Papers/Original Articles

An audit on the prescription habits of non-steroidal anti-inflammatory drugs (NSAIDs) in the medical clinics of a Base Hospital in Sri Lanka

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(Key words: NSAIDs - Non Steroidal Anti inflammatory Drugs)

Abstract

Objectives: To study prescription pattern of NSAIDs and other related matters in medical clinics at Base Hospital - Panadura.

Design and Setting: A non stratified sample of 200 adult patients attending medical clinics, taking NSAIDs from 04/04/97 to 05/03/98 were interviewed and their notes were examined.

Main outcome measures: Deficiencies in the prescription habits of NSAIDs were identified and guidelines were drawn to recitfy the same.

Results: Sex distribution: Male: Female = 64:136. Age distribution: 20-80 years. Osteoarthritis, lumbago, arthralgia and rheumatoid disease were the major indications to prescribe NSAIDs. Duration of therapy was 6 months to > 5 years. Consultants have initiated therapy in the majority. Indomethacin was the mostly prescribed drug. 62 received combined therapy of NSAIDs. In 33 steroids were co-prescribed. Alternative treatment modalities were scarely prescribed. There were 108 dyspeptics, 16 upper gastrointestinal bleeds without having any investigations. 49 were smokers and 64 were alcohlolics. Cessation of NSAID therapy was un-attempted in 146. 27 self medicated with aspirin. 144 and 8 received antacids and cimetidine respectively. All upper gastrointestinal bleeds were treated with antacids only. Dyspepsia was the main indication to commence therapy with antacids/ cimetidine. 22 were aware of the potential hazards of NSAIDs. Clinical implications of the findings are discussed in the text

Conclusions: (1) There were serious flaws in NSAID prescription. (2) Appreciation and documentation of risk factors were poor. (3) Guidelines are needed to rationalise NSAID prescription.

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Introduction

It had been proved beyond doubt, that NSAIDs are a potent cause of serious gastrointestinal (GI) damage. The magnitude of this problem is such that about 4000 deaths each year in persons over age 60 have been reported as due to peptic ulcer disease in the U.K. (OPCS) data[1]. It has been estimated, 22-31% of ulcer complications are due to NSAIDS[2-6], and the effect, then NSAID use would account for some 1000 deaths annually. It has been variously estimated, in terms of risk to an individual, that the risk of hospitalisation due to GI causes is 1 in 50 to 1 in 150 patient years. The risk of an upper GI bleed is about 1 in 100 to 1 in 500 patient years. Based on an annual rate of 12 m NSAID prescriptions, to the elderly, a GI related death would occur in 1 in 1000 to 1 in 5000 patient years. The costs associated with NSAID use can be considerable. In the U.K. more than 22 NSAID prescriptions are written annually, and based on BNF costs for diclofenac and these scripts may, thus account for over £ 250m annually.

In Sri Lanka, the magnitude of NSAID related upper injury, remains, largely unknown, as we do not have freely available open access endoscopy, services, and sufficient numbers of trained, personnel to objectively, assess the dyspepsias and the upper GI bleeds. In majority of the cases, they are blindly treated. The documented statistics of the peptic ulcer disease (PUD) by the department of statistics by the National Hospital of Sri Lanka, from 1991 to 1994 are as follows:

	1991	1992	1993	1994
Number of live discharges of patients having PUD	162	144	212	113
Number of deaths due to PUD	7	4	1	4

The above figures were not categorised according to the aetiology. It seems logical to assume that the statistics shown above are a gross under estimate of the real magnitude of the problem island-wide, which would be appreciably high if endoscopy facilities were freely available. The estimated annual cost of NSAIDs amounted to nearly Rs. 9 Million in 1995. This figure is supposed to increase annually.

The following study was designed to, evaluate the prescription habits of NSAID, to evaluate the appreciation and documentation of the risk factors which would enchance the incidence and risk of such damage and to develop protocols to prevent and minimise the same, when NSAID are prescribed. The out come of above study, gives some invaluable information, to the medical profession, to rationalise our approach to prescription of NSAIDs.

Criteria and Methodology

Objectives

1. To study the pattern of prescription of NSAIDs at the Base Hospital Panadura.
2. Appreciation and documentation of the risk factors by the prescriber, which are incriminated to enhance the gastric injury due to NSAIDs, in comparison to those found in larger studies. Viz age, sex, past history of PUD, smoking, alcohol, steroid co-prescription, type, dose and duration of NSAID.
3. Formulation of guidelines to minimise such damage and management of the same.

Selection criteria

A non-stratified random sample of 200 patients who were attending the Out-patients' Medical Clinic - Base Hospital Panadura, and were on long term NSAIDs treatment, from 04/04/1997 to 05/03/1998 was selected. Interviews were held with them and a questionnaire was filled which embodied various aspects of prescription of NSAIDs and related matters.

