	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*			*NAP*		
Subjects exposed	*N=1248*			*N=354*			*N=192*			*N=82*			*N=71*			*N=85*		
Adverse events	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*	*Count (%)*	*Sev*	*Rel*
# of subj with any adverse events	*65 (5.2)*	*4*	*28*	*14 (4.0)*	*4*	*12*	*12 (6.3)*	*0*	*2*	*0*			*0*			*1(1.2)*	*0*	*1*
Cardiovascular system	1 (0.1)	1																
Hemorrhage	1 (0.1)	1																
Digestive system	10 (0.8)		3				9 (4.7)		2									
Diarrhea	1 (0.1)		1															
Flatulence							1 (0.5)											
Nausea	7 (0.6)		2				7 (3.6)		2									
Vomiting	2 (0.2)						1 (0.5)											
Nervous system	23 (1.8)		6	5 (1.4)	3	6	3 (1.6)											
Dizziness	6 (0.5)		2	5 (1.4)	3	5	1 (0.5)											
Somnolence	14 (1.1)		3				1 (0.5)											
Vertigo	1 (0.1)		1			1	1 (0.5)											
Paresthesia	1 (0.1)																	

	Ketoprofen			*Ibuprofen*			*Placebo*			*Acetaminophen*			*Aspirin*			*NAP*		
Subjects exposed	*N=1248*			*N=354*			*N=192*			*N=82*			*N=71*			*N=85*		
Adverse events	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***	***Count (%)***	***Sev***	***Rel***
# of subj with any adverse events	***65 (5.2)***	***4***	***28***	***14 (4.0)***	***4***	***12***	***12 (6.3)***	***0***	***2***	***0***			***0***			***1(1.2)***	***0***	***1***
Respiratory system	3 (0.2)			1 (0.3)			1 (0.5)											
Pharyngitis	1 (0.1)						1 (0.5)											
Rhinitis	2 (0.2)			1 (0.3)														
Skin and Appendages	12 (1.0)	3	13	4 (1.1)	4	5												
Rash	1 (0.1)	1																
Pruritus	1 (0.1)	1	1															
Sweating				4 (1.1)	4	5												
Vein irritation	11 (0.9)	1	11															
Urogenital						5	1 (0.5)											
Polyuria							1 (0.5)											
Urine abnormality						5												

TABLE 3 Premature Termination Due to Adverse Events

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 6.25mg	S90-002	1037 SPC	Ear Pain	None	Two hours after molar extraction, the patient discontinued from the study because of severe ear pain, thought to be referred pain related to the surgical procedure. The patient was treated with acetaminophen 1000mg with relief.
KET 12.5mg	S90-003	2007 GJC	Dizziness (moderate) Headache (moderate)	Probable (both events)	This 43-year old Caucasian female with a history of chronic sinusitis and headache took aspirin and Entex-LA for her symptoms prior to entering the study. The consumer took KET (2 x 12.5 mg) on 2/12/91 to treat a moderate headache. She experienced no relief with the KET and developed sharp pains in her head and dizziness following the KET dose. The consumer stopped study drug and the AEs resolved the same day.
KET 12.5mg	S90-003	2831 MFR	Dyspepsia (moderate)	Probable	This 37-year old Caucasian female took ibuprofen and aspirin for headache and menstrual cramps prior to entering the study. The consumer took KET (4 x 12.5 mg) over a 5-hr period on 1/10/91 for a moderate backache. The KET gave her fair relief from her backache. On the same day (1/10/91) she developed dyspepsia for which she took TUMS. The consumer stopped study drug and the dyspepsia resolved 3 days post study.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 12.5mg	S90-003	2925 MAS	Dizziness (moderate) Vasodila-tation (moderate)	Probable (both events)	This 44-year old Caucasian male took aspirin for headaches prior to entering the study. He also was taking allergy shots for allergic rhinitis. The consumer took KET (2 x 12.5 mg) over a one-hour period for moderate muscular aches. The KET provided fair relief of his symptoms. On the same day (1/31/91) he experienced dizziness and hot flashes within 1 hour after the second dose. He took diphenhydramine for these symptoms. Consumer stopped study drug and AEs resolved one day post study.
KET 12.5mg	S90-003	3309 RM	Nausea (moderate)	Probable	This 24-year old Hispanic female took acetaminophen for headaches prior to entering the study. This consumer took KET (1 x 12.5 mg) once a day for 2 days for moderate backache. The KET gave her no relief from her backache. On the second day (1/24/91) the consumer developed nausea after dosing. The consumer stopped study drug and the nausea resolved the same day.
KET 12.5mg	S90-003	4417 FFL	Nausea (moderate)	Possible	This 27-year old Caucasian female took ibuprofen for headaches prior to entering the study. She has a history of pharyngitis, sinusitis, allergic rhinitis, persistent URI, GI disease and back pain. The consumer took KET (3 x 12.5 mg) over a 4-hr period on 1/10/91 for moderate backache. The KET offered poor relief. After taking the KET the consumer experienced nausea for which she took Anacin-3. The consumer stopped study drug and the nausea resolved the same day.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 12.5mg	S90-003	5016 DBM	Dyspepsia (moderate)	Possible	This 59-year old Caucasian female took ibuprofen and aspirin for headache and arthritis prior to entering the study. She also has a history of hypertension and stomach discomfort. The consumer took KET (3 x 12.5 mg) over a 4-hr period on 1/23/91 for moderate arthritis pain. The KET offered no relief. After taking the KET the consumer reported stomach discomfort. The consumer stopped study drug and the stomach discomfort resolved one day post-study.
KET 12.5mg	S90-003	6512	Myalgia (severe)	Remote	This 47-year old black female took ibuprofen, aspirin and acetaminophen for myalgia prior to entering the study. She also has a history of depression. The consumer took KET (2 x 12.5 mg) over a 4-hr period on 2/8/91 for moderate muscular aches. The KET offered no relief. The consumer developed myalgia of chest, flank and abdomen after taking KET which resolved when consumer stopped study drug.
KET 12.5mg	S90-003	6520 BRS	Amblyopia (severe) Headache (Severe)	Possible (both events)	This 63-year old Caucasian female took aspirin, ibuprofen and acetaminophen for myositis prior to entering the study. She also has a history of IDDM, hypothyroidism and diabetic retinopathy. The consumer took KET (10 x 12.5 mg) over 3 days for moderate muscular aches. The KET offered fair relief. On Day 2, the consumer developed blurred vision and a headache. The headache was treated with aspirin. The AEs resolved when consumer stopped study drug.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 12.5mg	S90-003	6609 IEB	Nausea (severe) Abdominal pain (severe)	Probable (both events)	This 74-year old Caucasian female took acetaminophen for backache prior to entering the study. She also has a history of hypertension and hypercholesterolemia. The consumer took KET (1 x 12.5 mg) on 1/8/91 for severe backache. The KET offered good relief. The consumer developed nausea and abdominal pain which subsided after study drug was stopped. The consumer has reported similar reactions to aspirin in the past.
KET 12.5mg	S90-003	7329 LKC	Diarrhea (severe) Dyspepsia (moderate)	Probable (both events)	This 45-year old Caucasian female took aspirin for back pain prior to entering the study. She also has a history of arthritis, migraine headaches and sinus infections. The consumer took KET (8 x 12.5 mg) over 7 days for moderate arthritis. The KET gave her good relief. On Day 6 (1/30/91) consumer began experiencing diarrhea and indigestion. Study drug was stopped on Day 7 and AEs resolved one day later.
KET 12.5mg	S90-003	7450 KJT	Abdominal Pain (moderate)	Possible	This 19-year old Caucasian male took ibuprofen for headaches prior to entering the study. He took KET (1 x 12.5 mg) on 12/31/90 to treat a moderate headache and got no relief. After taking study drug, the consumer had abdominal pains. Consumer stopped study drug and took acetaminophen for headache and abdominal pain. The AE resolved on 1/1/91.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 12.5mg	S90-003	10655 TLC	Dyspepsia (moderate)	Possible	This 39-year old Caucasian male took acetaminophen for headaches prior to entering the study. He took KET (1 x 12.5 mg) on 3/10/91 to treat a moderate headache and got no relief. After taking study drug, he experienced stomach irritation which resolved the same day after stopping study drug. Acetaminophen was taken to relieve headache.
KET 12.5mg	S90-003	12301 RP	Abdominal Pain (moderate)	Probable	This 39-year old Hispanic female took ibuprofen for headache and menstrual cramps prior to entering the study. At the time of study entry, the consumer had a moderate upper respiratory infection for which she was taking astemizole and cefaclor. She also took KET (8 x 12.5 mg) over 2 days to treat this condition and got fair relief from her symptoms. On the second day of study drug (12/19/90) the consumer had burning in her stomach which she treated with Gaviscon. The AE resolved the same day after stopping study drug.
KET 12.5mg	S90-003	12837 KEL	Vasodila-tation (moderate) Nervousness (moderate)	Possible	This 32-year old Caucasian female took acetaminophen for headache and cramps prior to entering the study. On 2/20/91, the consumer took KET (2 x 12.5 mg) for moderate menstrual cramps and got fair relief from her symptoms. After taking study drug she experienced flushing and shakiness which resolved the same day once study drug was stopped.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 12.5mg	S90-003	14322 MEF	Abdominal Pain (moderate)	Possible	This 22-year old Caucasian female took ibuprofen for headache and muscle aches prior to entering the study. On 1/27/91 she took KET (3 x 12.5 mg) over a 3 1/2 hr period for moderate muscular aches, and got poor relief from her symptoms. After taking study drug, the consumer experienced abdominal pain which resolved the same day.
KET 12.5mg	S90-003	14815 RRZ	Taste perversion (mild)	Probable	This 26-year old Caucasian female took ibuprofen for muscle aches prior to entering the study. On 2/9/91 she took KET (1 x 12.5 mg) for moderate muscle aches and got no relief. After taking study drug, she had a bad taste in her mouth which resolved the day after stopping study drug.
KET 12.5mg	S90-003	15423 MSB	Nausea (severe)	Possible	This 36-year old Caucasian male took acetaminophen for headache and muscle aches prior to entering the study. He took KET 6 x 12.5 mg) over a 2-day period for moderate backache, and got fair relief from his symptoms. On the second day of study drug (1/31/91) the consumer reported nausea which resolved the next day.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 12.5mg	S90-003	16201 JLC	Dizziness (moderate) Somnolence (mild)	Dizziness (possible) Somno-lence (probable)	This 40-year old Caucasian female took acetaminophen for back pain prior to entering the study. She took KET (4 x 12.5 mg) over a 7-day period (12/20 - 12/26/90) for moderate muscular aches, with fair relief from her symptoms. On the first day (12/20/90) she reported dizziness and a "dopey feeling" which resolved when study drug was stopped on 12/26/90.
KET 12.5mg	S90-003	17409 DTW	Dizziness (severe) Nausea (moderate) Peripheral edema (moderate) Thirst (severe)	Dizziness (possible) Nausea (probable) Peripheral edema (remote) Thirst (remote)	This 34-year old Caucasian female took ibuprofen for headaches and cramps prior to entering the study. She took KET (9 x 12.5 mg) over a 4-day period for moderate menstrual cramps, with fair relief from her symptoms. On the second day of study drug (1/23/91) she experienced dizziness, nausea and thirst. On Day 3 (1/24/91), she developed peripheral edema. All AEs resolved 3 days after stopping study drug.
KET 12.5mg	S90-003	17414 VCS	Dyspepsia (mild) Dyspepsia (moderate)	Possible (both events)	This 34-year old Caucasian female took flurbiprofen and ibuprofen for menstrual cramps prior to entering the study. She took KET (14 x 12.5 mg) over a 4-day period for severe menstrual cramps, with fair relief from her symptoms. On Day 2 of study drug (2/11/91) she experienced mild GI upset which became moderate on 2/13/91. She took Rolaids for the GI upset on 2/13-14/91. Study drug was stopped on 2/13/91 and the GI upset resolved by 2/14/91.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 12.5mg	S90-003	17508 MAB	Abdominal Pain (mild)	Remote	This 22-year old Caucasian female took ibuprofen and acetaminophen for headache and menstrual cramps prior to entering the study. On 1/6/91 the consumer took KET (1 x 12.5 mg) for a moderate headache with no relief. The next day the consumer reported stomach cramps lasting 1 day and also took acetaminophen for headache relief on this day (1/7/91). The consumer reported having "stomach trouble" in the past.
KET 12.5mg	S88-002	186 I-R	Palpebral edema, Itching of throat and eyes, bilateral conjunctiviti s, coarse voice (All events: moderate)	Probable (all events)	The patient experienced an allergic reaction consisting of moderate palpebral edema lasting 105 minutes; moderate itching of throat and eyes lasting 55 minutes; moderate bilateral conjunctivitis lasting 100 minutes; and a moderate coarse voice lasting 85 minutes. The drug code was broken and the patient was discontinued from further hourly assessments. These adverse effects were thought to be related to the study medication. Patient was treated with benadryl 50mg i.m. with improvement in symptoms. Vital signs were normal. Patient reported a similar reaction (consisting of eye edema) with a prior use of ibuprofen.
KET 12.5mg	0287	139 C-Y	Cerebral Pressure, Bleeding, Coma (all events: severe)	None	The patient was hospitalized but died three days after an intake of 25mg ketoprofen of an intracranial hemorrhage caused by metastasis of a previously unknown melanoma. There was no causal relationship to study drug. The headache caused by the increased intracranial pressure was misdiagnosed as a tension-type headache.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
KET 25mg	S90-004-02	2028 L-R	Cervix Disorder (Moderate)	None	This patient had moderate squamous dysplasia on cervical biopsy which was reported 15 days after stopping ketoprofen 25mg. The patient was referred for calposcopic evaluation and follow-up.
Placebo	S92-012-02	2032 AMW	Surgery (Severe)	None	The patient had a breast biopsy (3/1/93) which showed malignancy. A mastectomy was performed on 3/8/93-eleven days after taking cycle 2 study drug (placebo). The patient began chemotherapy on 4/2/93. The patient reported all of these events on 4/8/93.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
IBU 200mg	S90-003	1319 EM	Diarrhea (moderate) Abdominal pain (moderate)	Probable (both events)	This 41-year old Caucasian female took ibuprofen for muscle aches and headaches prior to entering the study. On 1/5/92 the consumer took IBU (1 x 200 mg) for a mild headache with fair relief. She reported diarrhea with stomach cramps and pain after taking study drug. The consumer has a history of irritable bowel syndrome. She stopped study drug after 1 dose and the AEs resolved the next day. Acetaminophen was taken on 1/6/91 for headache.
IBU 200mg	S90-003	2011 ESN	Face edema (mild)	Probable	This 73-year old Caucasian female took aspirin for arthritis pain prior to entering the study. She has a history of hypertension and pancreatic insufficiency. From 1/24/91 to 1/30/91 the consumer took IBU (22 x 200 mg) for mild arthritis pain, with good relief of symptoms. On Day 6 of study drug (1/28/91) the consumer reported eyelid swelling. Study drug was stopped on 1/30/91 and the AE resolved 6 days post study (2/5/91).
IBU 200mg	S90-003	3340 DS	Rash (mild)	Probable	This 26-year old Hispanic female took ibuprofen for headaches prior to entering the study. On 1/24/91 the consumer took IBU (1 x 200 mg) for a moderate backache with poor relief of symptoms. She developed a slight facial rash after taking study drug. Hydrocortisone ointment was used, study drug was stopped and the rash disappeared the same day.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
IBU 200mg	S90-003	3903 JKW	Nausea (moderate) Vomiting (moderate)	Probable (both events)	This 34-year old Caucasian female took ibuprofen, acetaminophen and Darvocet for headaches prior to entering the study. She has a history of asthma, eczema, mitral valve prolapse and allergic rhinitis. On 12/21/90 the consumer took IBU (2 x 200 mg) within half an hour for a moderate headache with no relief. After the first dose, nausea was reported; vomiting occurred 1/2 hour later when the second dose was taken. Study drug was stopped. AEs resolved the same day and acetaminophen was taken to relieve the consumer's headache.
IBU 200mg	S90-003	10537 DJT	Nausea (moderate) Vasodil-atation (moderate)	Possible (both events)	This 40-year old Caucasian female took ibuprofen for headache and backache prior to entering the study. On 1/31/91 she took IBU (2 x 200 mg) for a moderate backache with no relief. After taking study drug she experienced nausea and warm flashes. Study drug was stopped, and the AEs resolved the next day (2/1/91). The consumer took ibuprofen on 2/1/91 for relief of backache.
IBU 200mg	S90-003	11001 VMH	Constipation (severe)	Remote	The 72-year old Caucasian female took acetaminophen for "aches and pains" prior to entering the study. She has a history of arthritis and hypertension. From 12/28/90 - 1/5/91 the consumer took IBU (23 x 200 mg) for moderate arthritis pain with fair relief of symptoms. On Day 7 (1/3/91) the consumer reported constipation. Study drug was stopped on 1/5/91, glycerin suppositories were used for the constipation and it resolved 3 days post study.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
IBU 200mg	S90-003	15418 LLK	Dyspepsia (mild)	Probable	This 23-year old Caucasian female took ibuprofen for headache prior to entering the study. She has a history of migraine. On 2/2/91 the consumer took IBU (6 x 200 mg) over a 5 1/2 hr period for moderate menstrual cramps with fair relief. She reported indigestion after taking study drug. Study drug was stopped on 2/2/91 and the indigestion resolved that same day. Rolaids were taken for relief of indigestion.
IBU 200mg	S90-003	16002 EB	Pain Flatulence Dyspepsia (all events)	Probable (all events)	This 43-year old Caucasian female took ibuprofen for muscle aches prior to entering the study. She has a history of gastritis, costochondritis, headaches and depression. On 2/9/91 the consumer took IBU (4 x 200 mg) over a 5-hr period for moderate muscular aches with fair relief. After taking study drug, the consumer reported an upset stomach, cramps and gas. Study drug was stopped on 2/9/91 and the AEs resolved that same day.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
IBU 200mg	S90-003	11015 REM	Abdominal pain (mild)	Probable	This 62-year old Caucasian male took aspirin and ibuprofen for arthritis prior to entering the study. On 1/17/91 - 1/18/91 the consumer took IBU (3 x 200 mg) for moderate arthritis pain with fair relief of symptoms. On 1/17/91 the consumer reported stomach cramps. Study drug was stopped on 1/18/91 and AE resolved the same day.
IBU 200mg	S90-003	13705 NSO	Dizziness (mild)	Probable	This 33-year old Caucasian female took Excedrin and acetaminophen for headaches prior to entering the study. The consumer had history of lightheadedness when taking ibuprofen. On 1/17/91 the consumer took IBU (2 x 200 mg) within 1 1/2 hours for a moderate headache with fair relief. After taking study drug, she became lightheaded. Study drug was stopped on 1/17/91 and the AE resolved that same day.
IBU 200mg	S90-003	13806 CD	Dyspepsia (moderate)	Possible	This 27-year old Caucasian female took aspirin for leg pain and headache prior to entering the study. On 1/21/91 she took IBU (3 x 200 mg) within 7 hours for a mild headache with fair relief. The same day, she reported an upset stomach. Study drug was stopped on 1/21/91 and the AE resolved the next day.

