Ranitidine 6.25 mg/hr by continuous infusion	Placebo	See table 3	8
Burgess et al, 1995[14]	A	Surgical ICU	34	R=38.4 P=34.5	Ranitidine 6.25 mg/hr by continuous infusion	Placebo	See table 3	6
Hanisch et al, 1998[15]	A	Surgical ICU	114	R=55 P=58	Ranitidine 50 mg tid iv	Placebo	See table 3	6
Ruiz-Santana et al, 1991[11]	B	ICU	54	S=37 P=39	Sucralfate 1 g by nasogastric tube every 4 hours	Placebo	See table 4	7
Apte et al, 1992[12]	C	Medical ICU	34	R=27† P=26†	Ranitidine 50 mg iv every 6 hours	Placebo	See table 5	5
Metz et al, 1993[13]	C	ICU	163‡	R=35.4 P=32.5	Ranitidine 6.25 mg/hr by continuous infusion	Placebo	See table 5	7
Hanisch et al, 1998[15]	C	Surgical ICU	114	R=55 P=58	Ranitidine 50 mg tid iv	Placebo	See table 5	6
Ben-Menachem et al, 1994[18]	D	Medical ICU	200	S=60.1 P=59.6	Sucralfate 1 g given orally every 6 hours	Placebo	See table 6	7
Eddleston et al, 1994[17]	D	ICU	26	S=47.6 P=54.9	Sucralfate 2 g by nasogastric tube every 8 hours	Placebo	See table 6	5
Pickworth et al, 1993[19]	E	Surgical ICU	83	R=27.3 S=26.8	Ranitidine 50 mg iv every 6 hours	Sucralfate 1 g by nasogastric tube every 6 hours	See table 7	6
Eddleston et al, 1991[20]	E	ICU	60	R=54.1 S=44.3	Ranitidine 50 mg iv every 6 hours	Sucralfate 1 g by nasogastric tube every 6 hours	See table 7	7
Thomason et al, 1966[25]	E	Trauma, surgical, or neurosurgical ICU	160	R=31.0† S=27.7†	Ranitidine 6.25 mg/hr by continuous infusion	Sucralfate 1 g administered orally then 1 g by nasogastric tube every 6 hours	See table 7	5
Prod'hom et al, 1994[21]	E	Medical and surgical ICU	163	R=52.2 S=46.4	Ranitidine 6.25 mg/hr by continuous infusion	Sucralfate 1 g by nasogastric tube every 4 hours	See table 7	6
O'Keefe et al, 1998[26]§	E	ICU	96	R=34.3 S=34.2	Ranitidine 0.25 mg/kg/hr, after loading dose of 0.5 mg/kg	Sucralfate 1 g by nasogastric tube every 6 hours	See table 7	6
Laggner et al, 1989[22]	E	ICU	32	R=60 S=47	Ranitidine 50 mg iv every 4 hours	Sucralfate 1 g by gastric tube every 4 hours	See table 7	5
Cook et al, 1998[3]	E	ICU	1200	R=58.8 S=58.7	Ranitidine 50 mg iv every 8 hours	Sucralfate 1 g by nasogastric tube every 6 hours	See table 7	9
Mustafa et al, 1995[23]	E	ICU	31	Not reported	Ranitidine 100 mg iv every 8 hours	Sucralfate 2 g by nasogastric tube every 6 hours	See table 7	1

*In assessment of blinding we assigned score of 1 to single blind studies in which outcome assessor was blind and both caregiver and patient were unblind.
†Median.
‡Population studied in effectiveness analysis (n=167) differed from that included in analysis on pneumonia (n=163) because four patients had pneumonia at baseline.
§Results of this clinical trial have in part been reported previously.[24]
R=ranitidine; P=placebo; S=sucralfate; ICU=intensive care unit.

