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Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine

R S B Ehsanullah, M C Page, G Tildesley, J R Wood

Abstract

Objective—To evaluate the prophylactic effect of ranitidine 150 mg twice daily in patients requiring one of the following non-steroidal anti-inflammatory drugs: naproxen, piroxicam, diclofenac, and indomethacin. In addition, risk factors were studied in order to help in targeting of such treatment to specific groups of patients.

Design—Double blind, placebo controlled, randomised, parallel group with endoscopic assessments at 0, 4, and 8 weeks.

Setting—Multicentre outpatient study at secondary referral centres in five European countries.

Patients—297 patients with rheumatoid arthritis or osteoarthritis over the age of 18 without lesions in the stomach and duodenum at baseline endoscopy (after one week without taking non-steroidal anti-inflammatory drugs). Those taking other antirheumatic agents, concomitant ulcerogenic drugs, or treatment for peptic ulcers within the previous 30 days were excluded. Age, sex, arthritic disease, and type of non-steroidal anti-inflammatory drug used were comparable in the two treatment groups. In all, 263 patients completed the trial.

Interventions—Ranitidine 150 mg twice daily or placebo (plus the selected non-steroidal anti-inflammatory drug) was prescribed within five days after the baseline endoscopy for two consecutive periods of four weeks. Paracetamol was permitted during the study, but not antacids. Patients were withdrawn if the most severe grade of damage (including ulceration) was found at the four week endoscopy or when indicated, or with lesser damage at the investigator's discretion.

End point—Frequency of gastric and duodenal ulceration or lesions, or both.

Measurements and main results—The cumulative incidence of peptic ulceration by eight weeks was 10.3% (27/263); 2 out of 135 (1.5%) developed duodenal ulceration in the ranitidine group, compared with 10 out of 126 (8%) taking placebo. The frequency of gastric ulceration was the same (6%) for the two groups at eight weeks. Though significantly fewer gastric lesions developed in the ranitidine group by four weeks, this difference was not evident by eight weeks. The frequency of non-ulcerative lesions in the duodenum did not differ greatly for the two groups at either time point. Twelve out of 75

(16%) patients taking piroxicam developed peptic ulceration, of whom two thirds had duodenal ulceration. Patients with a history of peptic ulcer were particularly susceptible to recurrent ulceration, against which ranitidine offered some protection.

Conclusions—Ranitidine 150 mg twice daily significantly reduced the incidence of duodenal ulceration but not gastric ulceration when prescribed concomitantly with one of four commonly used non-steroidal anti-inflammatory drugs.

Introduction

Non-steroidal anti-inflammatory drugs for the treatment of arthritis are the most widely prescribed group of drugs world wide. In the United Kingdom 23 million prescriptions were issued in 1986 for this group of drugs, accounting for around 5% of all NHS prescriptions. These drugs, however, account for 25% of all the suspected adverse drug reactions reported to the United Kingdom Committee on Safety of Medicines each year and 21% reported to the United States Food and Drug Administration.^{1,2} The commonest and most serious of these reactions are gastrointestinal.³⁻⁵ Up to 60% of patients taking these drugs report dyspepsia,⁵⁻⁷ but this has not proved to be a reliable guide to the presence of gastroduodenal lesions.⁸⁻¹²

Aspirin causes gastroduodenal damage in more than 80% of subjects,^{13,14} varying from acute microscopic gastric changes¹⁵ to potentially more serious chronic gastric ulceration or haemorrhage.^{7,16-18} In a large prospective study gastric lesions were found in a third of patients taking non-steroidal anti-inflammatory drugs for a year and in half of those receiving two or more such drugs.⁸ Langman calculated a rate of one episode of gastrointestinal haemorrhage per 6000 prescriptions for non-steroidal anti-inflammatory drugs¹⁹; estimates for attributable mortality in the United Kingdom range from 200²⁰ to over 4000²¹ deaths annually. Epidemiological data also point to rising rates of ulcer perforation in the elderly, partly attributable to the increased use of this group of drugs.²² Other centres in the United Kingdom have noted this association,²³⁻²⁵ though some studies from Australia and America do not show similar trends.^{26,27}

Attempts to decrease the risks associated with anti-inflammatory treatment by using enteric coated formulations, suppositories, or prodrugs have not

Department of
Gastroenterology, Glaxo
Group Research Limited,
Greenford, Middlesex
UB6 0HE