Age distribution

Range-years	*No.*
20-30	07
31-40	06
41-50	08
51-60	66
61-70	89
71-80	24
Total	**200**

Sex distribution

Male:Female = 64:136

Indication for long term NSAID treatment

Condition	*Number of patients*
Osteoarthritis	76
Lumbago	61
Arthralgia	36
Rheumatoid Disease (RD)	25
Ankylosing spondylities (AS)	02
Total	**200**

Duration of treatment

Duration in Months	*No.*
0 - 6	32
7 - 12	24
13 - 18	32
19 - 24	30
25 - 30	02
31 - 36	24
37 - 48	16
49 - 60	24
>60	16

Prescriber

Consultant in 135 instances
Junior Medical Officers in 65 instances.

Trial of other modes of treatment where appropriate

Physiotherapy	26
Intra-articular	02
Anti-depressants	05

Symptoms due to NSAIDs

None - 92
Dyspepsia - 108 — Without symptoms of reflux - 50; With symptoms of reflux - 58
Others - 00

Past history of upper GI bleed

Malena	11
Haematemesis	05

Endoscopic or radiological evaluation of symptomatic patients in the past or at present

None

Type of NSAIDs prescribed	No. of patients	Daily dosage
Ibuprofen	10	200 mg ~ 1200 mg
Indomethacin	80	75 mg ~150 mg
Diclofenac + Ibuprofen	48	50 mg ~ 150 mg
Indomethacin + Ibuprofen	12	combination of above dose ranges
Diclofenac + Ibuprofen	26	
Diclofenac + Indomethacin + Ibuprofen	24	

Smoking		**Alcohol**	
Yes	29	Yes	64
No	151	No	136

Steroid co-prescription

Yes	167
No	33

Dose	Dose
5 ~ 10 mg daily	1 ~ 3 years

Attempts to stop treatment

No	-	126
Yes	-	74 - at 3 month intervals, but failed.

Self medication with NSAIDs other than what was prescribed eg. aspirin

Yes	-	27
No	-	173

Nature of prophylactic treatment offered

Antacids	-	144	- 05 patients who had malena and 11 patients who had haematemesis were in this group.
H_2 receptor blockers	-	08	
None	-	91	

Indications to prescribe prophylaxis

Dyspepsia	-	85	- (77 were on antacids and 08 were on H^2 receptor blockers).
Routine	-	91	

The patient's awareness of NSAID related GI injury

Yes	-	22
No	-	178

Salient features observed with respect to the local practice

1. Majority of the patients were in the middle age or elderly group , prone to high risk of NSAID induced gastric injury.
2. As in other studies females predominate in numbers = 2:1.
3. Other alternative forms of therapy such as intra-articular steroids, heat therapy or antidepressants were not treid out in appropriate cases. eg. OA, Lumbago and in non specific athralgias, which are often helpful to wean off from NSAIDs.
4. Consultants have initiated treatment and the junior medical officers have blindly continued the treatment in the majority of cases. The consultants have not re-evaluated the necessity for continuation of NSAIDs in the vast majority.
5. Those who had dyspepsia or malena in the past were not investigated at any point.
6. Ibuprofen was the major NSAID prescribed and the doses fell within safe limits. Indomethacin was the second fashionable drug prescribed overlooking diclofenac, which had been proved to be safer than the former. Aspirin was hardly ever used in the management of chronic arthritic conditions.
7. Combination of NSAIDs was seen which does not confer any added benefits, but higher risk of GI damage.
8. No attempts were made to stop the prescription of NSAIDs in 60% of instances.
9. Proved forms of prophylactic treatment against upper GI damage which could occur from NSAID therapy was offered to only eight patients. ie. H_2 receptor blockers or PPIs, including those who had dyspepsia, malena and steroid co-prescription.

Discussion

Endoscopy of population on NSAIDs has shown prevalence of GUs in approximately 13% of patients and DUs in 11%[9]. By no means in all the damage seen at endoscopy is clinically significant. It is well established that the symptoms do not correlate well with the endoscopy damage. The presence of dyspepsia does not serve as a marker for ulcers, and NSAIDS may provoke these symptoms, without causing ulceration. Equally, ulcers may be frequently[10] silent, and the patient may present with a complication of an ulcer, as the first symptom. A potentially life threatening complication is often the initial presentation of an NSAID ulcer. In one study of 235 patients with life threatening ulcer complications, 60% were taking NSAIDS and 10.6% died at home[11]. The risk of upper GI haemorrhage, and ulcer perforation is increased with NSAID treatment, and in the present series 14 and 05 out of 200 patients have had a history of either malena or haematemesis respectively, i.e. aproximately 10% had shown clinical evidence of a upper GI bleed, which is a matter of grave concern. Had open access endoscopy facilities been available to evaluate the dyspeptic patients this figure could have been appreciably high.

Studies in healthy volunteers show that endoscopic damage occurs very quickly, within hours of treatment, virtually in every case[12]. With continued treatment the intial acute damage may heal through a process of adaptation. At the end of the 7th day the damage is less than on the first day and by the 28th day it could be completely resolve.

In response to cell injury, arachidonic acid is released from the cell membrane and subsequently metabolized to prostaglandins (PGs), leukotriones (LTs), and other substances. Adaptation could proceed by a number of mechanisms[12].

