

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 H₂ 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 H₂ receptor antagonists.

Several arguments emphasise the need for up to date information on this issue. Firstly, ranitidine has become the main H₂ receptor antagonist used for prophylaxis for stress ulcers, and cimetidine has generally been abandoned¹; 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. 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 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 2 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%) | — | — |

1999 and Drugdex (CD Rom Drugdex, vol 104, Micro-medex, Englewood, Colorado, United States).

Selection

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 incidence of nosocomial pneumonia (meta-analysis C: ranitidine *v* placebo; meta-analysis D: sucralfate *v* placebo; meta-analysis E: ranitidine *v* 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. In meta-analyses C, D, and E the inclusion criterion gastrointestinal bleeding was replaced by the assessment of pneumonia.

Data extraction and assessment of quality of trials

Data were extracted with a structured form. We assessed methodological quality by evaluating five items for each trial (patient selection, patient characteristics, randomisation, blinding, definition of bleeding or of pneumonia).² Methodological quality was graded for each of the five items on a scale of 0, 1, or 2 (maximum score = 10).

Data synthesis

Assessment of clinical heterogeneity was focused in particular on a comparison of the definitions of bleeding and pneumonia across the trials. Qualitative information is given in the longer version of this paper on the *BMJ's* website. The odds ratio was used as the principal measure for comparing the treatment effect within each trial. The calculations of summary odds ratios presented here were based on a random effect

model.^{6,7} Odds ratios based on a fixed effect model are given on the *BMJ's* website.⁶ Heterogeneity was assessed as previously described.⁶

Results

Effectiveness of ranitidine v placebo (meta-analysis A)—We identified five trials,^{8–12} with a mean (SD) quality score of 6.6 (0.9). With respect to the end point of clinically important bleeding, this meta-analysis (table 1) failed to show any significant benefit of ranitidine (summary odds ratio 0.95, 0.37 to 2.43, $P=0.92$; χ^2 for heterogeneity 6.8, df 4, $P=0.15$).

Effectiveness of sucralfate v placebo (meta-analysis B)—We found only one trial⁸ that met the inclusion criteria and so no meta-analysis was carried out. The quality score of this trial was 7.0. The bleeding rate in the sucralfate group was 4% (1/24) and 3% (1/30) in the placebo group (1.26, 0.12 to 12.9, $P=0.70$).

Incidence of pneumonia with ranitidine v placebo (meta-analysis C)—Our third meta-analysis included three randomised studies^{9–12} that compared the incidence of pneumonia between ranitidine and placebo. The mean (SD) quality score for these trials was 6.0 (1.0). The analysis of these three trials (table 2) found no significant difference in the rate of pneumonia with ranitidine and placebo (summary odds ratio 1.10, 0.45 to 2.66, $P=0.84$; 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^{13–14} that compared the incidence of pneumonia between sucralfate and placebo. The quality score for these trials was 5 and 7, respectively. There was no significant difference in the rate of pneumonia with sucralfate and placebo (summary odds ratio 2.11,

Table 3 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 roentgenogram 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 ($>38^{\circ}\text{C}$) or increase in blood leucocyte count ($>3 \times 10^9$ cells/l) |
| Total | 13/114 (11%) | 6/112 (5%) | — | |

Table 4 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 $>38.5^{\circ}\text{C}$, white blood cell count $>10\,000$ cells/mm ³ , 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 PaO ₂ , positive culture from tracheal aspirate plus either pyrexia ($>38^{\circ}\text{C}$) or increase in leucocyte count of $>3000/\text{mm}^3$ |
| 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/mm ³ ; Gram negative organisms on tracheal or blood culture; tracheal Gram stain showing moderate to heavy bacteria or polymorphoneutrophils ($>25/\text{high power field}$); pathogens isolated from tracheal culture; temperature $>38^{\circ}\text{C}$ |
| 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 $<37.5^{\circ}\text{C}$ to $>38.5^{\circ}\text{C}$ |
| O'Keefe et al, 1998 ²⁶ | 14/49 | 10/47 | 1.46 (0.59 to 3.70) | Leucocytes $>12\,000/\text{mm}^3$, new or changing infiltrate in chest x ray picture, temperature $>38.5^{\circ}\text{C}$ or $<36.5^{\circ}\text{C}$, 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 ($>15\,000/\text{mm}^3$), and fever $>38.5^{\circ}\text{C}$ |
| 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 $>38.5^{\circ}\text{C}$ or $<35.0^{\circ}\text{C}$; leucocyte count $>10\,000$ cells/mm ³ or <3000 cells/mm ³ ; 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%) | — | |

0.79 to 5.64, $P=0.14$; χ^2 for heterogeneity 0.30, df 1, $P=0.58$) (table 3).

Incidence of pneumonia with ranitidine v sucralfate (meta-analysis E)—Our fifth meta-analysis included eight randomised studies^{3 15-22} that compared the incidence of pneumonia with ranitidine and sucralfate. The quality score for these trials was 5.6 (2.3). The analysis of these eight trials (table 4) showed a significantly increased risk of pneumonia with ranitidine compared with sucralfate (summary odds ratio 1.51, 1.00 to 2.29, $P=0.05$; 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 sucralfate⁸ does not allow any conclusion to be drawn; the trials on ranitidine⁸⁻¹² show no difference compared with placebo.

Design of new trials

Authoritative recommendations suggest the use of ranitidine for prophylaxis for stress ulcers,²³ but 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.

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 because cimetidine has been shown to be possibly effective,² but this would mean 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

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

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. The statistical power of these comparisons was better for meta-analysis E (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 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.

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Contributors: AM had the original idea for the present study, set up the project, designed the protocol, organised searches, supervised data extraction, supervised cross checking and validation work, assessed methodological quality of the trials, carried out statistical calculations, and discussed analysis and subsequent results. ST had the original idea for the present study, set up the project, designed the protocol, organised searches, checked accuracy of data extraction, supervised cross checking and validation work, carried out statistical calculations, and discussed analysis and subsequent results. MV was involved in the original project, helped to devise protocol, organised searches, extracted data from the studies, assessed methodological quality of the trials, arranged statistical input, collaborated in analyses, and discussed analysis and subsequent results. MG was involved in the original project,

helped to devise protocol and organise searches, assessed methodological quality of the trials, collaborated in analyses, and discussed analysis and subsequent results. AC was involved in the original project, helped to devise protocol and organise searches, supervised data extraction, collaborated in analyses, and discussed analysis and subsequent results. The paper was written jointly by AM and ST. AM is guarantor.

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