R S B Ehsanullah, PHD,
principal clinical research
scientist

M C Page, MRCP, senior
clinical research physician
J R Wood, MB, director

Hartlepool General
Hospital, Hartlepool,
Cleveland TS24 9AH
G Tildesley, FRCP, consultant
physician

Correspondence to:
Dr Wood.

solved this problem. Antiulcer drugs are often prescribed concomitantly, though little is known about their efficacy and advantages. Theoretically any decrease in acid secretion should minimise gastro-duodenal damage and ease recovery. In a study on bleeding induced by aspirin, inhibition of acid secretion represented the best strategy to reduce gastric mucosal bleeding.²⁸ In other studies ranitidine and cimetidine protected against damage induced by aspirin in volunteers.²⁹⁻³²

We evaluated the protection given by ranitidine 150 mg twice daily in a large population of patients requiring non-steroidal anti-inflammatory drugs. In addition, we studied risk factors to target treatment to specific subgroups of patients.

Patients and methods

Patients with rheumatoid arthritis or osteoarthritis, aged over 18, and requiring treatment with non-steroidal anti-inflammatory drugs were recruited into a double blind trial conducted in 18 centres in five countries—France, Ireland, Norway, Sweden, and the United Kingdom. Criteria for inclusion were verification by endoscopy of a “clean” stomach and duodenum as defined by a score of zero on a grading scale modified from that of Lanza *et al*³ (table I) and at least one week without taking non-steroidal anti-inflammatory drugs before entry to the trial. Patients taking gold, penicillamine, azathioprine, or chloroquine were excluded. Other exclusion criteria comprised concomitant use of ulcerogenic drugs, treatment for peptic ulcers during the preceding 30 days (except for low dose antacids), use of corticosteroids, pregnancy or lactation, gastro-intestinal malignancy, dysphagia, rheumatoid arthritis of the cervical spine, and impairment of liver or kidney function. Patients gave their informed consent to the study, which was approved by ethics committees in each country. The trial was conducted in accordance with the Declaration of Helsinki.

Patients were allocated on a double blind sequential basis to receive treatment with either ranitidine 150 mg twice daily or a matching placebo tablet twice daily according to a predetermined randomisation code balanced in blocks of 10 generated by Glaxo Group Research Limited. Non-steroidal anti-inflammatory drug treatment was started concomitantly with each centre using one of the following four agents at doses not less than those indicated: naproxen (750 mg/day), piroxicam (20 mg/day), diclofenac (100 mg/day), or indomethacin (100 mg/day). Treatment was started within five days after the initial endoscopy. Use of paracetamol, but not antacids, was permitted during the study period. All drugs for the trial were prepacked and supplied by the company.

Endoscopy was repeated after four weeks; patients with little or no gastroduodenal damage at this examination continued treatment for a further four weeks and were then reassessed and examined by endoscopy. Patients with grade 4 gastroduodenal damage were withdrawn from the study and those with grade 3 either continued or were withdrawn at the discretion of the investigator. Biopsy was performed on gastric ulcers to exclude malignancy. Any patient returning for an unscheduled visit because of dyspepsia was encouraged to undergo a gastroscopy.

STATISTICAL METHODS

Calculation of the sample size was based on the proportion of patients showing clinically important gastroduodenal damage when examined by endoscopy. This was prospectively defined as grade 2, 3, or 4 on a modified Lanza scale and was expected to develop in 30% of patients receiving the placebo. A sample size of 320 patients was chosen to give a 90% power of

detecting a reduction to 15% on ranitidine at $p \leq 0.05$. Patients were included in the analysis of gastroduodenal damage if they had undergone a follow up endoscopy up to and including four weeks and up to and including eight weeks. The eight week analyses were cumulative, incorporating all four week data.

The statistical analysis of the trial examined two aspects. The first of these, and the primary objective of the trial, was to compare the incidence of clinically important gastroduodenal damage in the ranitidine and placebo groups. The damage to the stomach and duodenum was graded and analysed separately. The proportion of patients with evidence of damage was analysed using the Mantel-Haenszel χ^2 test without continuity correction.³³ The odds ratio (odds of developing damage on placebo/odds of developing damage on ranitidine) was estimated together with 95% confidence limits.³⁴ Further analyses were performed stratified for various risk factors but they led to similar levels of significance and are not reported here. The Mantel-Haenszel approach also included tests for treatment by risk factor interactions and the one interaction detected is reported. The incidence of ulcers was analysed using Fisher's exact test as the numbers were small. All significance tests were two tailed.