Study Drug Dose	Study #	Consumer # Initials	Event (COSTART) (Severity)	Relation to Study Drug	Comments
IBU 200mg	S90-003	14804 JCM	Dyspepsia (mild)	Possible	This 34-year old Caucasian female took aspirin and acetaminophen for headaches prior to entering the study. At the time of study entry she had a sinus infection and was taking amoxicillin and Guaifed. On 1/13/91, the consumer took IBU (1 x 200 mg) for a moderate headache. She reported an upset stomach after taking study drug. The consumer stopped study drug and the upset stomach resolved the same day (1/13/91). The consumer was considered a drop-out because she stopped treatment of the first event because of an AE. In violation of protocol, the consumer treated a second event before terminating the study on Day 9.
IBU 200mg	S90-003	14813 FM	Abdominal pain (moderate)	Probable	This 67-year old Caucasian male took acetaminophen for arthritis prior to entering the study. The consumer also has history of hypertension. On 2/11/91, he took IBU (2 x 200 mg) within 4 hours for moderate arthritis pain with good relief. The consumer experienced stomach distress after taking study drug. Drug was stopped and AE resolved the same day.
IBU 200mg	S90-003	14938 RJH	Dyspepsia (severe)	Probable	This 30-year old Caucasian male took aspirin, acetaminophen and ibuprofen for headache and back pain prior to entering the study. From 12/29/90 - 12/30/90 the consumer took IBU (3 x 200 mg) for moderate muscular ache with good relief. On 12/29/90 the consumer reported heartburn. Study drug was stopped on 12/30/90 and the heartburn resolved on 12/31/90.

Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs

M J S Langman, J Weil, P Wainwright, D H Lawson, M D Rawlins, R F A Logan, M Murphy, M P Vessey, D G Colin-Jones

Summary

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is associated with an increased risk of peptic ulcer complications, but it is not clear whether some drugs are more likely than others to cause such complications.

We compared previous use of NSAIDs in 1144 patients aged 60 and older admitted to hospitals in five large cities with peptic ulcer bleeding and in 1126 hospital controls and 989 community controls matched for age and sex. Peptic ulcer bleeding was strongly associated with use of non-aspirin NSAIDs of any type during the 3 months before admission (411 cases, 351 controls; odds ratio 4·5 [95% CI 3·6 to 5·6]). The odds ratios for peptic ulcer bleeding were lowest for ibuprofen (2·0 [1·4–2·8]) and diclofenac (4·2 [2·6–6·8]), and intermediate for indomethacin, naproxen, and piroxicam (11·3 [6·3–20·3], 9·1 [5·5–15·1], and 13·7 [7·1–26·3]). Azapropazone and ketoprofen carried the highest risks (31·5 [10·3–96·9] and 23·7 [7·6–74·2]). Risks also increased with drug dose (low dose 2·5 [1·7–3·8], intermediate 4·5 [3·3–6·0], and high 8·6 [5·8–12·6]) for all drugs combined.

Appropriate clinical strategies could prevent many episodes of peptic ulcer bleeding: NSAIDs should be used only in patients who do not respond to other analgesics; the lowest possible doses should be used; and the least toxic NSAIDs should be selected.

Lancet 1994; 343: 1075–78

See Commentary page 1051

University of Birmingham (Prof M J S Langman FRCP, J Weil MRCP, P Wainwright BSc), **Glasgow Royal Infirmary** (D H Lawson FRCPE); **University of Newcastle upon Tyne** (M D Rawlins FRCP); **University of Nottingham** (R F A Logan FRCP); **University of Oxford** (M Murphy MFPHM, M P Vessey FRS); **and Queen Alexandra Hospital, Portsmouth, UK** (D G Colin-Jones FRCP)

Correspondence to: Prof M J S Langman, Department of Medicine, Queen Elizabeth Hospital, Birmingham B15 2TH, UK

Introduction

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is associated with liability to peptic ulcer complications.[1–4] Individual risks are low, of the order of 1 episode for every 10 000 NSAID prescriptions issued to people of 60 and older in the UK. However, because many such prescriptions are issued, there are many episodes: about two-thirds of the estimated 3500–4000 treatment-associated episodes can be attributed to treatment. These findings are consonant with the number of serious adverse reaction (yellow card) reports, to the UK Committee on Safety of Medicines.[5]

The reasons for individual reactions are unclear. Some clinical data and reports of suspected adverse reactions suggest that there may be large differences in individual NSAID toxicity,[2,4,5] whereas others indicate that there may be no substantial differences.[3,6]

Interpretation of findings is difficult. Spontaneous reports cannot be assumed to reflect accurately the frequency of adverse reactions in the community, and data collected in computerised prescription data-bases will not contain information about concurrent non-prescribed NSAID use or about potential confounding factors. Experimental clinical data, predominantly on endoscopic abnormalities in younger individuals, may have little relevance to serious disease in older people. We have carried out a large case-control study in which we compared previous anti-inflammatory drug use and various putative risk factors in older people admitted to hospital with peptic ulcer bleeding and in matched hospital and community controls.

Patients and methods

Patients aged 60 and older with confirmed diagnoses by endoscopy or at operation of acute upper gastrointestinal bleeding due to gastric or duodenal ulceration admitted to hospitals in Glasgow (200 patients), Newcastle (124), Nottingham (506), Oxford (143), and Portsmouth (170) between 1987 and 1991 were questioned by trained research associates. Standard questionnaires were used to seek details of all previous drug intake, whether prescribed or self-administered, and various other features including smoking habits, alcohol consumption, and history of gastrointestinal disease. Drug histories volunteered were compared with those recorded in hospital notes and by general practitioners where obtainable.

Each patient was matched wherever possible with 2 controls of the same sex and age (within 5 years) who were asked the same questions by the same research associate in relation to the period before the interview. 1 control was a hospital control, chosen from among acute medical inpatients (excluding those with acute myocardial infarction, acute rheumatic diseases, and active non-bleeding ulcers). The second control for each case was a community control, selected from the register of the same general practitioner as the case—the next person of the same sex and age (within 5 years) on the alphabetically ordered register. An

	% of group		
	Cases (n = 1144)	Hospital controls (n = 1126)	Community controls (n = 989)
Male	55·4	55·3	56·5
Aged (yr)			
60–69 yr	34·4	34·2	33·6
70–79 yr	39·2	40·6	40·7
≥ 80 yr	26·1	25·0	25·6
Social class			
I-II	22·1	18·7	22·9
III	51·3	52·7	58·6
IV-V	20·1	23·2	17·1
Home circumstances			
At home alone	30·5	33·0	29·2
At home with spouse	41·7	41·4	50·4
Sheltered accommodation	7·8	10·3	6·1
With home help	17·8	24·3	10·6
Risk factors			
Current smoker*	28·3	21·7	22·3
Current drinker†	16·1	10·7	12·9
Osteoarthritis	30·7	25·6	28·9
Rheumatoid arthritis	5·7	2·6	2·2

*Smoking at least one cigarette daily. †Drinking at least 7 units of alcohol per week.

Table 1: Demographic characteristics of cases and controls

interview with the community control was requested by letter, and, if necessary, by a second letter. Approval was given by local ethics committees.

To adjust for confounding factors, unconditional logistic regression was carried out with SAS software. Results for each non-aspirin NSAID were individually adjusted for: previous history of proven peptic ulcer disease, history of dyspepsia, smoking, and alcohol intake. Age and sex were not found to be confounders. Statistical significance tests for comparison of logistic regression models were based on the difference between −2 log likelihood scores. The reference category for all odds ratios was cases and controls not exposed to non-aspirin NSAIDs or aspirin.

For analyses of risk according to drug dose, categories were defined on the basis of recommendations in the *British National Formulary* (cut-off points for low, medium, and high dose categories for azapropazone <600, 600–899, ≥900 mg/day; diclofenac and indomethacin <75, 75–149, ≥150 mg/day; ibuprofen <1200, 1200–1799, ≥1800 mg/day; ketoprofen <100, 100–199, ≥200 mg/day; naproxen <500, 500–999, ≥1000 mg/day; piroxicam <10, 20, ≥30 mg/day).

Initial calculations suggested that if, as seemed likely, the bulk of prescribing was limited to four or five individual NSAIDs, a study of 1200 patients and their controls had a power of 80% to detect risks differing by three-fold between the drugs.

Results

We questioned 1144 patients, 1126 hospital controls, and 989 community controls. Cases and controls were generally well matched for social class and circumstances (table 1). Cases were slightly more likely than controls to be current smokers or drinkers and to have rheumatoid arthritis self-classified as active; there was no difference for osteoarthritis.

	Cases	Hospital controls	Community controls	Odds ratio (95% CI)*
Azapropazone	22	2	2	31·5 (10·3–96·9)
Diclofenac	71	30	31	4·2 (2·6–6·8)
Ibuprofen	88	61	75	2·0 (1·4–2·8)
Indomethacin	57	16	14	11·3 (6·3–20·3)
Ketoprofen	31	2	4	23·7 (7·6–74·2)
Naproxen	90	23	21	9·1 (5·5–15·1)
Piroxicam	57	13	11	13·7 (7·1–26·3)
Any non-aspirin NSAID	411	169	182	4·5 (3·6–5·6)
Not on NSAID or aspirin†	457	807	657	1·0

*All odds ratios from unconditional logistic regression model with terms for aspirin use, smoking, alcohol, previous peptic ulcer, and history of dyspepsia. For azapropazone, to obtain convergence, aspirin use was not included. †Reference category.

Table 3: Risks of ulcer complications associated with individual non-aspirin NSAID use during previous 3 months

The diagnosed site of the bleeding ulcer was gastric in 506 patients and duodenal in 547. 52 had combined gastric and duodenal ulcers, 5 had combined bleeding and perforated ulcers, and 11 had perforated but non-bleeding ulcers (4 gastric, 7 duodenal). The remaining 23 had no evidence of peptic ulceration and were excluded from further analyses.

Non-aspirin NSAIDs were taken at some time in the 3 months before admission by 411 (36·7%) of the cases, and in the 3 months before interview by 169 (15·0%) of hospital controls and 182 (18·4%) of community controls.

Data were primarily assessed on whether subjects themselves said they had been taking the drug in question, but when possible this information was checked against hospital and general practice records. The information came from the patient and at least one other source in 338 (82%), from the patient only in 27 (7%), and from general practice or hospital records only in 46 (11%). The corresponding figures for hospital controls taking NSAIDs were 138 (82%), 19 (11%), and 12 (7%). For the community controls no hospital records were used and the information came from the patient and general practitioner notes in 124 (69%) and from the patient alone in 58 (31%).

Matched analyses were possible in only 836 of the 989 complete triplets because the codes detailing matching were stolen from a researcher's car. Matched analyses examining the association between the intake of any non-aspirin NSAID and ulcer complications gave an odds ratio of 3·5 (95% CI 2·4–5·3) with 1:2 matching for dichotomous exposures, whereas an unmatched analysis gave an odds ratio of 3·8 (3·1–4·5) compared with hospital and community controls combined (table 2). There was also a significant association of ulcer complications with aspirin, but not with paracetamol use. Odds ratios for matched and unmatched analyses agreed closely, but confidence intervals were wider for matched analyses because of the smaller numbers. All subsequent analyses were done with the combined control groups unmatched.

Six NSAIDs (aspirin, diclofenac, ibuprofen, indomethacin, naproxen, and piroxicam) were each taken during the 3 months before admission by at least 50 cases

Drug use in previous 3 mo	Cases (n = 1121)	Hospital controls (n = 1126)	Community controls (n = 989)	Odds ratio (95% CI)‡	
				Matched	Unmatched
Any non-aspirin NSAID*	411	169	182	3·5 (2·4–5·3)	3·8 (3·1–4·5)
Aspirin†	324	175	179	3·1 (2·0–4·8)	2·9 (2·4–3·5)
Paracetamol (no NSAID)	140	229	199	1·1 (0·7–1·7)	1·1 (0·8–1·3)
No NSAID or aspirin§	457	807	657	1·0	1·0

*Irrespective of concurrent aspirin use.
†Irrespective of concurrent non-aspirin NSAID use.
‡For cases vs combined controls; unmatched analysis by crossed odds ratios.
§Reference category.

Table 2: Risks of ulcer complications associated with drug use during previous 3 mo

	Odds ratio (95% CI)			
	A	B	C	D
Diclofenac	4·4 (2·7–7·3)	3·6 (1·8–7·2)	3·7 (2·2–6·3)	35·6 (7·5–169·8)*
Ibuprofen	1·8 (1·2–2·7)	1·1 (0·6–1·9)	1·5 (1·0–2·3)	4·3 (1·6–11·8)*
Indomethacin	12·2 (6·6–22·4)	12·8 (5·4–30·5)	10·8 (5·5–21·2)	12·2 (2·8–52·7)*
Naproxen	9·8 (5·8–16·5)	5·8 (3·0–11·4)	10·0 (5·6–17·7)	14·8 (3·6–60·2)
Piroxicam	13·1 (6·8–25·5)	18·0 (7·2–45·0)	13·6 (6·9–27·0)	21·6 (2·2–213·5)*
Any non-aspirin NSAID	4·8 (3·8–6·0)	3·8 (2·9–5·1)	4·4 (3·4–5·5)	9·6 (5·5–16·8)

Unconditional logistic regression model with terms for aspirin use, smoking, alcohol, previous peptic ulcer, and dyspepsia. *Aspirin omitted from covariates convergence.
A = taken in previous month, irrespective of whether taken previously or with other non-aspirin NSAIDs.
B = taken in previous month, duration of use at least 3 months.
C = taken in previous month, irrespective of whether taken previously, excluding those taking a second non-aspirin NSAID.
D = started in previous month.

Table 4: Risks of ulcer complications associated with use of selected non-aspirin NSAIDs in previous month according to duration of use and other concurrent NSAID use

and two (azapropazone and ketoprofen) were taken by more than 20 cases each. No other NSAID was taken by more than 10 cases. The odds ratios for ulcer complications associated with the seven most commonly taken non-aspirin NSAIDs varied more than ten-fold from the highest (azapropazone and ketoprofen) to the lowest (ibuprofen; table 3). All risks were significantly greater than 1. Substitution of NSAID use in the previous month (irrespective of duration) did not substantially alter the risks (table 4, column A). Nor did odds ratios differ much among long-term users (column B) or when we excluded individuals who had taken both the relevant NSAID and another non-aspirin NSAID (column C).