Incidence of pneumonia with ranitidine v placebo (meta-analysis C)—Our third meta-analysis included three randomised studies[12 13 15] that compared the incidence of pneumonia between ranitidine and placebo (two of these trials[12 13] had already been included in the meta-analysis by Cook et al). The mean (SD) quality score for these trials was 6.0 (1.0). The analysis of these three trials (table 5) found no significant difference in the rate of pneumonia with ranitidine and placebo (summary odds ratio 0.98, 0.56 to 1.72, P=0.94 for fixed effect model; 1.10, 0.45 to 2.66, P=0.84 for random effect model; χ^2 for heterogeneity 4.38, df 2, P=0.11).

Incidence of pneumonia with sucralfate v placebo (meta-analysis D)—Our fourth meta-analysis included two randomised studies[17 18] that compared the incidence of pneumonia between sucralfate and placebo (both trials had already been included in the meta-analysis by Cook et al). The quality score for these trials was 6.0 (1.4). The analysis of these two trials (table 6) found no significant difference in the rate of pneumonia with sucralfate and placebo (summary odds ratio 2.21, 0.86 to 5.65, P=0.10 for fixed effect model; 2.11, 0.79 to 5.64, P=0.14 for random effect model; χ^2 for heterogeneity 0.30, df 1, P=0.58).

Incidence of pneumonia with ranitidine v sucralfate (meta-analysis E)—Our fifth meta-analysis included eight randomised studies[3 19-26] that compared the incidence of pneumonia with ranitidine and sucralfate (five of these trials[19-23] had already been included in the

Table 3 Meta-analysis A: rates of gastrointestinal bleeding in patients treated with ranitidine or placebo (five randomised studies)

Reference	Bleeding rate		Odds ratio (95% CI)	Definition of bleeding
	Ranitidine	Placebo		
Ruiz-Santana et al, 1991[11]	2/19	1/30	2.81 (0.41 to 28.1)	Acute upper gastrointestinal bleeding
Apte et al, 1992[12]	5/16	6/18	0.92 (0.23 to 3.65)	Gross gastric bleeding
Metz et al, 1993[13]	0/86	1/81	0.31 (0.00 to 2.83)	Bright red blood per nasogastric tube (without including cases with persistent blood occult positive and "coffee grounds" nasogastric tube aspirates)
Burgess et al, 1995[14]	0/16	5/18	0.10 (0.00 to 0.86)	5% decrease from baseline in haematocrit occurring at least 8 h after study drug initiation and haematemesis, haematochezia, bright red blood per nasogastric tube, or "coffee grounds" nasogastric tube aspirates
Hanisch et al, 1998[15]	3/57	2/57	1.43 (0.29 to 8.08)	Bright red blood per gastric tube or melaena combined with haemodynamic changes (systolic blood pressure <100 mm Hg, tachycardia >100 beats/min) and requirement of blood transfusion (fall in haemoglobin concentration >20 g/l within 24 hours) and endoscopic identification of bleeding site and activity
Total	10/194 (5%)	15/204 (7%)	—	

Table 4 Meta-analysis B: rates of gastrointestinal bleeding in patients treated with sucralfate or placebo (one randomised study)

Reference	Bleeding rate		Odds ratio (95% CI)	Definition of bleeding
	Sucralfate	Placebo		
Ruiz-Santana et al, 1991[11]	1/24 (4%)	1/30 (3%)	1.26 (0.12 to 12.9)	Acute upper gastrointestinal bleeding

Table 5 Meta-analysis C: rates of nosocomial pneumonia in patients treated with ranitidine or placebo (three randomised studies)

Reference	Rate of nosocomial pneumonia		Odds ratio (95% CI)	Definition of pneumonia
	Ranitidine	Placebo		
Apte et al, 1992[12]	13/16	9/18	3.86 (0.99 to 19.0)	Appearance of new infiltrates on chest radiograph or bronchial breath sounds on examination and positive tracheal culture with fever axillary temperature (>38°C), leucocytosis (>13 000 cell/mm^3), and purulent sputum (>25 leucocytes per low power field)
Metz et al, 1993[13]	12/84	15/79	0.72 (0.31 to 1.61)	Chest radiograph indicating pulmonary infiltrates and one of six groupings of clinical findings established by Centers for Disease Control
Hanisch et al, 1998[15]	10/57	12/57	0.80 (0.32 to 1.99)	Radiological signs of pneumonia and purulent tracheal secretion or positive microbiological findings in tracheal aspiration and temperature >38°C and leucocytosis >10 000 mm^3
Total	35/157 (22%)	36/154 (23%)	—	—