The second aspect of the analysis examined the importance in terms of gastroduodenal damage of various risk factors irrespective of trial treatment. The different levels of each risk factor were initially compared using the Mantel-Haenszel test, grouping the trial treatments. The results were confirmed using logistic regression to allow for the confounding effects of other risk factors.³⁵

Results

There were 297 patients entered into the trial. Thirty four patients were excluded at four weeks because they did not have an endoscopy at that time. These comprised 14 taking ranitidine, of whom five

TABLE II—Demographic details of patients in trial

	Ranitidine	Placebo
No of patients	137	126
Sex (men:women)	58:79	47:79
Age (years):		
Mean (SD)	57 (11)	60 (13)
Range	25-85	22-87
Smoking state:		
None	79	90
<20 cigarettes/day	44	24
≥20 cigarettes/day	10	5
Cigar or pipe	4	7
Alcohol intake:		
None	65	76
<50 g/day	71	50
≥50 g/day	1	0
Arthritic disease:		
Osteoarthritis	101	96
Rheumatoid arthritis	34	28
Other	2	2
Median duration (range) of arthritis (years)	8 (0-50)	6 (0-45)
Previous dyspepsia	71	72
Previous peptic ulcer	11	11
Previous H ₂ receptor antagonist	20	21
No previous use of non-steroidal anti-inflammatory drugs	60	46

failed to return or refused to continue and nine were withdrawn without endoscopy because of adverse reactions, and 20 taking placebo, of whom 14 and six fell into these two categories respectively. Of the remaining 263 patients, 137 received ranitidine and 126 placebo. The two treatment groups were comparable with respect to patient demography (table II). The non-steroidal anti-inflammatory drugs used during the trial were naproxen (161 patients), piroxicam (75), diclofenac (17), and indomethacin (10).

By counting ranitidine and placebo tablets returned

TABLE I—Grading of gastroduodenal mucosal lesions. Modified from Lanza *et al*³

Grade	No of erosions and submucosal haemorrhages
<i>Stomach:</i>	
0	0-2
1	3-5
2	6-10
3	>10
4	Too many to count
	Gastric ulcer (>0.5 cm in diameter)
<i>Duodenum:</i>	
0	0-1
1	2-5
2	6-10
3	>10
4	Duodenal ulcer

at four weeks we judged that 75% of patients took more than 90% of their oral treatment.

GASTRODUODENAL DAMAGE

After four weeks of treatment there were significantly fewer patients with gastric mucosal lesions (including ulcers) in the ranitidine treatment group than in the placebo group (15% *v* 25%, odds ratio 1.9, 95% confidence interval 1.0 to 3.5 (table III)). No

TABLE III—Numbers (percentages) of patients with gastric and duodenal damage after four and eight weeks

	Stomach		Duodenum	
	Ranitidine (n=137)	Placebo (n=126)	Ranitidine (n=137)	Placebo (n=126)
<i>Ulcers</i>				
Four weeks	4 (3)	6 (5)	2 (1.5)	10 (8)*
Eight weeks	8 (6)	7 (6)	2 (1.5)	10 (8)*
<i>Grades 2-4</i>				
Four weeks	21 (15)	32 (25)†	13 (9)	16 (13)
Eight weeks	38 (28)	40 (32)	17 (12)	17 (13)

*p=0.024 (Fisher's exact test).

†p=0.042 (Mantel-Haenszel χ^2 test).

additional benefit was observed in the stomach after continuing treatment for a further four weeks. After four weeks' treatment gastric ulceration was found in 3% of those receiving ranitidine and 5% of those taking placebo (p=0.527) and in 6% in both treatment groups after eight weeks. In the duodenum there was a significantly lower frequency of ulceration in the ranitidine group than in the placebo group (1.5% *v* 8%, odds ratio 5.8, confidence interval 1.4 to 23.6) after four and eight weeks (when no new duodenal ulcers had formed). No patient developed both a gastric and a duodenal ulcer.