Risks were generally greater among subjects who had started taking a NSAID during the previous month (table 4, column D). For the drugs combined, risks were significantly greater among those who had started a non-aspirin NSAID in the previous month than in those who had taken one both in the previous month and in the past year.

Among subjects who took a non-aspirin NSAID during the previous month risk increased with dose (table 5).

There were no consistent differences in risks associated with bleeding from gastric (odds ratio 4·0 [3·1–5·3]) or duodenal (4·7 [3·5–6·1]) ulceration for overall non-aspirin NSAID use or the five most frequently used NSAIDs. The same was true for aspirin (gastric ulcer 3·3 [2·5–4·4]; duodenal ulcer 3·1 [2·3–4·2]). Paracetamol use was not associated with either gastric or duodenal ulcer bleeding.

Dose*	Cases	Controls	Odds ratio (95% CI)†
Low	63	88	2·5 (1·7–3·8)
Medium	194	165	4·5 (3·3–6·0)
High	147	63	8·6 (5·8–12·6)
Not on NSAID or aspirin‡	457	1464	1·0

*For definitions of dose categories, see methods section.
†Odds ratios by unconditional logistic regression controlling for aspirin use, alcohol, smoking, previous peptic ulcer disease, and dyspepsia.
‡Reference category.

Table 5: Risks of ulcer complications associated with use of non-aspirin NSAIDs within previous month according to dose

Odds ratios for ulcer complications associated with NSAIDs did not differ substantially between age groups in the study (4·2 [2·7–6·4] for age 60–69; 4·4 [3·1–6·2] for age 70–79; and 4·8 [3·2–7·3] for age 80 or older).

Discussion

We have shown that in patients with bleeding ulcers there are clinically important differences in exposure rates to various NSAIDs. None of the NSAIDs for which we have sufficient data was free of risk. The risks could be calculated in two ways. First, results for each drug could be compared with the full set of other data, whether or not other NSAIDs or aspirin were taken concurrently. Second, the comparison could be restricted by contrasting findings for each individual drug with those for non-takers of other NSAIDs or aspirin.

The first method would be appropriate if only one agent were associated with risk but is inappropriate when several agents act as risk factors. The second method allows the selection of one particular drug so that takers of this drug can be contrasted with an appropriate base of non-takers of other non-aspirin NSAIDs. Its use gives higher (but appropriate) odds ratios, because takers of other NSAIDs have been removed from the "non-exposed" comparison group.

This study is one of the largest so far and therefore confidence intervals around estimates of risk are small. The data give consistent conclusions with similar rank orders for risk whether drug exposure was of short or long duration.

	Adjusted for non-prescribed drug use and social habits						No data on non-prescribed drugs, social habits, or both			
	International[11]	New Zealand[12]	Spain[4]	UK[6]	Italy[14]	Australia[15]	Canada[16]	UK[5]	UK[18]	USA[3]
Drug										
Azapropazone	..	..	..	31·5	..	..	..	.	23·4	..
Diclofenac	0·9/2·4†	3·3	7·9	4·2	4·4	1·7	4·0	..	3·9	..
Diflunisal	..	..	..	..	..	1·0	..	.	.	.
Fenoprofen	..	..	..	..	..	..	..	..	2·9	4·3
Ibuprofen	1·0	1·9	..	2·0	..	0·7	..	1·0	6·3	2·3
Indomethacin	..	13·9	4·9	11·3	9·2	2·5	5·1	4·1	5·4	3·8
Ketoprofen	..	..	2·6	23·7	..	3·6	..	..	3·1	..
Meclofenamate	..	..	..	..	..	..	..	..	18·0	8·7
Naproxen	4·0/12·0†	5·1	6·5	9·1	..	2·8	3·8	2·7	.	4·3
Piroxicam	..	6·6	19·1	13·7	7·7	4·8	4·2	6·5	.	6·4
Sulindac	..	3·6	.	..	..	2·1	3·1	.	.	4·2
Tolmetin	..	..	..	..	..	..	..	.	.	8·5
Total non-aspirin NSAID	74/501‡	205	125	411	97	252	685	80	247	465
Controls										
Hospital	Yes‡	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
Population	Yes‡	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes

*This study. †Gastric/duodenal ulcers. ‡One or the other according to study site.

Table 6: Risks of ulcer complications or gastrointestinal hospital admission associated with non-aspirin NSAIDs in case-control studies

Similar patterns were seen for gastric and for duodenal ulcer and for various age groups. The results cannot be explained by the operation of confounding influences; allowance for concurrent aspirin or other NSAID intake, smoking habits, alcohol consumption, or previous peptic ulcer disease did not substantially change the findings. We have previously failed to find evidence that smoking, alcohol consumption, poor social circumstances, or a history of ulcer affect the risk of NSAID-associated ulcer bleeding.[7] Recall or interviewer bias seem unlikely because there was good concordance between question outcome and hospital or practitioner records of drug prescribing. We are led to believe that non-steroidal anti-inflammatory activity is important by the observed dose-response effect and by evidence that paracetamol analgesic intake was not associated with risk.

Risk for most of the drugs, and overall, tended to be greater in those who had lately started treatment. New users may be more likely to take full recommended doses than those who have been taking drugs long term. Other explanations of this pattern include adaptive protective responses to injury during continued treatment, or withdrawal of a population susceptible to damage, for instance with dyspepsia, with time.

The high risks associated with azapropazone and ketoprofen exposure were unexpected. We checked for lost cases of exposure to these drugs in the control groups but found none. The risk for azapropazone was especially associated with treatment of gout, but no such differential risk was detected for ketoprofen or indomethacin nor NSAIDs in general. Numbers of control users of azapropazone and ketoprofen were small, however, so confidence intervals round these estimates of risk are large.

Fifteen studies have compared rates of non-aspirin NSAID exposure in patients who had peptic ulcer complications or required admission to hospital for upper gastrointestinal disease. Two[5,6] considered spontaneous reports of adverse reactions in the UK and the USA, and risks associated with individual drugs cannot be calculated. Another[8] used ibuprofen takers as the reference group, so overall rate ratios are unclear, and two[9,10] included very small numbers.

Table 6 summarises findings in the remaining ten studies.[1,2,4,11-16] Six took account of non-prescribed drug use and of potential for confounding due to individual social habits: ours is the largest of these. The other four did not take account of non-prescribed drug use, social habits, or both. The seven sets of data for ibuprofen show low rate ratios compared with those for indomethacin, naproxen, and piroxicam (nine data sets each). Results for sulindac and diclofenac are intermediate.

Rate ratios above 20 were found in the only two studies of azapropazone and in one of three of ketoprofen, and ratios approaching 20 were found in two of nine of piroxicam. Much lower risks were detected in the other two studies of ketoprofen, but all except two of the nine studies of piroxicam gave ratios higher than 5. Formal meta-analysis is inappropriate because comparable data sets cannot be extracted from all studies. Concurrent users of other NSAIDs are not generally separated, and use of over-the-counter aspirin or other drugs is not always known.

Among the 10 million people aged 60 and older in England and Wales, the overall risk of ulcer bleeding (10 000 episodes per year) is 1 in 1000. From our data, about 35% will be associated with non-aspirin NSAID use and another 28% with aspirin use. Expected population use rates for our data would be 15% for each. We can then (assuming no overlapping use) calculate that 3500 episodes occur in 1·5 million non-aspirin NSAID recipients, 2800 in 1·5 million aspirin recipients, and 3700 in 7 million receiving neither drug. If the use of aspirin and non-aspirin NSAIDs were abandoned, about 4000 episodes might be prevented. A more realistic strategy would be to use the NSAIDs with the lowest risk. This approach could halve the number of drug-associated events, with a persisting excess of 2000 episodes. The number of episodes could be cut further if all NSAIDs were used in low doses (table 5).

Few of our patients had rheumatoid disease. Others have found that many patients are unclear about why they are taking NSAIDs. We conclude that substantial risks of ulcer complications are associated with NSAID use and that appropriate clinical strategies could prevent many episodes. These strategies include administration of NSAIDs only to patients who do not respond adequately to non-NSAID analgesics, selection of the least toxic NSAIDs when such treatment is needed, and starting treatment with low doses.

We thank the Medical Research Council for support, our professional colleagues for their ready cooperation, and our monitors Ms Clare Clifford, Ms Gail Faulkner, Ms Gillian Paice, Ms Ellen Thompson, Ms Shirley Wood, and Ms Shirley Powell, without whom the study would not have been possible.

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Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs

Luis Alberto García Rodríguez, Hershel Jick

Summary

Exposure to non-steroidal anti-inflammatory drugs (NSAIDs) is known to increase substantially the risk of upper gastrointestinal bleeding and perforation (UGIB). We have carried out a population-based retrospective case-control study to assess the variation in risk associated with various individual NSAIDs, with adjustment for features of use and other independent risk factors.

The study sample comprised 1457 cases of UGIB and 10 000 control subjects identified from general practitioners' computerised records in the UK. The adjusted estimate of relative risk of UGIB associated with current NSAID use was 4·7 (95% CI 3·8–5·7). Previous UGIB was the single most important predictor of UGIB (relative risk 13·5 [10·3–17·7]). For all NSAIDs together, the risk was greater for high doses than for low doses (7·0 [5·2–9·6] *vs* 2·6 [1·8–3·8]). The estimates of risk associated with the individual NSAIDs varied widely. Users of azapropazone (23·4 [6·9–79·5]) and piroxicam (18·0 [8·2–39·6]) had the highest risk of UGIB among the NSAIDs studied. All the other NSAIDs with sufficient data for individual analysis (ibuprofen, naproxen, diclofenac, ketoprofen, and indomethacin) had relative risks similar to that for overall NSAID use.

NSAIDS should be used cautiously in patients who have other risk factors for UGIB; these include advanced age, smoking, history of peptic ulcer, and use of oral corticosteroids or anticoagulants.

Lancet 1994; 343: 769–72

Boston Collaborative Drug Surveillance Program, Boston University Medical Center, 11 Muzzey Street, Lexington, MA 02173, USA (L A García Rodríguez MD, H Jick MD)

Correspondence to: Dr L A García Rodríguez

Introduction

Several studies have shown that a person exposed to non-steroidal anti-inflammatory drugs (NSAIDs) has three to four times the risk of upper gastrointestinal bleeding, perforation, or both (UGIB) of a non-user.[1,2] Other independent risk factors for UGIB are age, use of alcohol, anticoagulants, and corticosteroids, and history of peptic ulcer with or without complications.

Assessment of the gastrointestinal toxicity of individual NSAIDs is difficult, since sample sizes are usually too small to allow meaningful variations in risk to be detected, and some NSAIDs are available only in certain countries. Moreover, the possibility that patients treated with different NSAIDs have diverse background profiles is always an alternative explanation for the findings of epidemiological studies.

We have carried out a population-based retrospective case-control study in the UK to assess the variation in risk of UGIB associated with various individual NSAIDs, with adjustment for the characteristics of use and other independent risk factors.

Population and methods

More than 4 million people in the UK are registered with general practitioners (GPs) who use office computers provided by Value Added Medical Products (VAMP) Research (London, UK). These computers store information on patient care, and largely replace manual notes. GPs record medical information in a standard way and supply it (without patients' names) to VAMP Research. The research organisation does several preliminary standard checks on a practice to assess the quality of its information, before that practice's data are made available for research projects. Among other items, the recorded information includes the patient's demographic details, medical diagnoses and comments arising from the patient's visit to the GP, referral letters from consultants, and hospital admissions. GPs generate prescriptions directly with the computer, and all drugs prescribed are automatically transferred to the patient's computer record. As a result, an anonymous chronological patient profile of prescriptions, medical notes, consultant visits, and hospital admissions can be created for each individual, and used for the purposes of medical research.[3]

A distinctive feature of this computerised medical information system is that the GP is asked to provide the indication for each new course of medication. A modification of the OXMIS code[4] is used to register medical diagnoses, and a coded drug dictionary based on the Prescription Pricing Authority dictionary is used for the recording of medicines.

Two validation studies have shown that more than 90% of information from the manual medical records present in the GP's office was recorded on the computer.[3,5] The indication for more than 95% of newly prescribed drugs was present in the computer file.

The study started in January, 1990, and ended in February, 1993. The source population included 1922 858 people aged 25–77 years in January, 1990, who were registered with GPs using VAMP

Drug	Cut-off daily dose (mg)*	Drug	Cut-off daily dose (mg)*
Azapropazone	900	Ketoprofen	150
Diclofenac†	100	Mefenamic acid	1250
Diflunisal	750	Nabumetone	1000
Etodolac	400	Naproxen†	750
Fenbufen	900	Piroxicam	15
Fenoprofen	1200	Sulindac	300
Flurbiprofen	200	Tenoxicam	20
Ibuprofen†	1500	Tiaprofenic acid	450
Indomethacin†	75		

*Values ⩽ cut-off = low dose; values > cut off = high dose. †Sufficient data available for individual low-dose/high-dose comparison.

Table 1: Daily dose definition for individual NSAIDs

computers. All participants were followed until the earliest of first hospital admission or referral for UGIB, death, or end of the study period.

Case detection

In a first step, a computer search identified 4727 people with an OXMIS code for UGIB recorded for the first time during the study period.* 1013 patients were directly excluded by computer-based algorithms, because of a recent history of alcoholism, oesophageal varices, cirrhosis, Mallory-Weiss syndrome, coagulopathies, cancer, any hospital admission in the month before the date of the UGIB code, or pregnancy. The complete individual medical histories (patient profiles) of the remaining 3714 people were manually reviewed.

Validation of computerised OXMIS codes

Three categories of case status were defined based on information recorded on the patient profile (except data on drug use). Patients in category 1 were judged not to be cases, since the bleeding was clearly not from the upper gastrointestinal tract or because one of the above exclusion criteria applied. Patients in category 2 were judged borderline cases; no exclusion criterion was found, but the specific site of the UGIB was not recorded. Patients in category 3 were classified as cases; no exclusion criterion was found and the specific site of UGIB or a diagnosis of "peptic ulcer" only was recorded on the patient profile.

To validate the case status classification based on the computerised information, the paper-based medical records of 76 randomly selected patients were obtained and reviewed to ascertain the actual medical diagnosis. 12 of 13 patients in category 1 were confirmed as non-cases, and 23 (72%) of the 32 borderline cases in category 2 were found to be cases. All of 31 patients in category 3 were confirmed as cases. We therefore decided to use in our final analyses all the patients who met the criteria for category 3, based on the computer records.

Of the 3714 patients initially identified through the computer search, 789 were assigned to category 1, 1224 to category 2, and 1701 to category 3. 244 patients in category 3 with recorded bleeding/perforation in the oesophagus were not included into the final analysis. Thus, 1457 patients had had an episode of bleeding or perforation involving the stomach, the duodenum, or a peptic ulcer. The date of hospital admission or referral was used as the index date.

Control selection

10 000 controls were randomly selected from the practices where the cases were registered and a random date during the study period was assigned to each as the index date. All inclusion and exclusion criteria applied to the selection of cases were also used in the control selection procedure. All analyses were done with logistic regression models.

Definition of NSAID exposure

A person was defined as a current NSAID user when the last NSAID prescription before the index date was ordered during the previous month (a month is the average dispensing duration of an NSAID prescription in the UK) or if the time from the date of the prescription to the index date was longer but the duration of therapy extended at least to the index date. Current use was subdivided into current single use (only 1 individual NSAID during the 150 days before the index date) and current multiple use (more than 1 individual NSAID during the 150 days before the index date).

An NSAID aggregate variable was created representing the use of any of the NSAIDs included in the study. The effect of dose was investigated for NSAIDs as a group and for four individual NSAIDs with sufficient information available for stratification into low and high daily dose categories (table 1). Duration of use was defined as the number of consecutive prescriptions (following each other with a maximum interval of 90 days) among current single users. Duration was classified as "unknown" when there was less than 6 months' history in the automated prescription file.

A person was defined as a recent past NSAID user when the last NSAID prescription before the index date was written 60–31 days

*A list of the OXMIS codes used is available from *The Lancet*.

	Cases (n = 1457)	Controls (n = 10 000)	Adjusted relative risk (95% CI)
NSAID exposure			
No use	1106	9083	1·0
All current use	241	365	4·7 (3·8–5·7)
Single	194	318	4·1 (3·3–5·1)
Multiple	47	47	9·0 (5·7–14·2)
Recent past use	44	169	1·9 (1·3–2·8)
Past use	66	383	1·4 (1·0–1·8)
Age (yr)			
25–49	374	5561	1·0
50–59	250	1740	1·6 (1·4–2·0)
60–69	376	1630	3·1 (2·5–3·7)
70–80	457	1069	5·6 (4·6–6·9)
Sex			
Male	958	5005	1·0
Female	499	4995	0·5 (0·4–0·5)
Ulcer history			
No history	862	9017	1·0
Dyspepsia	147	445	2·9 (2·4–3·6)
Ulcer without complication	278	433	6·1 (5·1–7·3)
Ulcer with complication	170	105	13·5 (10·3–17·7)
Use of other drugs*			
Oral corticosteroids	38	64	2·2 (1·4–3·5)
Anticoagulants	19	13	6·4 (2·8–14·6)

*Reference category was people who did not receive a prescription for relevant drugs within 5 months before index date.