Table 6 Meta-analysis D: rates of nosocomial pneumonia in patients treated with sucralfate or placebo (two randomised studies)

Reference	Rate of nosocomial pneumonia		Odds ratio (95% CI)	Definition of pneumonia
	Sucralfate	Placebo		
Ben-Menachem et al, 1994[18]	12/100	6/100	2.05 (0.79 to 5.76)	Each of criteria: chest roentenogram obtained ≥72 hours after admission to intensive care that showed new and persistent infiltrate; fever, leucocytosis, or both; purulent tracheobronchial secretions; Gram stained sputum showing >25 polymorphonuclear leucocytes and <10 squamous epithelial cells/low power field; recovery of accepted nosocomial pathogen from sputum culture
Eddleston et al, 1994[17]	1/14	0/12	2.78 (not computable)	New and progressive infiltrate on chest radiograph; unexplained reduction in PaO$_2$; positive culture from tracheal aspirate plus either pyrexia (>38°C) or increase in blood leucocyte count (>3×10^9 cells/l)
Total	13/114 (11%)	6/112 (5%)	—	

meta-analysis by Cook et al). The quality score for these trials was 5.6 (2.3). The analysis of these eight trials (table 7) showed a significantly increased risk of pneumonia with ranitidine compared with sucralfate (summary odds ratio 1.35, 1.07 to 1.70, P = 0.012 for fixed effect model; 1.51, 1.00 to 2.29, P = 0.05 for random effect model; χ^2 for heterogeneity 12.9, df 7, P = 0.08).

Discussion

Our overview of the controlled trials of ranitidine or sucralfate compared with placebo provides a picture of poor effectiveness. The single trial available on sucralfate[11] does not allow any conclusion to be drawn;

the trials on ranitidine[11-15] show no difference compared with placebo.

Our results on ranitidine need to be compared with those previously published by Cook et al.[2] In their assessment of effectiveness of H$_2$ receptor antagonists Cook et al included five trials that used cimetidine[29-33] and three trials with negative results that used ranitidine[11-13] (plus one trial on ranitidine published in Spanish[34] and one trial with negative results that used a combination of ranitidine and antacids,[35] both of which did not meet the criteria for our meta-analysis). Cimetidine is probably effective at statistical levels, as out of the trials that used cimetidine three had positive results, one had significant results in patients at low

Table 7 Meta-analysis E: rates of nosocomial pneumonia in patients treated with ranitidine or sucralfate (eight randomised studies)