The overall incidence of gastric and duodenal ulceration was 16% (12/75) in patients receiving piroxicam, 9% (14/161) with naproxen, and 6% (1/17) with diclofenac. Piroxicam caused significantly more duodenal damage than naproxen at both four and eight weeks (table IV). In both ranitidine and placebo

TABLE IV—Numbers (percentages) of patients with duodenal damage after treatment with naproxen or piroxicam

	Ranitidine		Placebo		p Value for naproxen <i>v</i> piroxicam†
	Naproxen (n=85)	Piroxicam (n=38)	Naproxen (n=76)	Piroxicam (n=37)	
<i>Ulcers</i>					
Four weeks*	1 (1)	1 (3)	3 (4)	7 (19)	0.024 (0.008)
<i>Grades 2-4</i>					
Four weeks	7 (8)	6 (16)	7 (9)	9 (24)	0.014 (0.013)
Eight weeks	10 (12)	7 (18)	8 (11)	9 (24)	0.039 (0.046)

*No further patients had developed duodenal ulceration by eight weeks.

†Value in parenthesis is after adjusting for trial treatment, sex, history of ulcers, smoking, and arthritis type.

groups combined there were four (2%) duodenal ulcers in those treated with naproxen and eight (11%) in those given piroxicam. There was no significant difference in ulceration of the stomach between patients taking these two drugs; eight (5%) and 10 (6%) patients developed gastric ulcers during treatment with naproxen, and two (3%) and four (5%) with piroxicam after four and eight weeks' treatment respectively. At four weeks 7 out of 41 (17%) women had duodenal and gastric ulcers associated with piroxicam compared with 3 out of 34 (9%) men, whereas at eight weeks the frequency of ulcers was more balanced (17% women compared with 5 out of 34 (15%) men). In the naproxen treatment group 4 out of 96 and 6 out of 96 women had peptic ulcers (gastric only) at four and eight weeks

respectively, compared with 8 out of 65 (12%) men at both time points.

RISK FACTORS

The 22 patients with a history of peptic ulceration showed a significantly greater susceptibility to recurrent ulceration while taking non-steroidal anti-inflammatory drugs and seemed to obtain greater protection with ranitidine than patients without a history of ulcers (table V).

TABLE V—Ulceration in patients with or without history of peptic ulcer. Values are numbers (percentages) of patients

	Ranitidine		Placebo		p Value for history <i>v</i> no history*
	History (n=11)	No history (n=126)	History (n=11)	No history (n=115)	
Four weeks	1 (9)	5 (4)	5 (45)	11 (10)	0.011 (<0.001)
Eight weeks	2 (18)	8 (6)	6 (55)	11 (10)	0.001 (<0.001)

*Value in parenthesis is after adjusting for trial treatment, sex, smoking, arthritis type, and non-steroidal anti-inflammatory drug.

Duodenal damage (but not ulceration alone) was influenced by the patient's sex, smoking habit, type of non-steroidal anti-inflammatory drug, and type of arthritic disease but not by age, history of dyspepsia, or previous use of non-steroidal anti-inflammatory drugs. The incidence of duodenal damage in the women at both four (4%) and eight weeks (6%) was significantly less than that in men (21% and 23% respectively; table VI). Furthermore, the women obtained significantly more protection from ranitidine than men (table VI) (test for treatment by sex interaction,

TABLE VI—Duodenal damage at four weeks for men and women, smokers and non-smokers, and patients with osteoarthritis and rheumatoid arthritis. Values are numbers (percentages) of patients

	Ranitidine		Placebo		p Values for comparisons of all patients*
	Men (n=58)	Women (n=79)	Men (n=47)	Women (n=79)	
Ulcers	2 (3)	0	5 (11)	5 (6)	0.303 (0.145)
Grades 2-4	13 (22)	0	9 (19)	7 (9)	<0.001 (<0.001)
	Smoker (n=58)	Non-smoker (n=79)	Smoker (n=36)	Non-smoker (n=90)	p Value for smokers <i>v</i> non-smokers
	Ulcers	Grades 2-4	Ulcers	Grades 2-4	
Ulcers	1 (2)	1 (1)	5 (14)	5 (5)	0.449 (0.259)
Grades 2-4	11 (19)	2 (3)	8 (22)	8 (9)	<0.001 (0.003)
	Osteo- arthritis (n=101)	Rheumatoid arthritis (n=34)	Osteo- arthritis (n=96)	Rheumatoid arthritis (n=28)	p Value for osteoarthritis <i>v</i> rheumatoid arthritis
	Ulcers	Grades 2-4	Ulcers	Grades 2-4	
Ulcers	1 (1)	1 (3)	10 (10)	0	0.345 (0.624)
Grades 2-4	11 (11)	2 (6)	16 (17)	0	0.023 (0.104)