Table 2: Relative risks of UGIB associated with various risk factors

Type of case	Cases	Adjusted relative risk* (95% CI)
Bleeding only (n = 1196)		
No use	939	1·0
Current use	171	3·9 (3·1–4·9)
Recent past use	36	1·9 (1·3–2·9)
Past use	50	1·2 (0·8–1·6)
Perforation (n = 261)		
No use	167	1·0
Current use	70	7·9 (5·7–10·9)
Recent past use	8	2·1 (1·0–4·4)
Past use	16	1·9 (1·1–3·3)
Gastric (n = 483)		
No use	350	1·0
Current use	100	5·4 (4·1–7·0)
Recent past use	13	1·6 (0·9–3·0)
Past use	20	1·2 (0·7–1·9)
Duodenal (n = 787)		
No use	615	1·0
Current use	115	4·4 (3·4–5·6)
Recent past use	23	1·9 (1·2–3·1)
Past use	34	1·3 (0·9–1·9)

*9083 controls were non-users, 365 current users, 169 recent past users, and 383 past users.

Table 3: Relative risk of UGIB associated with NSAID use according to diagnostic category

	Cases	Controls	Adjusted relative risk (95% CI)
No peptic ulcer history			
n	862	9017	
No use of NSAIDs	615	8222	1·0
Current use	171	314	5·1 (4·1–6·3)
Single	138	271	4·6 (3·6–5·8)
Multiple	33	43	8·9 (5·4–14·7)
Recent past use	30	146	2·2 (1·5–3·5)
Past use	46	335	1·6 (1·2–2·3)
With peptic ulcer history			
n	595	983	
No use of NSAIDs	491	861	1·0
Current use	70	51	2·8 (1·9–4·2)
Single	56	47	2·4 (1·6–3·7)
Multiple	14	4	7·4 (2·4–23·6)
Recent past use	14	23	1·1 (0·5–2·3)
Past use	20	48	0·8 (0·4–1·4)

Table 4: Relative risk of UGIB associated with NSAID use according to history of peptic ulcer disease

before that date and the prescribed course of therapy finished before the index date.

A person was defined as a past-user when the last NSAID prescription before the index date was written 150–61 days before that date and the computer-recorded duration of therapy finished before the index date.

A person was defined as a non-user when there was no NSAID prescription within the 5 months before the index date.

The use of over-the-counter aspirin as a proportion of total aspirin use is known to be large in the UK. We do not present an estimate of the risk associated with aspirin use in our study because of the underascertainment of exposure. In our analysis, prescribed aspirin use was used only as an additional variable in the adjustment for the risk estimate associated with NSAIDs.

Definition of ulcer history

The whole medical history recorded on computer was used to find out the ulcer history for each patient. An episode of UGIB recorded before the study period would therefore be identified. A person was defined as having no history of ulcer if there was no recorded diagnosis of dyspepsia or ulcer with or without complication (bleeding, perforation) up to 1 month before the index date. A person was defined as having a history of dyspepsia if that was the only recorded gastrointestinal diagnosis up to 1 month before the index date. Finally, a person was defined as having history of ulcer with or without complication (bleeding and/or perforation) according to the recorded information up to 1 month before the index date.

Results

Among the 1457 cases of UGIB, the site of the bleeding or perforation was gastric in 483 and duodenal in 787; 40 patients had multiple bleeding sites and 147 peptic ulcer only. 64 patients died. Perforation was reported in 261 cases.

The relative risk of UGIB (table 2) associated with NSAID current use was 4·7 (3·8–5·7). The relative risk was significantly higher for current multiple users than for current single users. The risk was substantially lower for recent past users and that for past users was similar to the risk in non-users. Adjustment for current aspirin use did not substantially affect the results.

Other independent risk factors for UGIB were increasing age, male sex, smoking, and history of ulcer (table 2). The relative risks associated with NSAIDs were similar in the four age categories (not shown). We estimated the interaction between age and NSAID use, with people younger than 60 and not exposed to NSAIDs as the reference group. The relative risk was 2·8 (2·5–3·3) in people under 60 exposed to NSAIDs, 3·7 (2·6–5·4) in those of 60 and older not exposed to NSAIDs, and 13·2 (10·1–17·1) in those of 60 and older exposed to NSAIDs. The proportion of disease among subjects with both risk factors that is attributable to the interaction was 59% (43–73%).[6] The relative risk associated with current NSAID use was slightly greater among women than men (5·2 [3·9–6·8] *vs* 4·1 [3·1–5·4]). Smoking increased the risk of UGIB by 40% (not shown).

	Cases (n = 862)	Controls (n = 9017)	Adjusted relative risk (95% CI)
Daily dose			
No use	615	8222	1·0
Low dose	45	150	2·6 (1·8–3·8)
High dose	90	118	7·0 (5·2–9·6)
Unknown	3	3	6·7 (1·2–37·4)
No of NSAID prescriptions			
No use	615	8222	1·0
1	40	104	4·0 (2·7–6·1)
2–3	15	37	3·2 (1·7–6·1)
4–6	10	27	2·8 (1·3–6·0)
7–12	30	34	6·7 (3·9–11·4)
⩾13	38	53	6·4 (4·0–10·2)
Unknown	5	16	3·5 (1·2–10·3)
Daily dose and no of prescriptions			
No use	615	8222	1·0
Low dose, 1–6	25	96	2·3 (1·4–3·7)
Low dose, ⩾7	20	44	3·8 (2·2–6·8)
High dose, 1–6	40	71	5·4 (3·5–8·4)
High dose, ⩾7	46	41	9·3 (5·9–14·8)

Only patients with no history of peptic ulcer were included.

Table 5: Relative risk of UGIB associated with NSAID current single use according to dose and duration of treatment

The relative risks associated with NSAID use were slightly greater for gastric than for duodenal bleeding and greater for perforation than for bleeding only (table 3).

Previous bleeding or perforation of the upper gastrointestinal tract was the single most important predictor of UGIB (relative risk 13·5 [10·3–17·7]). The relative risk of UGIB associated with NSAID use was higher in people without a history of peptic ulcer disease than in those with such a history (table 4). To examine the joint effect of exposure to NSAIDs and history of peptic

	Cases (n = 862)	Controls (n = 9017)	Adjusted relative risk (95% CI)
NSAID current use			
No use	615	8222	1·0
Ibuprofen	20	74	2·9 (1·7–5·0)
Other*	13	39	2·9 (1·5–5·6)
Naproxen	15	46	3·1 (1·7–5·9)
Diclofenac	25	53	3·9 (2·3–6·5)
Ketoprofen	14	20	5·4 (2·6–11·3)
Indomethacin	20	24	6·3 (3·3–12·2)
Multiple NSAIDs	33	43	8·9 (5·4–14·7)
Piroxicam	20	11	18·0 (8·2–39·6)
Azapropazone	11	4	23·4 (6·9–79·5)
Daily dose†			
No use	615	8222	1·0
Ibuprofen ⩽1500 mg	12	59	2·1 (1·1–4·1)
Ibuprofen >1500 mg	8	14	6·5 (2·6–16·4)
Naproxen ⩽750 mg	5	14	4·0 (1·3–11·8)
Naproxen >750 mg	10	31	3·1 (1·4–6·6)
Diclofenac ⩽100 mg	18	35	4·1 (2·2–7·6)
Diclofenac >100 mg	7	18	3·4 (1·4–8·5)
Indomethacin ⩽75 mg	3	15	1·4 (0·3–5·8)
Indomethacin >75 mg	16	8	14·4 (5·7–36·4)

Only patients with no history of peptic ulcer were included.
*Mefenamic acid, fenbufen, fenoprofen, flurbiprofen, diflunisal, sulindac, tenoxicam, tiaprofenic acid, etodolac, and nabumetone.
†Among current users of the four NSAIDs listed were 4 people with unknown daily dose.

Table 6: Relative risk of UGIB associated with individual NSAIDs

ulcer we used a common reference group—people not currently exposed to NSAIDs and with no history of peptic ulcer (history of dyspepsia alone was not included). The relative risk was 5·4 (4·4–6·8) for those exposed to NSAIDs only, 8·7 (7·4–10·3) for those with a history of peptic ulcer only, and 17·2 (10·0–29·6) for those with both risk factors. In view of this effect measure modification and the small number of people with a history of peptic ulcer, further analyses of the risk associated with NSAID use are presented for the subset of patients without history of peptic ulcer.

The relative risk associated with NSAID current single use was significantly higher among people exposed to high doses than among those exposed to low doses (table 5). With respect to duration, the relative risk after the first prescription (4·0 [2·7–6·1]) was no greater than the overall risk, and the risk increased slightly with long-term therapy.

There were important differences in the risk associated with the individual NSAIDs (table 6). Azapropazone and piroxicam had relative risks greater than 10. The five other NSAIDs assessed individually showed some variation in risk, but all had relative risks similar to that for overall NSAID use. Ibuprofen had the smallest risk. We were able to study a dose-effect relation for four individual NSAIDs. For indomethacin and ibuprofen there was a substantial increase in risk from a low to a high daily dose.

Discussion

This study has confirmed that use of NSAIDs is independently associated with an increased risk of UGIB. The excess risk of UGIB associated with NSAID use was similar irrespective of the site of bleeding, but the risk of perforation was greater than that of bleeding only. Both short and long duration of NSAID exposure increased the risk of UGIB. An adjustment for current aspirin use recorded on computer did not greatly alter our findings. Overall, there was a striking dose-response effect. Also, the increased risk with a high daily dose was independent of treatment duration. Similarly, people who had lately changed from one NSAID to another and/or received more than one NSAID simultaneously had more than twice the risk of individuals exposed to only one NSAID. The estimate of the risk in this group of multiple NSAID users was of the same magnitude as that among single NSAID users receiving a high daily dose. We looked at the indications for NSAID use among cases and controls without peptic ulcer history receiving their first prescription. The clinical indications were the same in the two groups. Specifically, for 13% of cases and 10% of controls the recorded indication was an ill-defined back pain. Ulcer disease and its complications may sometimes present with abdominal pain radiating to the back. It is possible that this clinical condition may identify a special group of patients in whom a surreptitious bias would be present. The small difference in prevalence of ill-defined back pain between cases and controls would preclude any confounding by indication in this population.

History of peptic ulcer was not only the most important risk factor for the occurrence of an episode of UGIB but also an important effect modifier of the risk of UGIB associated with NSAIDs. Our estimated relative risk of UGIB associated with the use of NSAIDs was smaller in people with a history of peptic ulcer. However, since such patients are nine times more likely than other people to develop UGIB, they are vulnerable to any further increase in risk due to NSAID exposure. NSAIDs should be administered very cautiously to patients with history of peptic ulcer.

The finding of lowest risk among users of ibuprofen is not new.[7] The risk was substantially greater for high-dose than low-dose ibuprofen users. Thus, the overall risk associated with ibuprofen is largely accounted for by the estimate of risk in the low daily dose category, where most of the use (80%) occurred in our study population. The highest recorded dose of ibuprofen was 2400 mg daily, prescribed to only 2 subjects in the whole study population.

Among individual NSAIDs, the highest risk was found for users of azapropazone. We did not find any clinical feature among users of azapropazone that could account for this increased risk. Numbers were too small to assess with confidence a dose-effect response. 7 cases and 4 controls were receiving a daily dose of 1200 mg or less and 3 cases and no controls doses greater than 1200 mg. According to the manufacturers' recommendations, such high doses should be given only during acute exacerbations of gout. The prevalence of use of azapropazone (as well as of other NSAIDs in our control population) was similar to that in the source population of close to 2 million people. A patient at greatest risk of presenting with an episode of UGIB is a male smoker of advanced age who has a history of peptic ulcer, and is a user of oral corticosteroids, anticoagulants, and NSAIDs.

This study was funded by a grant from Rhône-Poulenc Rorer Research and Development. The Boston Collaborative Drug Surveillance Program is supported by grants from Bayer AG, Burroughs Wellcome Co, Ciba-Geigy Corporation, Hoechst AG, Hoffmann-La Roche Inc, R W Johnson Pharmaceutical Research Institute, Marion Merrell Dow Inc, Pfizer Inc, The Proctor & Gamble Company, and Sanofi Winthrop Pharmaceuticals.

We thank Dr Laurent D Jacobs for comments and suggestions, the staff at VAMP, especially Dr Alan D Dean and Ms Anne Costello, and the participating GPs for their cooperation with this study.

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Variability in the Risk of Major Gastrointestinal Complications From Nonaspirin Nonsteroidal Anti-inflammatory Drugs

DAVID HENRY,* ANNETTE DOBSON,‡ and CATHY TURNER‡

*Discipline of Clinical Pharmacology, Faculty of Medicine, and ‡Department of Statistics, University of Newcastle, Newcastle, New South Wales, Australia

Background: We have assessed the extent to which the risk of serious gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) varies with the age and sex of recipients, use of aspirin or alcohol, administration by the oral or rectal route, and dose and choice of drug. *Methods:* A case-control study was performed with prospective recruitment of cases of gastrointestinal bleeding or ulcer perforation and age- and sex-matched controls. Information on preadmission drug use obtained by structured interview. *Results:* Six hundred forty-four patients and 1268 controls were recruited. The odds ratio for upper gastrointestinal complications in users compared with nonusers of NANSAIDs increased with age: ≤59 years, odds ratio 2.0; 60–79 years, odds ratio 3.0; ≥80 years, odds ratio 4.2; and was higher in women (5.4) than in men (1.9). There was a linear dose-response curve that was steeper in women than in men. Combined exposure suggested additive risks: NANSAIDs and aspirin, odds ratio 6.7; NANSAIDs and alcohol, odds ratio 6.0. NANSAIDs by the oral route were associated with an odds ratio of 2.3, compared with 11.4 with rectal administration. Piroxicam was associated with the highest risk, odds ratio 4.8; and ibuprofen the lowest risk, odds ratio 0.7. *Conclusions:* A number of factors can alter the risk of major gastrointestinal complications with NANSAIDs and need to be considered when individual prescribing decisions are made.

Since 1986, a large number of publications have reported on the association between use of nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and the development of peptic ulcer complications.[1–16] The literature on aspirin is older and only a few epidemiological studies have been published during this period.[11,15–17] Despite the size and scope of this literature, which has been the subject of recent meta-analyses, important questions remain regarding the risks associated with the use of NANSAIDs.[18–19]

The majority of investigations have been of case control design and these have recorded higher overall estimated relative risks than have the cohort studies.[19,20] The results of the case control studies have themselves been heterogenous, with overall estimated relative risks ranging from around three to more than nine but higher in some subgroup analyses.[1,14–16,19] Findings have been variable in respect of the importance of sex and age in determining the level of the relative risk.[14,15,19] Few investigations have been large enough to assess the importance of dose and duration of treatment or differences in the levels of risk with individual drugs.[6,14,15,19] It is not clear whether the risks of NANSAIDs are increased when they are taken in combination with aspirin or alcohol. The safety of suppository formulations has not been investigated. The majority of studies have concentrated on gastrointestinal bleeding, and there have been few investigations of ulcer perforation; all but one were poorly controlled.[5,19,21–23] Within the gastrointestinal bleeding group, duodenal and gastric ulcers have been extensively studied, whereas other sources such as esophageal lesions and mucosal erosions have not been conclusively linked to use of NANSAIDs in epidemiological studies.

The gaps in the available literature reflect the need for further large epidemiological studies to address these secondary, but important, questions. The need for additional research is underscored by the continuing very widespread use of these drugs, which means that the morbidity they cause has implications for the health of the public as well as that of individual users. As we show in this work, the prevalence of use of NANSAIDs by elderly Australians is higher than their prevalence of cigarette smoking or potentially harmful alcohol consumption.

We report here the results of a large case control study that addresses a number of these outstanding issues. The work was conducted in Newcastle, New South Wales, Australia, an area that, historically, has been characterized by heavy consumption of analgesics.[24]

Materials and Methods

We recruited patients with upper gastrointestinal hemorrhage and ulcer perforation admitted to three public hospitals in Newcastle, New South Wales. The catchment area has a population of approximately 450,000, and at the time of the study, virtually all patients with suspected ulcer

Abbreviations used in this paper: CI, confidence interval; NANSAID, nonaspirin nonsteroidal anti-inflammatory drug.

0016-5085/93/$3.00

complications who were thought to need admission were referred to one of these hospitals. The study methods were approved by the research ethics committees of the Hunter Area Health Service and the University of Newcastle, New South Wales.