Reference	Pneumonia rate		Odds ratio (95% CI)	Definition of pneumonia
	Ranitidine	Sucralfate		
Pickworth et al, 1993[19]	5/44	6/39	0.72 (0.21 to 2.40)	Presence of new infiltrate in chest *x* ray picture and three of: rectal temperature >38.5°C, white blood cell count >10 000 cells/mm³, positive sputum culture obtained by leukans trap, or sputum sample obtained by leukans trap with Gram stain containing many white blood cells (>25 white blood cells, <10 epithelial cells, and numerous bacteria/high power field)
Eddleston et al, 1991[20]	10/30	3/30	4.02 (1.18 to 17.1)	New and progressive infiltrate in chest *x* ray picture, unexplained reduction in PaO₂, postive culture from tracheal aspirate plus either pyrexia (>38°C) or increase in leucocyte count of >3000/mm³
Thomason et al, 1966[25]	27/80	30/80	0.85 (0.45 to 1.61)	According to Garner et al[27]: infiltrate in chest *x* ray picture plus three of: leucocytosis >10 000 cells/mm³; Gram negative organisms on tracheal or blood culture; tracheal Gram stain showing moderate to heavy bacteria or polymorphoneutrophils (>25/high power field); pathogens isolated from tracheal culture; temperature >38°C
Prod'hom et al, 1994[21]	21/80	10/83	2.53 (1.15 to 5.86)	According to Salata et al[28]: new or progressive infiltrate in chest *x* ray picture and at least one of: microbiological or histopathological evidence of pneumonia; presence of at least two of: leucocytes on Gram stain, new leucocytosis, temperature increase from <37.5°C to >38.5°C
O'Keefe et al, 1998[26]	14/49	10/47	1.46 (0.59 to 3.70)	Leucocytes >12 000/ mm³, new or changing infiltrate in chest *x* ray picture, temperature >38.5°C or <36.5°C, and positive sputum and Gram stain for specific pathogens. Results of this clinical trial have in part been reported in separate publication (Maier et al, 1994[24])
Laggner et al, 1989[22]	2/16	0/16	5.67 (not computable)	New infiltrate in chest *x* ray picture with bronchial colonisation, leucocytosis (>15 000/mm³), and fever >38.5°C
Cook et al, 1998[3]	114/596	98/604	1.22 (0.91 to 1.64)	By consensus of specific pneumonia adjudication committee. Main criteria included new infiltrate in chest *x* ray picture plus at least two of: temperature >38.5°C or <35.0°C; leucocyte count >10 000 cells/mm³ or <3000 cells/mm³; purulent sputum or positive culture
Mustafa et al, 1995[23]	9/16	3/15	4.52 (1.12 to 23.6)	No specific definition
Total	202/911 (22%)	160/914 (18%)	—	

risk, and one had negative results. A separate meta-analysis that we carried out for this purpose (table 8) showed a significant reduction in bleeding (with P<0.001 and P<0.01 according to the fixed effect and the random effect models, respectively).

Can we accept the hypothesis that cimetidine is effective and ranitidine is ineffective? Is this hypothesis pharmacologically plausible? Our separate analyses for individual drugs did not actually settle the entire question. In fact, the cohorts included in the studies that used these two drugs were small and the incidence of events was low, particularly in the case of ranitidine (10 cases of bleeding with the drug *v* 15 without prophylaxis; table 3); so the different results might reflect casual variations in the outcome rather than a true difference between the two H₂ receptor antagonists. Another point of uncertainty about cimetidine is the methodological quality of studies published many years ago.

Design of new trials
Our results indicate that some points of consensus need to be revised. For example, recent randomised studies on prophylaxis for stress ulcers[3 4] have invariably compared (unproved) active treatments with one another but no longer use a placebo group, and authoritative recommendations suggest the use of ranitidine for prophylaxis for stress ulcers.[36]

New large scale randomised trials seem to be the only way to resolve this issue. New trials, however, may raise the ethical question of which treatment is appropriate for the control group. One possibility is to give cimetidine to the control group, but this solution raises the question of reusing a drug that has largely been abandoned. Another possibility is to conduct new large scale controlled trials of ranitidine compared with placebo, but the use of placebo can be questionable from

an ethical point of view. A third solution could be to design new randomised trials according to a strategy of early treatment of stress ulcer with or without prophylaxis. In this latter case, after randomisation to prophylaxis or placebo the patients could be subjected to intensive gastrointestinal monitoring (for example, by examining nasogastric aspirate at short intervals) and, at the first signs of bleeding, their participation in the trial could be stopped with immediate initiation of an aggressive antisecretory treatment. A drawback of this third solution is that the clinical weight of the end point of early bleeding is less than that of the end point of clinically important bleeding.

Effect on pneumonia
The results of three meta-analyses that evaluated pneumonia were contradictory in some respects (ranitidine v placebo and sucralfate *v* placebo had the same incidence of pneumonia; for ranitidine *v* sucralfate there was a significantly higher incidence of pneumonia with ranitidine, P=0.012).The statistical power of these comparisons was better for meta-analysis E

Table 8 Meta-analysis on effectiveness of cimetidine: rates of gastrointestinal bleeding in patients given cimetidine or placebo