*Value in parenthesis is after adjusting for trial treatment, sex, history of ulcers, smoking, and arthritis type.

p=0.012 at four weeks; p=0.039 at eight weeks). The incidence of duodenal mucosal damage in the women was independent of age, though four of the duodenal ulcers occurred in those over 55 and only one in those under 55. Smokers showed significantly more duodenal damage than non-smokers irrespective of treatment, and patients with osteoarthritis showed significantly more duodenal damage than those with rheumatoid arthritis (table VI). None of these factors, however, seemed to influence the degree of gastric damage, though the frequency of such damage in patients with osteoarthritis taking placebo was 29% compared with 11% in those with rheumatoid arthritis.

GASTROINTESTINAL SYMPTOMS

The prevalence and severity of gastrointestinal symptoms (epigastric pain, heartburn, nausea, and vomiting) were similar for the two treatment groups before the trial and at four and eight weeks—for

example, before the trial 18% of all the patients presented with some degree of epigastric pain; at four and eight weeks 25% and 21% respectively had this symptom. This trial was not designed to evaluate patients with symptoms; among the patients with severe gastroduodenal damage graded 3 and 4 at four weeks, however, 79% had symptoms whereas among those with lesser grades of damage 43% had symptoms ($p < 0.001$).

ADVERSE REACTIONS

Adverse reactions were reported by 25 of the 151 (17%) patients taking ranitidine and 22 of the 146 (15%) patients taking placebo. Their distribution was comparable for the two treatment groups. Most reactions (43% and 64% respectively) were gastrointestinal symptoms. A total of 37 patients, 19 in the ranitidine group and 18 in the placebo group, withdrew from the study because of adverse reactions. Of these, 10 and 13 patients in the two groups, respectively, discontinued treatment because of adverse gastrointestinal effects. Other reasons for withdrawal included headache (eight patients), dizziness (three), angina (two), disturbed sleep (two), depression (one), and rash (one).

Discussion

The results of this prospective trial, the largest of its kind to date, show that ranitidine 150 mg twice daily administered over eight weeks to arthritic patients without gastroduodenal lesions taking non-steroidal anti-inflammatory drugs provides significant prophylaxis against the development of duodenal ulceration and gastric mucosal lesions during the first four weeks. There was no significant difference between the groups in the incidence of gastric ulceration but, despite the size of the trial, there were relatively few gastric ulcers in either group.

Selecting patients without lesions at the first endoscopy, a group possibly less susceptible to damage, may partly account for two thirds of the patients showing insufficient damage to enable any protective effect of ranitidine to be detected. Inclusion of such patients may also have influenced the results in the studies on prophylaxis reported by Roth³⁶ and Bianchi Porro.³⁷ The failure of Roth to show a protective effect with cimetidine may have been because of less than adequate acid inhibition. Furthermore, since the clinical relevance of mucosal lesions in these studies is not clear, basing conclusions on the evaluation of actual ulceration is preferable.

In our study few ulcers were seen between four and eight weeks and none in the duodenum, suggesting possible adaptation of the mucosa, as shown in some studies of aspirin and indomethacin treatment.^{13 38 39} Damage induced by non-steroidal anti-inflammatory drugs has generally been assumed to occur in the stomach. Several studies, however, have implicated the duodenum as an alternative or additional site.^{10 11 31} We noted a higher incidence of duodenal ulceration (mostly in patients receiving piroxicam) than of gastric ulceration. Piroxicam was associated with a higher incidence of peptic ulceration than was naproxen (16% and 9% respectively), and treatment with piroxicam was associated with eight of the 12 duodenal ulcers that developed during the study. Several anecdotal reports have implied that piroxicam causes more ulcers than other non-steroidal anti-inflammatory drugs, especially in the elderly,⁴⁰⁻⁴³ though such conclusions have been disputed.¹⁴⁴ Husby compared piroxicam with naproxen in the treatment of over 2000 patients with osteoarthritis over 12 weeks, and gastrointestinal side effects were reported by 31% of patients taking piroxicam and 38% of those taking naproxen. The

incidence of serious side effects—such as peptic ulcer or gastrointestinal haemorrhage—was reported as only 1% for both drugs. These patients, however, were not subjected to routine gastrointestinal endoscopy.⁴⁵

We showed that patients with a history of peptic ulcers not only were more susceptible to recurrent ulceration from non-steroidal anti-inflammatory drugs than patients without such a history (an observation also made by Caruso and Bianchi Porro⁸ and Larkai *et al*¹²) but also seemed to benefit more from ranitidine prophylaxis. Doctors are advised not to prescribe non-steroidal anti-inflammatory drugs to patients with a history of peptic ulcer disease or abdominal symptoms.²³ If they have to take these drugs they may particularly benefit from concomitant treatment with ranitidine.