The case control study was conducted in two phases, the first running from July 1st 1985 to June 30th 1987, the second from January 1st 1988 to December 1989. In phase 1, only subjects aged 60 years or greater were included. There was no age limit in phase 2. In other respects, the methods used in the two phases were identical. Preliminary analysis of the two data sets resulted in very similar estimated odds ratios.[25] Consequently the data were combined for the purposes of further analysis.

Case Patient Definition

Case patients met the definition of upper gastrointestinal bleeding if they had a history of hematemesis and/or melena resulting in hospitalization that was thought, on the basis of endoscopic or operative findings, to be due to ulceration or erosions of the stomach or duodenum, or inflammation, or ulceration of the esophagus. Patients with a Mallory Weiss tear, esophageal varices, or a tumor of the stomach or esophagus were excluded unless they had other eligible lesions thought by the endoscopist to be the primary source of the hemorrhage. Patients were also included if no definite endoscopic diagnosis was made, so long as there was firm evidence of bleeding from the upper gastrointestinal tract. This took the form of a clear history of hematemesis or melena, either confirmed by medical staff after a rectal examination or inspection of vomitus, or accompanied by a decrease in the hemoglobin level of 2 g or more, or an elevated ratio of urea to creatinine concentrations in the blood.[26]

A case patient met the definition for perforation if she or he was admitted with a typical history of acute upper abdominal pain and had evidence of pneumoperitoneum on an abdominal radiograph or was found to have a perforated ulcer of the stomach or duodenum at laparotomy.

An attempt was made to include all potential case patients, irrespective of their clinical condition at entry to hospital. Case finding was intensive. Research nurses made daily contact with the endoscopy unit staff and regularly spoke to the nurses and doctors working on medical and surgical wards. The admission records of the hospitals were examined several times weekly to find potential patients who might have been missed. Where there was any doubt about the diagnosis, the individual was labeled as a potential case patient and was followed up by the research nurse to determine if a definite diagnosis was made at a later date. If there was continuing doubt about the eligibility of a potential case patient, the relevant information was presented by the research nurse to the principal investigator who made a final decision regarding eligibility without knowing whether the individual had been a user of NANSAIDs or aspirin. Verbal witnessed consent was obtained from all participants. When subjects were too sick to be interviewed, regular return visits were made by the research nurses. If a case patient remained unfit for a structured interview, information was obtained from the case notes and from the patient's family physician. In such cases, exactly the same procedures were followed with that subject's controls.

Selection of Controls

In the first phase of the study, we matched a community control and a hospital control to each case patient. Use of NANSAIDs is widespread in the Australian community and comparison of the two sets of controls revealed them to be very similar in respect of their use of NANSAIDs (see below). It required considerably less effort and expense to recruit hospital controls than it did community controls. Consequently, in the second phase of the study, two hospital controls were matched to each case patient.

Hospital controls were subjects of the same sex and age (to within 5 years) as the case patients who were admitted to the medical wards of the same hospital within 1 week with any primary diagnosis that was neither an indication for, nor a known complication of, treatment with NANSAIDs. Consequently, potential controls were excluded if they had peptic ulceration, large bowel hemorrhage or perforation, or if the principal reason for admission was painful musculoskeletal disease. For each patient, the hospital admission lists covering the week in which the case patient was admitted were examined, and potential controls were selected on the basis of their sex and birth date. Controls were interviewed in the order they appeared in the lists until the requisite number of eligible consenting individuals had been recruited. The consent rate exceeded 90%.

Community controls met the same age, sex, and eligibility criteria as hospital controls and were drawn from the lists of the family practitioner who had most recently attended the case patient. Starting with the record of the patient and excluding subjects with the same family name, the practice records were inspected forwards or backwards (on the toss of a coin) until four potential controls were identified. These were contacted in the order they appeared in the practice records, and the first eligible individual who consented to interview became the community control for that case patient. The consent rate for community controls exceeded 80%.

Information Gathering

The index day for case patients and hospital controls was the day of admission to hospital. In the case of community controls, it was the day of interview. Case patients and controls had the same structured interview, administered by a research nurse, that requested information on all medications (prescribed and nonprescribed) that had been consumed in different time periods before the index day. Particular attention was paid to NANSAIDs and aspirin. Subjects were asked how many doses they had consumed in the previous week and month and whether they had used the drugs

in question between 1 month and 1 year from the index day. Open questions were followed by more directed questions and prompts in the form of the trade and generic names of all NANSAIDs and commonly used aspirin-containing medications. In Australia, use of prescribed drugs in the community tends to be low unless they are listed on the Commonwealth (federal) Government's schedule of pharmaceutical benefits. In the first phase of the study, the NANSAIDs listed were diclofenac, diflunisal, ibuprofen, indomethacin, naproxen, and sulindac. Piroxicam was listed on the schedule just before the end of the first phase of the study, and a sustained-release formulation of ketoprofen was listed during the second phase. Subjects were also asked about the frequency and quantity of alcohol consumption and their smoking history.

Interviewers were not blinded as to the case patient/control status of the participants. Accordingly, we took steps to reduce the influence of observer bias. Family practitioners were contacted by telephone and asked to consult their prescribing records to confirm the information obtained from the subject. For the majority of subjects, there was good agreement between the two information sources on what drugs had been taken, or any conflict was minor and easily explained. The subject's estimate of the number of doses consumed in the previous week was always accepted. In doubtful cases, the information from both sources was presented to the principal investigator who made a determination without knowing whether the subject was a case patient or control.

Medical records of the controls were inspected and information was extracted on up to three diagnoses listed in the discharge summary or the diagnoses recorded most recently in the family practitioner's record. For case patients, we recorded the reason for admission (suspected bleeding or perforation), the site of the lesion that had bled or perforated (esophagus, stomach, or duodenum), the nature of the lesion, and any other diagnoses that were listed later in the discharge summary. When multiple lesions were present, the endoscopist's or surgeon's opinion regarding which had been responsible for the complication was recorded. Wherever possible, the subject's weight was recorded.

Statistical Analysis

Individuals were categorized as users of NANSAIDs or aspirin on the basis of taking one or more doses in the week before the index day. Nonuse of the relevant drugs and drug combinations was used as a reference in all analyses. To examine the relationship between dose of NANSAIDs and risk, the total quantity of each drug consumed in the previous week was converted to the number of "standard dose units," using as a reference the minimum daily dose recommended by the manufacturer for rheumatoid arthritis.[27] The values were the same as those used by Griffin et al.[14] Duration of use was assessed for current users by classifying them as having started treatment within or before the previous 4 weeks. Elderly controls proved to have a high prevalence of use of NANSAIDs, and to establish their representativeness for the population at large, we compared their results with those obtained during a large community survey of drug taking habits in the Newcastle area, New South Wales.[28]

In the case of aspirin, the dosage data were analysed in two ways. First, we analyzed data from subjects who took only a low-dose formulation of aspirin (≤150 mg/day) as prophylaxis against thrombosis separately from other users. In a second analysis, we classified all aspirin users by the total dose of the drug taken in the previous week, irrespective of the dosage form used.

We used Student's t test to compare mean doses consumed in the previous week by patients and controls. For categorical variables, associations of interest were assessed by means of the odds ratio with its 95% confidence interval (CI) calculated for matched data sets. All variables were examined for their association with gastrointestinal bleeding or ulcer perforation. Alcohol consumption on more than 5 days of the week on a regular basis, regular consumption of more than five drinks on any occasion, and current smoking were significantly associated with the outcome in univariate analyses. Exposure odds ratios were adjusted for these factors by conditional logistic regression using the statistical program EGRET (Statistics & Epidemiology Research Group, Seattle, WA). An exception was the analysis of low dose aspirin in combination with NANSAIDs, in which it was necessary to break the matching. In this case, the odds ratios were adjusted using unconditional logistic regression analysis.

In the presentation of results, all odds ratios are calculated from matched analyses and are adjusted unless otherwise stated. To assess the relationship between dose of NANSAIDs and the level of the estimated relative risk, we performed a test for trend across the different levels of these variables using nonuse as the reference and treating the average dose per stratum as the observation of the covariate. In an attempt to account for the range of estimated relative risks with individual drugs, we compared the ranking of their odds ratios with that of the average numbers of standard dose units consumed by patients in the week before the index day and also with the rank order of their plasma half lives quoted by an authorative source.[29] The correlations between the ranked variables were estimated by means of the Spearman rank correlation coefficient.

Results

During the 5 years of the study, we recruited 644 case patients and 1268 controls; 229 of the controls came from the community, and the remainder came from hospital. We failed to obtain community matches for 20 case patients in phase 1 of the study. Matching hospital controls for age was successful in every case, but it was not possible to match seven very elderly men with controls of the same sex, and age-matched female controls were recruited instead. The

Table 1. Characteristics of Case Patients and Controls

Factors	Case patients n = 644	Controls n = 1268
Mean age (range, yr)	66.2 (15–95)	66.1 (16–97)
Females (n, %)	255 (39.6)	509 (40.1)
Prevalence (%)*		
Cardiovascular disease	36.9	43.9
Musculoskeletal disease	16.1	10.0
Digestive disease	9.1	2.8
Respiratory disease	8.3	13.4
Endocrine/metabolic disease	7.9	9.0
Neoplasms	3.3	4.2
Hematological disease	3.2	1.1
Genitourinary disease	2.6	3.0
Other diseases	12.6	12.6
Drug use in the previous week (%)† Antacids	27.4	13.8
Diuretics	24.5	29.5
Psychotropics	21.0	17.8
Digoxin	14.0	21.9
Beta-blockers	13.8	15.7
Potassium supplements	11.1	15.6
Antiulcer	9.8	0.3
Antianginal	9.0	15.5
Bronchodilators	8.2	11.3
Calcium channel blockers	6.8	6.9
Antibiotics	5.4	6.4
Current smokers (%)	23.9	15.1
Alcohol consumption (%)		
>5 days/wk	28.2	19.5
>5 drinks/session	22.7	12.6

*Refers to the principal diagnosis in controls and the most important diagnoses (other than GI bleeding or perforation) in case patients.
†Drugs other than NANSAIDS and aspirin. Patients could be taking more than one drug.

characteristics of case patients and controls are summarized in Table 1. Case patients had a lower prevalence of cardiovascular and respiratory diseases and a higher prevalence of digestive and musculoskeletal diseases, than controls. These differences were reflected in the patterns of drug consumption, with case patients having a lower prevalence of use of cardiovascular and respiratory drugs than the controls. Patients had a higher level of alcohol consumption than controls and were more likely to be smokers.

Overall Associations Between NANSAIDs and Aspirin and Upper Gastrointestinal Complications

In phase I of the study, NANSAIDs had been used in the previous week by 23% of hospital controls and 25.7% of community controls. These groups were combined for the purpose of further analysis.

Use of NANSAIDs and aspirin by case patients was higher than by controls across all age and sex strata (Table 2). The prevalence of use by female case patients aged 65 years or more was exceptionally high at 60.6%. Overall, NANSAIDs had been taken in the week before the index day by 252 (39.1%) case patients and 239 (18.8%) controls. The figures for aspirin were: case patients, 217 (33.7%), and controls, 239 (18.8%). For all subjects, the unadjusted unmatched odds ratio with use of any NANSAID was 2.8 (95% CI, 2.2–3.4), and the matched odds ratio adjusted for smoking and alcohol consumption was 3.0 (95% CI, 2.3–3.8). The unadjusted unmatched odds ratio for use of aspirin was 2.2 (1.8–2.7), and the matched adjusted odds ratio was 2.4 (1.9–3.0). The estimated population attributable risks (etiologic fractions) calculated from the prevalence of use of the drugs by the controls were NANSAIDs, 27%, and aspirin, 21%.

The results of analyses for possible interactions between NANSAIDs, aspirin, and alcohol are summarized in Figure 1. Both NANSAIDs and aspirin, taken alone, were associated with significantly increased odds ratios for upper gastrointestinal complications. The use of both NANSAIDs and aspirin in the previous week was associated with an odds ratio of 6.7 (95% CI, 4.3–10.4), approximately equal to the sum of their individual odds ratios. Consumption of both types of drug was associated with higher odds ratios when they were taken by individuals who regularly consumed more than five drinks during any drinking session. This level of alcohol consumption on its own was associated with an odds ratio for gastrointestinal complications of 2.8 (95% CI, 1.9–4.0). The combination of NANSAIDs, aspirin, and alcohol was associated with an odds ratio of 9.1, although the confidence interval was wide (3.1–26.7) due to small number of subjects in this category.

In a separate analysis, we found that the combination of NANSAIDs and low-dose aspirin (≤150 mg/day) was associated with an odds ratio of 3.4 (1.8–6.7), no higher than the estimate for NANSAIDs alone, 3.3 (2.6–4.3).

Table 2. Use of NANSAIDs and Aspirin by Case Patients and Controls Stratified by Age and Sex

Drugs	Age group (yr)	Case patients n	Case patients Users	Case patients %	Controls n	Controls Users	Controls %
NANSAIDs*							
Males	<65	196	44	22.4	367	57	15.5
	≥65	193	71	36.8	392	86	21.9
Females	<65	80	31	38.8	160	23	14.4
	≥65	175	106	60.6	349	73	20.9
Aspirin*							
Males	<65	196	56	28.6	367	70	19.1
	≥65	193	70	36.3	392	84	21.4
Females	<65	80	33	41.3	160	32	20.0
	≥65	175	58	33.1	349	53	15.2

*Any use in the week before the index day.

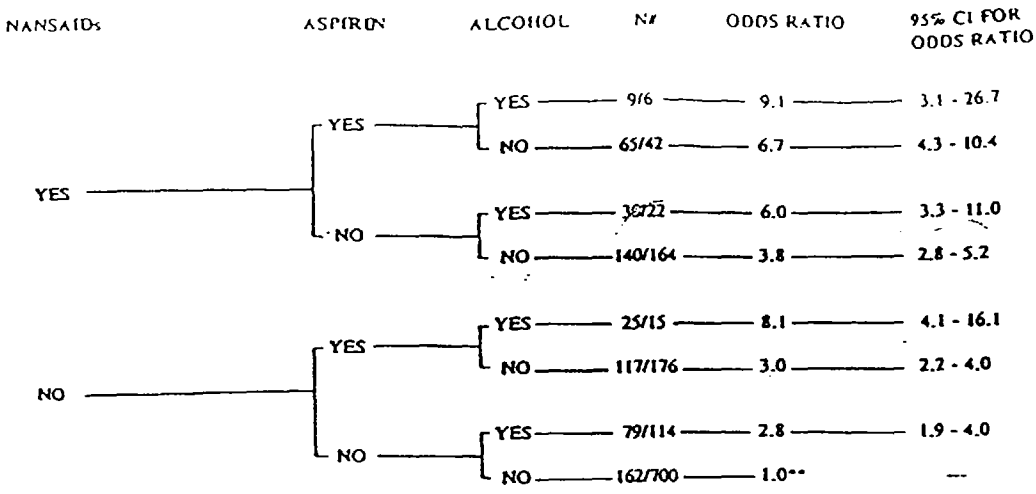

Figure 1. Associations between serious upper gastrointestinal complications and use of NANSAIDs, aspirin, or alcohol, alone or in various combinations. *Alcohol consumption of five or more standard drinks at any session. **Reference group for calculation of odds ratios. All odds ratios are matched for age and sex and adjusted for cigarette smoking. #Number of cases/controls in group.

Importance of Age and Sex

The odds ratios with use of NANSAIDs showed both age and sex dependence. The adjusted odds ratio was 2.0 (95% CI, 1.2–3.4) in those aged 59 years or less (n = 187), 3.0 (2.2–4.0) in those aged 60–79 years (n = 357), and 4.2 (2.3–7.6) in those aged 80 years or more (n = 100). The odds ratio was 1.9 (1.4–2.6) in men and 5.4 (3.6–8.0) in women. This sex-related difference was apparent in those under 65 years of age: the odds ratio for men was 1.6 (1.0–2.5) and for women was 4.7 (2.2–10.0); in those aged 65 years or more: men, 2.2 (1.4–3.3); women, 5.8 (3.6–9.2).

In contrast, the risk associated with use of aspirin showed less variation with age and sex. Odds ratios were 2.2 (1.4–3.4) in those aged 59 years or less, 2.5 (1.8–3.4) in those aged 60–79 years, and 2.1 (1.1–3.9) in those aged 80 years or above. Women had an odds ratio of 2.8 (1.9–4.0) and men 2.1 (1.5–2.8).

Importance of Dose and Duration of Use

The average numbers of daily dose units taken by patients and controls in the week before the index day are given in Table 3. Overall, case patients using NANSAIDs consumed a mean of 8.3 (95% CI, 7.6–8.9) dose units and controls using NANSAIDs 7.2 (6.6–7.8) dose units ($P < 0.005$, t test). The group who consumed the highest average dose were female case patients. After adjustment for body weight, the average dose they had consumed in the previous week was higher than for female controls, male case patients, and male controls, the differences ranging from 22% to 33% (Table 3).