Reference	Bleeding rate*		Odds ratio (95% CI)
	Cimetidine	Placebo	
Zinner et al[29]	14/100	20/100	0.66 (0.31 to 1.36)
Karlstadt et al[30]	1/54	7/33	0.10 (0.01 to 0.43)
Groll et al[31]	6/114	11/107	0.50 (0.18 to 1.32)
Halloran et al[32]	2/26	8/24	0.20 (0.04 to 0.78)
Peura et al[33]	1/21	7/18	0.11 (0.01 to 0.52)
Total	24/315 (8%)	53/282 (19%)	†

*Bleeding rates determined according to original definitions of this end point reported in studies; in trial by Halloran et al,[32] in which two different definitions were given, we used rates of "marked" bleeding.
†Summary odds ratio 0.37 (0.23 to 0.60), P<0.0001 for fixed effect model; 0.30 (0.13 to 0.68), P<0.004 for random effect model; χ^2 for heterogeneity 8.0, df 4, P=0.09.

What is already known on this topic

Ranitidine and sucralfate are widely used to prevent gastrointestinal bleeding in patients in intensive care

Several recommendations suggest this form of prophylaxis, but both the Food and Drug Administration and European Medicines Evaluation Agency have not given their approval

What this study adds

This analysis showed that ranitidine and sucralfate do not prevent gastrointestinal bleeding in patients in intensive care

Ranitidine can increase the risk of nosocomial pneumonia under certain circumstances

These findings are based on small numbers of patients and so firm conclusions cannot presently be proposed

Current recommendations on prophylaxis for stress ulcers should be revised according to these results

(1825 patients) than for meta-analysis C (311 patients); this could in part explain the higher incidence of pneumonia with ranitidine compared with sucralfate but not compared with placebo.

The large trial by Cook et al showed a trend towards an increased incidence of pneumonia with ranitidine *v* sucralfate (definite pneumonia associated with use of ventilator and pneumonia according to the definition of the Centers for Disease Control and Prevention was more common with ranitidine, at $P = 0.03$ and $P = 0.13$, respectively).[3] Discrepancies between large trials and meta-analysis have been pointed out in cases where the meta-analysis was conducted before the large trial.[37] In our study, however, the meta-analysis on pneumonia already included the large trial and, more importantly, its results did not differ much from those of the large trial (odds ratio of 1.35 *v* 1.18, respectively).

These arguments related to statistical power and agreement between large scale trials and meta-analyses do not, however, exclude the other explanation that the increase in rates of pneumonia after ranitidine was simply the result of casual variations in the outcome. In this context, the repeated application of statistical testing to many data sets might have contributed to the generation of some significant results.

Our main conclusion is that there are insufficient data on effectiveness to be able to conclude anything one way or the other. This can be an important argument for further trials.

Appendix
Literature search

Our literature search used the PubMed version of Medline on the internet (www.ncbi.nlm.nih.gov/entrez/). The syntax used for the Medline searches of our five meta-analyses was:

Meta-analysis A: ranitidine AND stress AND eng [LA] AND 1966:2000 [EDAT] AND (Randomized Controlled Trial [PT] OR random* [TW])

Meta-analysis B: sucralfate AND stress AND eng [LA] AND 1966:2000 [EDAT] AND (Randomized Controlled Trial [PT] OR random* [TW])

Meta-analysis C: ranitidine AND pneumonia AND eng [LA] AND 1966:2000 [EDAT] AND Randomized Controlled Trial [PT] OR random* [TW])

Meta-analysis D: sucralfate AND pneumonia AND eng [LA] AND 1966:2000 [EDAT] AND (Randomized Controlled Trial [PT] OR random* [TW])

Meta-analysis E: ranitidine AND sucralfate AND pneumonia AND eng [LA] AND 1966:2000 [EDAT] AND (Randomized Controlled Trial [PT] OR random* [TW])

In this syntax, "eng[LA]" identifies studies published in English language, "1966:2000[EDAT]" selects the year range according to the Entrez date, "Randomized Controlled Trial [PT]" selects this type of trials according to Medical Subjects Headings while "random*"[TW] indicates the word random (in its all variant endings) in the title or abstract; the last two conditions were stated with the "OR" Boolean operator to increase the power of the search.

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