Over four times as many of the men as the women sustained duodenal damage but the women obtained significantly more protection from ranitidine. This was confirmed when the possible confounding effects of smoking and other factors were taken into account. Age did not appear to be a risk factor. Clinch *et al* have reported an association between use of non-steroidal anti-inflammatory drugs and duodenal ulceration in elderly women,⁴⁶ and our data showed increased duodenal ulceration in the women over 55 compared with those below this age.

Patients with rheumatoid arthritis experienced significantly less duodenal and gastric damage than those with osteoarthritis, though Caruso and Bianchi Porro⁸ and Larkai *et al*¹² noted similar effects in both. There was no serious gastrointestinal illness in either group in our study. Those adverse reactions that occurred were probably because of the non-steroidal anti-inflammatory drugs.

We have shown that patients with a history of peptic ulcers are at increased risk of recurrent ulceration while non-steroidal anti-inflammatory drugs are being taken. Protection against duodenal ulceration, particularly that associated with piroxicam, was evident in those patients taking ranitidine, though some ulceration still occurred. Further work is needed to substantiate these findings and to evaluate whether greater suppression of acidity may provide any additional benefit.

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Incidence and implications of natural deaths of road users

M S Christian

Abstract

A prospective study was carried out over the 10 years 1978-87 to determine the incidence and implications of sudden death in road users—that is, drivers, pedestrians, cyclists, and motorcyclists. During the study period 30 000 patients were seen in the same accident and emergency departments of East Berkshire after road traffic incidents or accidents, of whom 267 either were brought in dead or died within two hours after arrival. Of these patients, 64 (24%) were found to have died of natural causes due to pre-existing disease or to have been killed in an incident that occurred as a result of a medical or psychiatric condition. Twelve of the patients sustained physical injury; all 64 came to necropsy. Only one incident resulted in the death of another person in addition to the natural death of a patient.

It is concluded that sudden natural death occurring in road users does not present an appreciable hazard to other road users.

Introduction

Any death or severe injury caused to road users by the sudden death of another road user in charge of a vehicle is usually followed by widespread publicity and expressions of public concern. Such cases are not common, but the implications of sudden natural death to a road user have been considered by several authorities and resulted in publications for the guidance of medical practitioners who may have to advise people of their fitness to drive.^{1,2} The incidence of natural deaths in road users does not appear to have been studied against a background of population density, types of roads serving the area, age groups, sex, and incidence of naturally occurring diseases.

This prospective study (1978-87) therefore had four objectives: (a) to determine the size of the problem; (b) to identify the degree of risk to other road users; (c) to determine the underlying pathological conditions leading to death; and (d) to consider whether in the light of the findings present advice to patients with certain medical conditions requires reassessment.

Patients and methods

Between 1 January 1978 and 31 December 1987 details were noted of all patients brought to the accident and emergency departments of East Berkshire who either were dead on arrival or died within two hours after arrival and in whom death was associated with a road "incident." As much history as possible was obtained from relatives, ambulance personnel, police, and witnesses. In particular, incidents involving only one vehicle were noted. Getting information about this category of patient was facilitated by the policy in East Berkshire of all patients apparently dead being brought into the resuscitation room, where death is confirmed after careful examination and certain basic investigations and examinations are performed authoritatively to confirm death.³ All such patients were subjected to a coroner's necropsy. Though in many cases there was a suspicion that a natural death had been a precipitating cause of the incident, the absence of severe external injury did not necessarily preclude traumatic death, nor did the presence of visible external injury indicate that trauma was an important factor leading to death.

Information from general practitioners was obtained when possible to ascertain the patients' previous medical history and drug treatments. In all cases full necropsy reports were obtained.

Accident and Emergency
Department, Wexham Park
Hospital, Slough SL2 4HL
M S Christian, FRCS,
consultant in charge