Across six intervals of dose, the odds ratio increased in a linear manner from 2.1 (95% CI, 1.2–3.6) with consumption of less than 2 standard dose units in the previous week to 4.0 (2.6–6.1) with consumption of 14 or more standard dose units ($P < 0.001$, test for trend). When dose was used in a logistic regression model as a continuous variable, the slope was equivalent to an increase of 12% (95% CI, 9%–15%) in the estimated relative risk for every unit increase in the dose taken in the previous week. The relationship between dose corrected for body weight and estimated relative risk was similar (data not displayed).

The effect of age on dose response is illustrated in Figure 2. In subjects aged 65 years or more, the odds ratios were higher than in those aged under 65 years for each interval of dose. However, the slope of the dose response appeared similar in each age group.

The dose response relationship was different in men and women. In men, the odds ratio did not increase with dose (Figure 3). In contrast, in women, the odds ratio increased from 3.4 (1.8–6.2) with consumption of less than 4 dose units in the previous week to 9.7 (5.5–17.3) with consumption of more than 7 dose units in this period (Figure 3). These relationships were not altered when doses were corrected for body weight (data not displayed).

Use of low dose aspirin formulations (≤150 mg per day) was associated with an odds ratio of 1.4 (95% CI, 1.0–2.1), compared with 2.7 (2.0–3.5) with use of

Table 3. Doses of NANSAIDs Taken by Subjects in the Study

Subjects	n	Mean dose*	95% CI for mean	n	Mean dose†	95% CI for mean
Males						
Case patients	115	8.1	7.0–9.1	107	0.104	0.090–0.118
Controls	143	7.5	6.7–8.3	134	0.101	0.089–0.112
Females						
Case patients	137	8.4	7.6–9.3	110	0.134	0.118–0.151
Controls	96	6.7	5.9–7.6	85	0.110	0.090–0.129

*Average number of standard dose units consumed in the week before the index day.
†Average number of standard dose units/kilogram body weight consumed in the week before the index day.

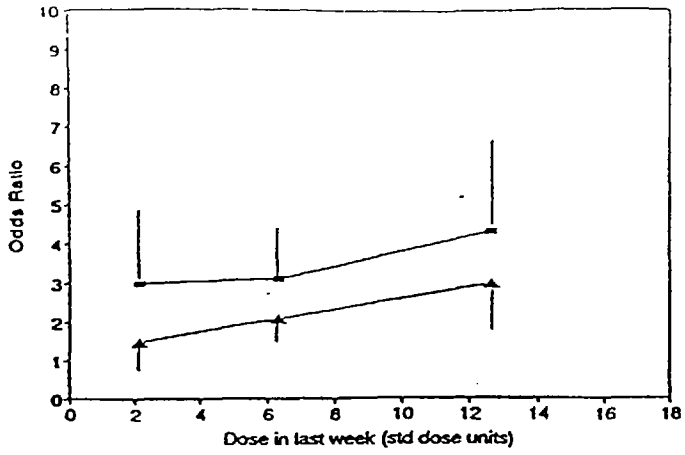

Figure 2. Relationship between the doses of NANSAIDs consumed in the previous week and odds ratios for upper gastrointestinal complications. The upper line describes the dose response in subjects aged ≥65 years (■). The lower line describes the dose response in subjects aged <65 years (▲). The vertical bars indicate 95% confidence limits for the odds ratios. In this figure, the odds ratios are unmatched and unadjusted. Nonuse of NANSAIDs was the reference in all calculations.

nonlow dose formulations. Among subjects who had consumed an average of 1050 mg aspirin or less in the previous week, irrespective of the formulation used, the odds ratio was 1.6 (1.2–2.1), compared with an odds ratio of 3.5 (2.3–5.3) with doses of 1200–2100 mg, 2.6 (1.0–4.2) with doses of 2250–4200 mg, and 3.3 (1.9–5.7) with doses of 4800 mg or above in the previous week. In other words, there was no apparent dose response curve with doses greater than 1050 mg in the last week.

Duration of use proved important both with NANSAIDs and aspirin. The odds ratio was substantially higher for current users who had started treatment in the previous 4 weeks, 6.3 (95% CI, 3.5–11.3) than for current users who had been taking the drugs for more than 4 weeks, 2.5 (2.0–3.3). The equivalent figures for aspirin were 4.2 (2.7–6.7) and 2.1 (1.7–2.8), respectively. Use of NANSAIDs or aspirin which had ceased before the month before the index day was associated with lower odds ratios: 0.9 (0.65–1.3) and 1.8 (1.2–2.7), respectively.

Importance of Route of Administration

Suppository formulations had been used by 37 case patients and 7 controls. Five of the suppository-using case patients and 1 of the suppository-using controls took the suppositories in combination with an oral formulation. The average total number of dose units taken by suppository-using patients in the previous week was 12.8 (range, 2–28) compared with 7.5 (0.33–34.9) for patients who only used oral formulations. The odds ratio for use of suppositories was 11.4 (95% CI, 4.6–28.2). In comparison, use of NANSAIDs by the oral route only was associated with an odds ratio of 2.3 (1.9–2.9).

Clinical Details of Patients

Five hundred ninety-eight case patients were admitted with a primary diagnosis of gastrointestinal bleeding and 46 with ulcer perforation. In all, 827 lesions were reported. The distributions of these lesions were as follows: gastric ulcers, 300; duodenal ulcers, 252; gastric or duodenal erosions, 124; esophagitis, 85; esophageal ulcer, 15; Mallory Weiss tear, 22; esophageal varices, 16; and anastomotic ulcers, 13. The lesions thought by endoscopists or surgeons to be the primary source of complications are summarized in Table 4. The most common sources were gastric and duodenal ulcers. In all, 42 cases were thought to have had definite clinical evidence of gastrointestinal bleeding but either were not investigated because of their age and/or general condition or had no definite source of bleeding found at endoscopy.

Importance of Site and Nature of Complication

The odds ratio for perforation with use of NANSAIDs was 6.1 (95% CI, 2.1–17.9), higher than the odds ratio for gastrointestinal hemorrhage, 2.8 (2.2–3.5). However, the confidence intervals for these odds ratios overlapped, and a similar pattern was not seen with aspirin (Table 4). All perforations involved either gastric or duodenal ulcers.

The odds ratios for complications categorized by the site and the nature of the responsible lesion are given

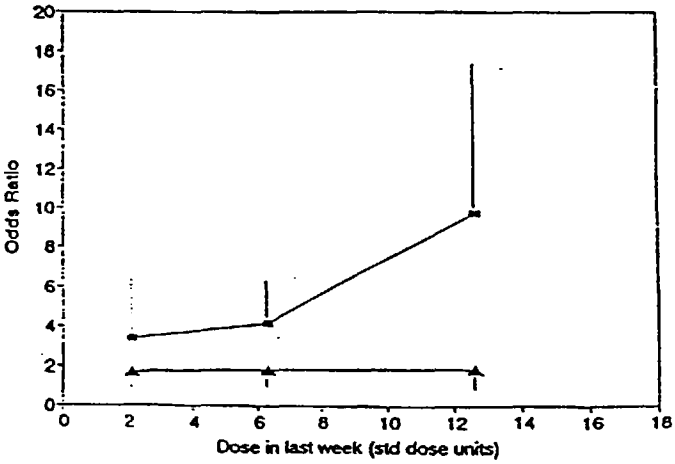

Figure 3. Relationships between doses of NANSAIDs consumed in the previous week and odds ratios for upper gastrointestinal complications. The upper line describe the dose response in females (■). The lower line describes the dose response in males (▲). The vertical bars indicate 95% confidence limits for the odds ratios. In this figure, the odds ratios are unmatched and unadjusted. Nonuse of NANSAIDs was the reference in all calculations.

Table 4. Type of Complications, Site, and Nature of Underlying Lesions and Estimated Relative Risks for NANSAIDs and Aspirin

Type of complication and underlying lesion	N	NANSAIDs OR[a]	NANSAIDs 95% CI	Aspirin OR[a]	Aspirin 95% CI
Complication					
Hemorrhage	598	2.8	2.2–3.5	2.4	1.9–3.1
Perforation	46	6.1	2.1–17.9	1.4	0.5–4.0
Site of lesion					
Gastric ulcer	273	3.7	2.6–5.3	3.1	2.1–4.5
Duodenal ulcer	200	2.9	1.8–4.5	2.6	1.7–3.9
Erosions	54	3.5	1.6–7.7	1.5	0.6–3.9
Esophageal lesions	65	0.7	0.3–1.6	2.1	1.0–4.3
Others[b]	52	1.0	0.1–7.3	0.2	0.02–2.6
Previous history of ulcer					
No previous ulcer	355	3.3	2.4–4.6	3.8	2.8–5.3
Previous ulcer	289	2.0	1.5–2.8	2.2	1.6–3.0
Recent history					
Any abdominal pain	342	2.9	2.1–4.0	2.4	1.7–3.3
None	242	2.6	1.8–3.9	2.1	1.5–3.0

[a]All odds ratios (OR) adjusted for cigarette smoking and alcohol consumption.
[b]Anastamotic ulcer (n = 10) or no lesion seen, or investigation not performed (n = 42).

in Table 4. The odds ratios for gastric ulcers were slightly higher than those for duodenal ulcers both for NANSAIDs and aspirin. The association between bleeding from erosions of the stomach and duodenum was significant for NANSAIDs but not for aspirin.

Bleeding from esophageal lesions was not associated with use of NANSAIDs. In contrast, use of aspirin appeared to be associated with an approximate doubling of the risk of bleeding from this site. Bleeding from anastomotic ulcers or unclassified lesions was not significantly associated with use of either NANSAIDs or aspirin.

Importance of Previous History

Three hundred fifty-five cases (55%) had no past history of peptic ulceration. In this group, the odds ratio for upper gastrointestinal complications with use of NANSAIDs was 3.3 (95% CI, 2.4–4.6), higher than the figure of 2.0 (1.5–2.8) in those who had such a history (Table 4). A similar pattern was seen with aspirin use.

Importance of "Silent" Ulceration

Three hundred ninety-three cases (61%) had no history of epigastric pain in the week before the event that resulted in hospitalization. The prevalence of "silent" ulceration increased with age: 54% of those aged <59 years; 62% of those aged 60–79 years; 70% of those aged ≥80 years. Using the lowest age group as reference, the odds ratios (unmatched and unadjusted) for "silent" ulceration in the other age groups were 1.4 (95% CI, 0.98–2.0) in the 60–79 year age group and 2.0 (1.2–3.4) in the ≥80 year age group. However, the odds ratios for "silent" ulceration in users compared with nonusers of NANSAIDs were not significantly increased in any age group: <59 years, OR 0.93 (0.46–1.87); 60–79 years, OR 0.94 (0.61–1.45); ≥80 years, 1.3 (0.55–3.1).

Relative Risk With Individual Drugs

The magnitudes of the estimated relative risks with individual NANSAIDs showed considerable variation. The confidence intervals around the odds ratios were wide and overlapping due to the relatively small numbers in some of the groups (Table 5). Piroxicam was associated with the highest relative risk, 4.7 (95% CI, 2.6–8.4) and ibuprofen the lowest, 0.7 (0.3–1.5). The average numbers of standard dose units consumed by patients who had used each of the NANSAIDs are also given in Table 5, as are the plasma half lives of these drugs quoted in a standard text.[29] When individual drugs were ranked by odds ratios, numbers of dose units consumed in the previous week, and plasma half lives, there was a significant relationship between the odds ratios and half lives (Spearman rank correlation coefficient 0.643, $P = 0.05$) but not between odds ratios and average doses ($r = 0.333$, $P > 0.05$). Differences in the estimated odds ratios for the individual drugs could not be explained on the basis of variations in the age and sex distribution of users (data not shown).

Discussion

This study contributes to the literature on risks of drug induced upper gastrointestinal complications

Table 5. Estimated Relative Risks of Upper Gastrointestinal Complications Associated With the Use of Individual NSAIDs

Name of drug	Odds ratio	95% CI	Average dose consumed by using case patients[a]	Half life[b] (hr)
Piroxicam	4.8	2.6–8.7	6.5	50
Ketoprofen[c]	3.6	2.0–6.6	11.3	8
Naproxen	2.8	1.8–4.3	7.7	14
Indomethacin	2.5	1.5–4.1	11.2	3
Sulindac	2.1	1.1–4.1	6.3	7
Diclofenac	1.7	1.1–2.5	5.5	1–2
Diflunisal	1.0	0.4–2.4	11.9	8–12
Ibuprofen	0.7	0.4–2.4	4.7	2

[a]Number of standard doses consumed in the week before the index day.
[b]Estimates of plasma half lives given in standard reference.[29]
[c]Sustained release preparation; the figure quoted in the apparent elimination half life (manufacturer's product information).

in a number of ways. We found an apparently linear increase in estimated relative risk with increasing dose of NANSAIDs. In contrast, a linear dose relationship was not seen with aspirin, although low dose preparations used as prophylaxis for thromboembolic disease appeared to be associated with a lower risk than larger doses used for other purposes. Our study also showed apparently additive risks when NANSAIDs were used in combination with aspirin or when either type of drug alone or in combination was taken with significant amounts of alcohol. We found a surprisingly high relative risk of ulcer complications with use of suppository formulations but were unable to confirm recent claims that use of NANSAIDs is associated with an increased risk of 'silent' ulceration in elderly subjects.[30,31]

The overall odds ratio for use of any NANSAID in the previous week, 3.0 (95% CI, 2.3–3.8), is close to the estimates from previously published case control studies[1–3] but lower than those from several recent studies.[14–16] The largest study, that of Griffin et al. from the United States, estimated an overall relative risk of 4.1 (95% CI, 3.5–4.7) and found a clear relationship between dose and level of risk.[14] Griffin et al. confined their analyses to subjects aged >65 years, so, on average, their subjects were older than ours. However, our estimates of relative risk for men and women >65 years of age were close to theirs, and the overall dose response relationships from the two studies were similar.

Griffin et al. performed a case control study using a population data base that enabled them to draw large numbers of controls from the same community as the patients.[14] In contrast, most of our controls were recruited from the hospital. However, we found the prevalence of use of NANSAIDs to be very similar in hospital and community controls. Somerville et al. made the same finding in a case control study in the United Kingdom.[1] Furthermore, our estimate of use of these drugs by subjects >65 years of age was confirmed by a recently published community prevalence study, suggesting that it is unlikely that any bias was introduced by combining the two control groups during the analysis.[28]

A limitation of most case-control studies is that they only estimate relative risks and do not provide direct estimates of incidence rates or excess risks for exposed subjects. In this study, we used intensive case-finding methods to recruit patients from a defined community. Relating the number of cases >65 years of age to the catchment population, we estimate an annual hospitalization rate of 174/100,000. This is close to an estimate of around 200/100,000 we have previously made for the population of the state of New South Wales.[32] It is also similar to the hospitalization rate in a Spanish community but is much lower then estimates for the U.S. population.[14,15] This may reflect a true difference in the incidence of ulcer complications, particularly in U.S. Medicaid enrollees, or it may reflect international differences in hospitalization policies for individuals suspected of having gastrointestinal bleeding.

From our estimates of relative risk, prevalence of use of NANSAIDs, and incidence rates, we are able to calculate an annual excess risk of hospitalization with bleeding or perforation for users of NANSAIDs of around 400/100,000. This is much lower than the excess risk attributed to use of NANSAIDs in an elderly U.S. Medicaid population, but the discrepancy is largely due to the higher hospitalization rate in the U.S. rather than differences in relative risk or estimates of prevalence of use of NANSAIDs.[14] Despite this, the etiologic fraction (population attributable risk) in subjects >65 years for NANSAIDs of 34% was somewhat higher than was calculated for a U.S. Medicaid population of the same age (29%).[14] Our figures are also higher than the estimates of 17% and 29%, respectively, for Spanish and English populations with similar age distributions.[1,15] This is due to the very high levels of use of NANSAIDs in New South Wales. At these levels, use of NANSAIDs, arguably, is a significant public health issue for elderly Australians. In addition to the effects of NANSAIDs on the upper gastrointestinal tract, these drugs are capable of inducing functional renal impairment and congestive heart failure in susceptible individuals.[33] Finding an appropriate balance of benefit and risk when using NANSAIDs is difficult and requires a careful appraisal of the needs and susceptibilities of the individual patient. However, we have difficulty in believing that at any particular time >20% of the elderly population in New South Wales need to take one of these drugs. We think that an appropriate public health response to this problem is to try to reduce the prevalence of use of NANSAIDs rather than coprescribing "protective" agents such as prostaglandin analogs in an attempt to reduce relative risk.[34] These should be reserved for high-risk individuals who really need such medication because of disabling symptoms.[35]

We found that the estimated relative risk of gastrointestinal complications increased significantly with age. This has not been a constant finding in the literature, although a recent meta-analysis concluded that the summary odds ratio was significantly higher in sub-

jects aged >65 years than in those aged below 65 years.[19] Our data suggest that the slope of the dose-response relationship is unaffected by age, although we found higher odds ratios in older subjects in each dose interval. When considering the relationship between age and the likelihood of gastrointestinal complications from these drugs, it must be remembered that the relative risk on its own is a relatively uninformative statistic. The background risk of gastrointestinal bleeding increases steeply with age, and the excess risk from NANSAIDs is much higher in the elderly than in young subjects, even when the relative risk is assumed to remain constant with age.[13]

Our finding of a higher odds ratio in women than in men has been an inconsistent finding in the literature.[9,13–16] A recent meta-analysis found no sex-related effect.[19] The excess relative risk we found in women was not due to their older age, being present in subjects above and below 65 years. Women, on average, received a higher dose of NANSAIDs per kilogram body weight then men, but this did not seem to explain the full difference in their estimated relative risks. The main factor appeared to be a much steeper dose-response curve in women than in men. This does not seem to have been reported previously, and at present, we have no explanation for this finding.

The overall estimated relative risk associated with the use of aspirin, 2.4 (95% CI, 1.9–3.0), was a little lower than that associated with use of NANSAIDs and comparable with estimates from two similar, but smaller, case control studies.[16,17] This is the first epidemiological study to show that low doses of aspirin used as prophylaxis against vascular thrombosis are also associated with an increased risk of serious gastrointestinal complications, although it should be noted that this result was only of marginal statistical significance. In this work we were able to show that use of both aspirin and NANSAIDs was independently associated with upper gastrointestinal complications, and use of a combination of these was associated with a higher risk than either type of drug used alone. The combination of low-dose aspirin and NANSAIDs was apparently not associated with an additive effect, but the number of users of the combination was small, and consequently the confidence interval around the estimated odds ratio was wide. We cannot confidently exclude an additive effect from these data. Previous work had shown that the risk of upper gastrointestinal complications with use of NANSAIDs was unlikely to be confounded by use of aspirin but had not tested for an interaction between these drugs.[14]

Although aspirin is associated with a higher rate of acute mucosal injury than NANSAIDs, when given to normal volunteers,[36] its overall importance as a cause of serious GI complications in the Australian community seems to be less. The main reason is that, as our data show, aspirin tends to be used in relatively low doses, and consumption is not so age-dependent as with NANSAIDs. Our data suggest that in subjects >65 years of age in New South Wales aspirin, overall, is responsible for around 20% of hospitalizations from upper gastrointestinal complications, compared with 34% due to NANSAIDs.

Some of the new information from this study is of potential clinical significance. In the case of NANSAIDs, we found a higher relative risk for perforation than for gastrointestinal bleeding. Despite our intensive case finding, we may have missed patients with ulcer perforation who were managed in small regional hospitals. As a result, the number of patients with ulcer perforation in the study was lower than expected, and the confidence interval around the estimated relative risk was wide. However, other studies have also documented increased relative risks for ulcer perforation, and a summary estimate for this complication was higher than for gastrointestinal bleeding.[19,21–23] However, most of the epidemiological studies have been of poor quality, and the inherent biases are likely to have resulted in overestimation of the relative risk, making any conclusions regarding any true differences in the strengths of the associations tenuous.[19] Even if the relative risk for perforation is higher, both from an individual and public health standpoint, gastrointestinal hemorrhage is more important because it is a commoner condition.

The relative risk for gastric ulcer complications was slightly higher than that for duodenal ulcers. This confirms the findings of several previously published studies.[1,16,14,19] The present study does not answer the question of whether the drugs are primarily ulcerogenic or cause pre-existing ulcers to bleed or perforate.

Although we did not find a higher relative risk of ulcer complications from NANSAIDs in those with a prior history of peptic ulcer than in those who did not have such a history, this finding requires careful interpretation. We did not control for past history of ulcer, and it is possible that subjects with such a history had been warned against taking NANSAIDs and aspirin. This would have had a greater impact in case patients than in controls and might have led to underestimation of the relative risk. Previous studies from Australia showed that subjects with a prior history of ulcers were likely to switch from aspirin to paracetamol.[37] The other consideration is that subjects with a prior

history of ulcer have a much higher subsequent incidence of ulcer complications than those who do not. Consequently, even a modest increase in the relative risk will result in a substantial excess risk for such individuals.

Despite the strength of evidence linking aspirin and NANSAIDs to acute mucosal damage in the upper GI tract, previous epidemiological studies have not documented the strength of the relationship between use of the drugs and serious hemorrhage from erosions in the stomach and duodenum. This study suggests that the association is significant but no stronger than for ulcers of the stomach and duodenum. Furthermore, gastroduodenal erosions were a relatively infrequent cause of bleeding in this series, and the importance of this entity has probably been exaggerated.

An association between use of aspirin, NANSAIDs, and damage to the lower esophagus has been suggested in two previously published studies of esophageal stricture.[38,39] We found an association between use of aspirin and bleeding from the esophagus, but NANSAIDs were not associated with damage in this area.

Superficially, the strength of the association between use of suppository formulations of NANSAIDs and the development of upper GI complications seems surprising, considering that these preparations tend to be used in the belief that they cause less mucosal damage than oral formulations. However, the finding is not unexpected given that suppositories contain high doses of drug and are sometimes combined with an oral preparation. Because some NANSAIDs are fairly well absorbed by the rectal route,[40] the resulting total systemic dose may be high, thus increasing the risk. However, the high estimated relative risk with suppositories could not be explained by dosage alone. Suppositories seem to be recommended for patients who have been intolerant of oral forms and who are therefore likely to be at higher than average risk of serious complications. The importance of these results is not so much that they point to an intrinsically high risk from suppositories but that they indicate that these preparations seem to be used in dangerous situations.

We were unable to confirm a previous report that NANSAIDs, due to their analgesic action, reduce the warning symptoms of peptic ulceration.[30] Although the epidemiological evidence has been weak there have been some confident assertions that "silent ulceration" is a risk with these drugs.[31] Skander and Ryan found a lower prevalence of abdominal pain among elderly individuals with endoscopic evidence of ulceration who had been using NANSAIDs than in nonusers.[30] However, in younger patients, symptoms were similar in users and nonusers. The present study, which is the largest investigation of this relationship, included uniform ascertainment of prior symptoms in a total of 644 patients hospitalized with upper gastrointestinal complications. Although the prevalence of epigastric pain declined with increasing age, within each age group symptoms were as common in those who had taken NANSAIDs as in those who had not.

The question of whether certain members of the NANSAID class are associated with a significantly higher relative risk of upper gastrointestinal complications than others cannot be answered definitively by any single study performed to date.[1,7,14,15] Concerns have been voiced that piroxicam, a long-acting agent, might be associated with a higher risk than shorter acting drugs.[41,42] However, these assertions were based on uncontrolled data. A recently published meta-analysis of epidemiological studies concluded that the pooled relative risk with piroxicam was the highest of five NANSAIDs tested.[19] The meta-analysis did not include the studies of Laporte et al. and Griffin et al.[14,15] The former found piroxicam to have the highest relative risk of five NANSAIDs, whereas the latter found it ranked third of eight drugs studied. In this work, the relationship we found between the plasma half lives of the drugs and the estimated relative risks was interesting but only of marginal statistical significance. However, taken together with other studies the data reinforced the concern about piroxicam. In view of this, concern should perhaps be extended to use of other long-acting drugs by elderly subjects.

In conclusion, the work we have presented here suggests that a number of factors ranging from the characteristics of individual patients to dose, route of administration, choice of individual agent, and concomitant consumption of aspirin and alcohol can significantly affect the risk of major upper gastrointestinal complications for users of NANSAIDs. These factors need to be considered when individual prescribing decisions are made.

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Received October 12, 1992. Accepted April 19, 1993.

Address requests for reprints to: David Henry, M.B., F.R.C.P., Discipline of Clinical Pharmacology, Clinical Sciences Building, Mater Misericordiae Hospital, Waratah, New South Wales 2298, Australia.

Supported by grants from the National Health & Medical Research Council of Australia and Pfizer Australia Pty., Ltd.

The preliminary results of this study were published in the form of a letter (Lancet 1991;337:370).

The authors are grateful to Pamela McGregor, RN, Caroline Forbes, RN, and Philippa Patey, RN, who performed the data collection and to Jean Eggleton who assisted with the data analysis. The authors are also grateful to John Duggan and the staff at the Gastroenterology Unit, Royal Newcastle Hospital, who provided invaluable help in identifying potential cases and to the general practitioners in the Hunter area, New South Wales, who assisted with the study.

VARIATION IN THE RISK OF PEPTIC ULCER COMPLICATIONS WITH NONSTEROIDAL ANTIINFLAMMATORY DRUG THERAPY

R. L. SAVAGE, P. W. MOLLER, C. L. BALLANTYNE, and J. E. WELLS

Objective. To assess the risk of perforation or hemorrhage of peptic ulcer on treatment with nonsteroidal antiinflammatory drugs (NSAIDs), both as a class and as individual agents.

Methods. A case–control study of medication histories in 494 patients and 972 matched control subjects.

Results. The increase in risk (odds ratio) with NSAID therapy was 5.1 times the risk in controls. The odds ratio for piroxicam was 6.3 (95% confidence interval [CI] 3.3–12.0), as compared with 2.9 for diclofenac, ketoprofen, and sulindac combined (95% CI 2.0–4.2). The effect of other risk factors was also considered, and the adjusted odds ratios were 4.1 for all NSAIDs, 6.4 (95% CI 2.8–15.0) for piroxicam, and 3.3 (95% CI 2.0–5.5) for diclofenac, ketoprofen, and sulindac combined.

Conclusion. The estimate of overall risk of peptic ulcer complications with NSAIDs is similar to that found in other studies. There appear to be differences in risk between agents.

From the Department of Medicine and the Department of Community Health and General Practice, Christchurch School of Medicine and Christchurch Hospital, Christchurch, New Zealand.

Supported by a 3-year grant from the Medical Research Council of New Zealand (MRC). Dr. Wells is an MRC-funded biostatistician. Merck Sharp & Dohme, Ciba-Geigy, Syntex, and May & Baker (Rhône-Poulenc Rorer) provided additional funding.

R. L. Savage, MBBS, MSc: Department of Medicine, Christchurch Hospital; P. W. Moller, MB, FRCPEd, FRCP, FRACP: Department of Medicine, Christchurch School of Medicine and Christchurch Hospital, and Medical Adviser, Rhône-Poulenc (NZ) Ltd.; C. L. Ballantyne, BA, RN: Department of Medicine, Christchurch School of Medicine; J. E. Wells, PhD: Department of Community Health and General Practice, Christchurch School of Medicine.

Address reprint requests to P. W. Moller, MB, FRCPEd, FRCP, FRACP, Christchurch School of Medicine, PO Box 4345, Christchurch, New Zealand.

Submitted for publication March 14, 1990; accepted in revised form August 25, 1992.

It is well known that treatment with nonsteroidal antiinflammatory drugs (NSAIDs) is associated with unwanted gastrointestinal (GI) side effects. Retrospective studies have suggested that NSAIDs are associated with an increased risk of perforated peptic ulcer (1,2), and case–control studies have shown a risk factor of 2–4 for hemorrhage of peptic ulcers (3,4) in patients aged 60 years and over. Data from the UK Committee on Safety of Medicines (5) showed that for the NSAIDs currently available in New Zealand, reports of GI reactions ranged from 21 to 75 per million prescriptions.

To ascertain the relative risks with the various NSAIDs, a case–control study of hemorrhage and perforation of peptic ulcer was begun early in 1986. The aim of this study was to confirm an increased risk of complications of peptic ulcer with NSAIDs and to determine whether there are significant differences between the available agents.

PATIENTS AND METHODS

Selection of patient population. It was estimated that to detect a 3-fold underrepresentation or a 2-fold overrepresentation in the case group of individual NSAIDs having 15% or more of the market share, and assuming an overall increase in risk of 3-fold, the study would require 450 index patients and 900 control subjects ($\alpha = 0.05$, $\beta = 1 - 0.8$). To this end, patients in Christchurch and surrounding areas (population 350,000) who were admitted to the hospital because of GI hemorrhage or possible perforation were identified within 24 hours by either the admitting diagnosis or the findings after admission. All such cases are admitted to

the public hospital, and the admitting office and acute care wards were visited daily by our nurse interviewer. If ulcers were found at endoscopy, surgery, or postmortem, the subjects were identified as index cases. Patients with gastritis or erosions, as defined by Maratka (6), were analyzed separately. The 2 patients in the acute-admission register who most closely matched the index patient by sex and age (within 5 years) were chosen as controls. For a small number of cases at the extremes of the age range, age matching was extended to 10 years. Medication histories, with particular reference to NSAIDs, were obtained during hospital admission from those patients who consented.

Patients were unaware of their status as "case" or "control." Observer bias was reduced by using a standard interviewing questionnaire for both the index patients and the controls. Information was requested on drug use in the past year, including over-the-counter (OTC) preparations, and use of tobacco and consumption of alcohol. Ibuprofen became available as an OTC preparation during the study, but only 2 patients used it. Eighty-nine index patients (18%) and 153 controls (16%) could not be interviewed, so we assessed general practice records, referral letters, notations of drugs the patients brought when they were admitted to the hospital, and hospital records for study information.

Perforation and hemorrhage of peptic ulcer were chosen as selection criteria because they are clearly defined problems necessitating admission to the hospital. Sampling bias was avoided because all such patients are admitted to our public hospital group, and therefore, all were assessed. Potential index and control patients who had bleeding disorders or were taking anticoagulants were not included. Excluded from the control group were patients with histories of peptic ulcer or bleeding, since these are contraindications for NSAID use, and patients with myocardial infarction, because of the negative association with long-term aspirin use.

Our approach was consistent with Feinstein's suggestion that patients with a range of diagnoses should be used in studies of this nature (7). Community controls may be a more "ideal" group, but would raise logistic problems. Also, the case–control study by Somerville et al (3) showed a similar prevalence of NSAID use by community and hospital controls. To confirm that our control group reflected the proportional use of NSAIDs in the community, computerized sales data for the individual NSAIDs were requested from retail pharmacies in Christchurch. Those supplying approximately 10% of the local market provided data.

Statistical analysis. Use of NSAIDs, paracetamol, aspirin, alcohol, or tobacco during the week prior to hospital admission was defined as "current use," regardless of the amount or the duration. "Regular use" of paracetamol or aspirin was defined as use on 2 or more days each week for 1 month or more. This "regular use" criterion was applied to current users of paracetamol and aspirin, so that overestimation of risk, which would occur if analgesics were taken for symptoms of peptic ulcer, would be avoided.

The frequency and quantity of alcohol intake were multiplied to obtain the average number of alcoholic drinks per week, which was converted to grams using the known alcohol content of standard New Zealand drinks (8). Exploration of the effects of various cutpoints, i.e., different levels of alcohol intake, showed where increased risk became significant. Patients whose notes indicated alcoholism were included in the high-intake group. Smoking was defined as "occasional" or "regular," and the number of cigarettes per day was recorded. Risks above and below 20 cigarettes per day were examined.

Odds ratios. All odds ratios, obtained by comparing the proportion of index and control patients exposed to each variable, were calculated on matched data. For uncommon disorders, the odds ratio approximates relative risk. Where the lower limit of the confidence interval is above 1, the increase in risk is significant. The methods for the statistical analysis of matched case–control triplets (1 case patient and 2 control patients) are those described by Breslow and Day (9). The etiologic fraction, a measure of the proportion of cases attributable to NSAIDs, is derived from the prevalence of the variable in the control group and from the odds ratio, as described by Schlesselman (10). The BMDP survival-analysis program 2L was used to estimate odds ratios by conditional maximum likelihood analysis (11,12). This program was able to cope with a variable number of controls per case, as occurred when there were missing data.

First, the odds ratios were calculated separately for each variable. Then the odds ratios for all 5 covariates—NSAIDs, aspirin, paracetamol, alcohol, and smoking—were adjusted for each other by entering them into a joint model which was fitted by conditional maximum likelihood. This was repeated in an expanded model including individual NSAIDs as covariates. For comparison among NSAIDs, the *t*-test for unequal variances was carried out on the coefficients and standard errors estimated in BMDP 2L.

RESULTS

A total of 494 index patients and 972 matched control patients were entered into the study. There were 478 matched triplets and 16 cases with 1 matched control each. Another 33 potential index patients and their controls were not entered, 10 because of uncertain diagnosis, 12 because of inadequate medication histories, 10 because they did not want to participate, and 1 because an overdose of piroxicam had been taken. A further 11 patients with peptic ulcers at endoscopy were excluded because they were taking warfarin or had a coagulopathy. Thus, the study cohort consisted of 1,466 patients and controls.

The odds ratio for hemorrhage or perforation of peptic ulcer with current NSAID use was 5.1 (95% confidence interval [CI] 3.8–6.8), with 40% of index patients (n = 198) and 13% of controls (n = 126) taking NSAIDs. The etiologic fraction showed that 30% of cases could be attributed to NSAIDs. The odds ratio for those who were also regular users was similar, at 5.0.

Characteristics of control patients. Control patients had a wide range of diagnoses requiring acute admission. Broadly grouped, there were 274 surgical,

515 medical, and 183 orthopedic (173 accident) patients. The prevalence of NSAID use was 12%, 11%, and 21% respectively.

Effects of characteristics of index patients. *Hemorrhage and perforation.* Thirty-nine percent of the 407 patients admitted because of hemorrhaging of a peptic ulcer were taking NSAIDs and the odds ratio was 5.2 (95% CI 3.6–7.0) for NSAID use in this group, compared with 5.2 (95% CI 2.6–10.3) for the 87 patients with perforation.

Gastric and duodenal ulcers. Two hundred eighteen index patients (44%) had gastric ulcers, 237 (48%) had duodenal ulcers, and 39 (8%) had both. Odds ratios for gastric and duodenal ulcers were 5.9 (95% CI 3.8–9.3) and 4.9 (95% CI 3.2–7.7), respectively.

Previous ulcers. Of the 460 index patients who were able to answer the question, 35% had experienced previous peptic ulcers or GI bleeding. Twenty-five percent of these were taking NSAIDs. Among patients with no previous history of peptic ulcer, 49% of the cases were taking NSAIDs, giving an odds ratio of 6.7 (95% CI 4.6–9.6).

Deaths. Forty-four (9%) of the index patients died; 14 (32%) of them were taking NSAIDs. There was no significant difference in mortality rates between index patients taking NSAIDs (7% of 198 patients) and those not taking NSAIDs (10% of 296 patients).

Effects of age and sex. The age range of index patients was 19–98 years; 220 were female and 274 male. There was no difference in risk between males and females (5.1). Of the 164 index patients aged <65, 27% were taking NSAIDs, compared with 10% of their age-matched controls, giving an odds ratio of 3.2 (95% CI 1.9–5.4). In contrast, the risk in patients aged ≥65 was 6.2 (95% CI 4.3–8.9), with 47% of the 330 index patients and 14% of controls taking NSAIDs. Seventeen percent of the older female control patients were taking NSAIDs, compared with 11% of the older males and 10% of the younger male and female controls.

Other risk factors. There was a significant increase in risk of hemorrhage or perforation (3.1) with current regular aspirin use above the modal dosage of 300 mg daily. There was no significant increase in risk for regular low-dose aspirin (≤300 mg/day) (1.3; 95% CI 0.8–1.9). Similarly, there was a significant increase in risk for regular paracetamol use (3.6) above the modal dosage of 1,000 mg daily, but not for regular use at or below 1,000 mg daily (1.2; 95% CI 0.7–2.1) (Table 1).

Table 1. Risks of perforation or hemorrhage of peptic ulcer on treatment with aspirin and paracetamol*

	Cases	Controls	Odds ratio	95% CI
Aspirin use				
No. with complete data	407	830		
Current, regular				
≤300 mg/day	33	50	1.3	0.8–1.9
>300 mg/day	37	25	3.1	1.8–5.1
Paractamol use				
No. with complete data	386	795		
Current, regular				
≤1,000 mg/day	21	42	1.2	0.7–2.1
>1,000 mg/day	40	28	3.6	1.9–6.2

* See Patients and Methods for definitions of cases and controls as well as of current and regular use. CI = confidence interval.

A dose–response relationship with alcohol was found, with odds ratios relative to abstainers of 1.2, 1.6, 2.6, and 3.2 for weekly alcohol intake of 1–149 gm, 150–244 gm, 245–349 gm, and ≥350 gm, respectively. The odds ratios became significant at 245–349 gm/week, i.e., approximately 5 drinks/day. Regular smoking was associated with a small but significant increase in risk, which was not related to the reported number of cigarettes consumed daily.

Table 2 shows the number of index and control patients exposed to each of the 5 risk factors. The univariate odds ratio for each risk factor and the adjusted odds ratio for the risk factors as covariates are shown. In the combined model, all the odds ratios were a little lower, but remained significant, including that for paracetamol. Although there was more use of

Table 2. Prevalence and odds ratios for risk factors*

Risk factor	No. (%) of cases	No. (%) of controls	Odds ratio (95% CI) Unadjusted	Adjusted
NSAID use current	199 (40)	125 (13)	5.1 (3.8–6.8)	4.1 (2.8–5.9)
Aspirin use current, regular >300 mg/day	37 (9)	25 (3)	3.1 (1.8–5.1)	2.8 (1.4–5.5)
Paracetamol use current, regular >1,000 mg/day	40 (10)	28 (4)	3.6 (1.9–6.2)	2.6 (1.3–5.0)
Alcohol use current >245 gm/week	70 (15)	60 (7)	3.0 (2.0–4.7)	2.4 (1.4–4.0)
Smoking current, regular	121 (26)	171 (19)	1.7 (1.2–2.2)	1.4 (1.0–2.0)

* n = 1,461 for nonsteroidal antiinflammatory drugs (NSAIDs), 1,237 for aspirin, 1,181 for paracetamol, 1,351 for alcohol, 1,395 for smoking in the unadjusted data. For the adjusted data, n = 972 (triplets removed if data missing for the case or both controls). See Patients and Methods for definitions of cases and controls as well as current and regular use. CI = confidence interval.

paracetamol in those taking NSAIDs, the effect of paracetamol did not disappear when adjustment was made for NSAID use.

A further model was constructed in which current use of ulcer-healing agents and dyspepsia were entered with paracetamol. The odds ratio for paracetamol remained at 3.6, showing that the effect was not due to its preferential use where there were symptoms of ulcer disease. It was not used preferentially by those with a previous history of peptic ulcer.

All 2-way interactions between the 5 risk factors in Table 2 were investigated. Two could not be estimated, and the remaining 8 were not significant, either individually or jointly. Interactions between the 5 risk factors and male or female sex were also not significant, but there were significant interactions between age and paracetamol, age and alcohol, and age and smoking. However, the interactions were small, difficult to interpret, did not involve NSAIDs, and so, are not reported.

In the maximum likelihood model shown in Table 2, the problem of missing data was approached in 2 ways. First, a variable "missing-x" was created if data for any of the 5 covariates were missing. The odds ratios for all of these missing variables were not significant, which shows that there was no disparity between cases and controls in terms of missing data. The second method was to include all the missing data in the analysis, with individual covariates coded "0" if missing. This analysis yielded similar but slightly higher odds ratios than for the model shown in Table 2, except for smoking, which just became nonsignificant.

Individual NSAIDs. The proportional use of individual NSAIDs by our hospital control patients is compared with community dispensing in Table 3. Where a patient was taking 2 or more NSAIDs, these were counted separately (6 cases and 4 controls). Table 4, column 1, shows the unadjusted odds ratios for the individual agents. There was a doubling of risk with piroxicam, 6.3 (95% CI 3.3–12.0), compared with diclofenac, ketoprofen, and sulindac as a group, 2.9 (95% CI 2.0–4.2) ($P < 0.05$). The small number of control patients taking indomethacin and ibuprofen gave unstable estimates of risk, as shown by the wide confidence intervals for indomethacin. This made comparison more difficult. They are included in Table 4 to show the extremes of the range. Furthermore, ibuprofen was used in low doses that were not equivalent to the antiinflammatory doses of the other agents and could not validly be compared with them.

The center column of Table 4 shows the odds ratios for patients with complete data on all covariates, as they compare with the data in column 1. Column 3 shows the outcome of adjusting for covariates. The increased odds ratio for sulindac could be explained by missing data. The altered risk with naproxen was due to significantly fewer smokers among the control patients who took naproxen than among the other con-

Table 3. Hospital and community use of individual nonsteroidal antiinflammatory drugs (NSAIDs)

	No. of NSAIDs taken by hospital patients (% of total NSAIDs)		% of doses from community pharmacies
	Cases (n = 198)	Controls (n = 126)	
Diclofenac	38 (19)	26 (20)	19
Ibuprofen	6 (3)	10 (8)	10
Indomethacin	19 (9)	5 (4)	7
Ketoprofen	21 (10)	16 (12)	14
Naproxen	37 (18)	21 (16)	14
Piroxicam	40 (20)	13 (10)	12
Sulindac	24 (12)	22 (17)	12
Other (n = 6)	20 (10)	16 (13)	12
Total	205 (100)	129 (100)	100

Table 4. Risk of perforation or hemorrhage of peptic ulcer on treatment with NSAIDs, assessed individually*

	Column 1: Odds ratios, unadjusted, all patients (95% CI)	Column 2: Odds ratios, unadjusted, only for patients in col. 3 (95% CI)	Column 3: Odds ratios, adjusted for all covariates (95% CI)
No. of patients	1,461	973	973
Diclofenac	3.0 (1.8–5.4)	2.5 (1.3–4.8)	3.3 (1.6–6.9)
Ibuprofen	1.2 (0.4–3.2)	1.5 (0.3–4.4)	1.9 (0.5–6.5)
Indomethacin	7.3 (2.7–9.5)	6.9 (3.6–24.5)	13.9 (3.3–57.8)
Ketoprofen	2.6 (1.4–5.0)	2.2 (1.0–5.0)	2.4 (1.0–5.9)
Naproxen	3.6 (2.1–6.3)	3.4 (1.7–6.8)	5.1 (2.4–11.1)
Piroxicam	6.3 (3.3–12.0)	5.4 (2.4–12.0)	6.4 (2.8–15.0)
Sulindac	2.3 (1.3–4.3)	3.5 (2.2–8.2)	3.6 (1.4–8.9)
Other (n = 6)	2.4 (1.2–4.8)	2.6 (1.1–6.4)	2.3 (1.4–6.1)

* NSAIDs = nonsteroidal antiinflammatory drugs; CI = confidence interval. See Results for details.

Table 5. Percentage of nonsteroidal antiinflammatory drugs (NSAIDs) taken at more than the maximum recommended maintenance dose (MRMD)

NSAID (MRMD, in mg/day)	No. with dose data		% above MRMD	
	Cases	Controls	Cases	Controls
Diclofenac (150)	32	19	19	5
Ibuprofen (1,600)	5	9	–	–
Indomethacin (100)	13	5	30	20
Ketoprofen (200)	19	13	5	8
Naproxen (1,000)	13	16	3	6
Piroxicam (20)	35	13	17	15
Sulindac (400)	18	18	5	0

trols. The small numbers of patients taking indomethacin allowed nonsignificant inequalities in covariate exposure to have a large effect. The difference in risk between piroxicam, 6.4 (95% CI 2.8–15.0) and diclofenac, ketoprofen, and sulindac, 3.3 (95% CI 2.0–5.5) did not reach significance. However, because of missing data, the power to find a 2-fold difference between NSAIDs as stated in Patients and Methods was reduced to just over 70%.

Table 5 shows the percentage use of each agent above its maximum recommended daily maintenance dose. This occurred more frequently for diclofenac, indomethacin, and piroxicam.

In index patients, a past history of peptic ulcer was not significantly related to individual NSAID use, except for diclofenac and piroxicam. These 2 drugs were prescribed less often for patients who had previously had ulcers.

Gastritis and erosions. There were 71 other index cases with hemorrhage from gastritis or erosions; 15.7% of the cases and 16.4% of the controls were taking NSAIDs. The odds ratio was 0.9 (95% CI 0.3–2.5).

DISCUSSION

Our results confirm an increased risk of 5.1 (95% CI 3.8–6.8) for hemorrhage or perforation of peptic ulcer with NSAID therapy, which is consistent with reported increased risks of 3.8 for hemorrhage of peptic ulcer (3) and 4.7 for deaths due to peptic ulcer in the elderly (13) in association with NSAIDs. In contrast, a relative risk of only 1.5 for upper GI bleeding (14) and 1.4 for gastrooesophageal bleeding in the elderly (15) have been reported for NSAID use. The odds ratio for hemorrhage from gastritis and erosions was 0.9 in the present study. This is much less than the odds ratios for peptic ulcer complications and suggests that NSAIDs are associated with the development of more significant gastroduodenal pathology.

The lack of risk with a regular daily aspirin intake of 300 mg or less confirms similar reports in the literature. These doses are now widely used for their antithrombotic effect. The lower overall risk with aspirin compared with NSAIDs is not unexpected, since these were usually not antiinflammatory doses. Similar risk estimates have been reported by Faulkner et al (16).

McIntosh et al (17) found an increased risk with paracetamol, which they attributed to its use for dyspeptic symptoms. Our finding of an increased risk with paracetamol at regular daily doses of >1,000 mg was not accounted for by previous peptic ulcer, dyspeptic symptoms, or by its concomitant use with NSAIDs. It is possible that people with pain sufficiently severe to require this level of analgesia have an associated increased risk of peptic ulceration. On the other hand, the weak inhibition of cyclooxygenase by paracetamol might be a predisposing factor.

Over several years, evidence has been presented of an increased incidence of adverse GI reactions with piroxicam treatment. Rossi and coworkers (18), using data from the US Food and Drug Administration, showed that the incidence of bleeding, perforation, or ulcer per million prescriptions was 6.52 for piroxicam, 3.56 for sulindac, and 3.11 for naproxen. However, it was suggested that if piroxicam is more ulcerogenic, then "differences of the magnitude suggested are probably outside the ability of spontaneous reporting systems to investigate further and measure with any reasonable degree of scientific certainty" (18). The Committee on Safety of Medicines (5) reported that piroxicam was associated with 58.7 GI reactions per million prescriptions, compared with 33.2 for ketoprofen, 32.8 for naproxen, 23.9 for sulindac, and 20.9 for diclofenac. However, they concluded that "it is not yet possible to determine whether the apparent differences between these drugs are due to their toxicity or to confounding factors and reporting bias" (5). More recently, Laporte et al (19) showed in a large case–control study from Spain, an increased risk with piroxicam compared with 3 other NSAIDs. Our study supports these differences between NSAIDs.

Several reasons for the findings of greater risks with particular agents have been suggested. Avila et al (20), in a controlled study, found that patients already taking cimetidine were more likely to be prescribed

one of the newer NSAIDs (e.g., piroxicam and sulindac) than patients who were not taking cimetidine. Our study did not show a preferential use of any NSAID for patients with a history of peptic ulcer.

In a record-linkage study in which data on NSAID usage and upper GI bleeding were derived from Medicaid billing records, Carson et al (21) suggested that the use of sulindac at 93% of the maximum recommended daily dose, compared with 65% for phenylbutazone and 49% for indomethacin, might explain their findings of an increased risk of GI toxicity with sulindac but not with phenylbutazone or indomethacin. Comparing risks on this basis, however, may not be valid because of the arbitrary nature of maximum recommended maintenance doses and the implicit assumption that the agents have dose-response curves for both efficacy and side effects which are similar. In our study, 95% of "case" patients taking ketoprofen, naproxen, or sulindac were at or below the maximum recommended dose, whereas only 81% of "case" patients taking diclofenac and 83% taking piroxicam were at or below this dose.

It has been suggested that there is a greater risk of perforated ulcers in women taking NSAIDs (1,22). Our results show no difference in the risk of hemorrhage or of perforation of peptic ulcer in older women than in older men. Hemorrhage and perforation attributable to NSAID use occur in more women than in men, however, because there are more women than men take NSAIDs. Thus in this study, based on the etiologic fraction (see Patients and Methods), 46% of ulcer hemorrhages and perforations in older women could be attributed to NSAIDs compared with 30% of those in older men.

Assuming that NSAID use in the control group reflects NSAID use in the community, we can attribute to NSAIDs approximately 0.9 deaths/100,000 population/year from hemorrhage and perforation of peptic ulcers. This value is just above the estimate of 0.5–0.7 deaths/100,000 population/year in Henry and coworkers' study of a New South Wales population (4).

Since many musculoskeletal disorders require prolonged therapy, the issue of side effects is of central importance. Our results suggest that the elderly are more at risk of hemorrhage or perforation of peptic ulcer than are patients younger than 65. We have demonstrated that 3 NSAIDs, diclofenac, ketoprofen, and sulindac, have similar risk and that this risk is lower than that of piroxicam. The data also suggest that paracetamol may not be without risk.

ACKNOWLEDGMENTS

We are grateful to the surgeons and gastroenterologists of the Canterbury Area Health Board and the retail pharmacists, general practitioners, and patients who provided information for this study.

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