Prostaglandin-dependent mucosal defence mechanisms include the secretion of mucus and bicarbonate[8,13], which creates a pH gradient, between acidic lumens and the muscosal surface, maintenance of mucosal blood flow and cell surface hydrophobicity[5]. Adaptation may occur independently of muscosal PG synthesis[14]. These mechanisms protect mucosa from the onslaught of gastric acid, pepsin and Helicobacter pylori. NSAIDS can impair the mucosal integrity by inhibiting bicarbonate secretion[8,15,13]. Experiments have shown that PG inhibition and breaking the barrier both must occur to produce overt muscosal injury.

Several risk factors are incriminated in enhancing the risk of upper GI muscosal damage, due to, NSAIDS. Elderly are at the greatest risk and the relative risk at 65-74 year age group is 3.8 times that in the general population[8]. In the present series 155 patients out of 200 i.e. 78% were in the 51-70 year group, the majority falling into 61-70 year category (n=89).

The possible reasons for this include (i) the presence of more underlying disease (ii) higher chances of NSAIDS being prescribed (iii) possibility of higher mucosal sensitivity.

The NSAID associated ulcers are commoner in females than males, as the possibility of drug exposure is higher in females. In current series, too there was female preponderance Male: Female = 64: 136. NSAID users who smoke may be more likely to have more duodenal ulcers and larger ulcers. Alcohol too is known to cause acute erosive ulceration of the upper the GI mucosa, and would have same implications as smoking on ulcer healing. The relative risk of NSAID damage is greatest within the first 30 days of treatment, which coincide with the first four weekly scripts.

The dose of the NSAID prescribed also has a direct effect on the mucosal damage. At three times the standard dose the risk is increased approximately by 8 folds[8]. Recent data suggest that co-administration of steroids enhances the mucosal sensitivity to NSAIDS[16]. This increases the risk of NSAID related mucosal injury by 2 fold[17]. In the series steroids were co-prescribed approximately in 16%.

Having an endoscopically proven history of upper gastrointestinal events doubles the likelihood of a patient bleeding[17]. Next comes the role of type of NSAID prescribed. The conclusions come from a recently published results of a collaborative meta analysis, on variability in risk of gastrointestinal complications with individual NSAIDS[18]. Both figure 1 and table 1 were adopted from this publication. Meta analysis of the available epidemiological studies shows wide differences between individual drugs in the high risk of inducing gastrointestinal bleeding and ulcer perforation[18]. Of the drugs in common use, ibuprofen and diclofenec rank low intoxicity where as azapropazone, ketoprofen and piroxicam rank high.

The low risk of severe gastrointestinal complications, with ibuprofen seems to be attributable mainly to the low doses of the drug used in clinical practice. It should not be assumed that the apparent advantage of ibuprofen persists when doses are increased beyond 1600 mg daily. The evidence available indicates that it does not[18]. Studies show that doses of aspirin even as low as 75 mg a day are harmful though to a lesser extent than 300 mg a day[19].

Table 1. Comparison of comparative toxicity of range of drugs with use of Ibuprofen as reference for calculating relative risks

Comparator	*No. of studies*	*Pooled relative risk*	*95% Confidence interval for pooled relative risk*	*Pvalue (heterogeneity*
Ibuprofen	–	1.0+	– +	– +
Fenoprofen	2	1.6	1.0 to 2.5	0.310
Aspirin	6	1.6	1.3 to 2.0	0.685
Diclofenac	8	1.8	1.4 to 2.3	0.778
Sulindac	5	2.1	1.6 to 2.7	0.685
Diflunisal	2	2.2	1.2 to 4.1	0.351
Naproxen	10	2.2	1.7 to 2.9	0.131
Indomethacin	11	2.4	1.9 to 3.1	0.488
Tolmetin	2	3.0	1.8 to 4.9	0.298
Piroxicam	10	3.8	2.7 to 5.2	0.087
Ketoprofen	7	4.2	2.7 to 6.4	0.258
Azapropazone	2	9.2	4.0 to 21.0	0.832

+ Reference category for calculating relative risk.

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Clinical implications of the study and the paper

1. Appreciation of the impact of NSAIDs on morbidity and mortality of patients.

2. Appreciation of the relative importance of risk factors enchancing the mucosal damage, proper documentation of the same in case notes, and identification of high risk groups to take appropriate measures.

3. Rationalising prescription of NSAIDs - choice and dosage.

4. Formulation of protocols to:

   (a) Manage NSAID damage.

   (b) Minimise NSAID damage.

With respect to the local practice the findings highlight that our concern and awareness of NSAID related G.I. damage have to be greatly improved in order to rationalise the prescription of the same. It is also logical to assume that the findings represent a cross section of what is probably happening island-wide. The magnitude of this problem could be even larger in smaller institutions, when a major teaching hospital reflects flaws in handling NSAID prescription. Therefore in conclusion the following proposals are made to rationalise our approach to prescription of NSAIDs. viz:

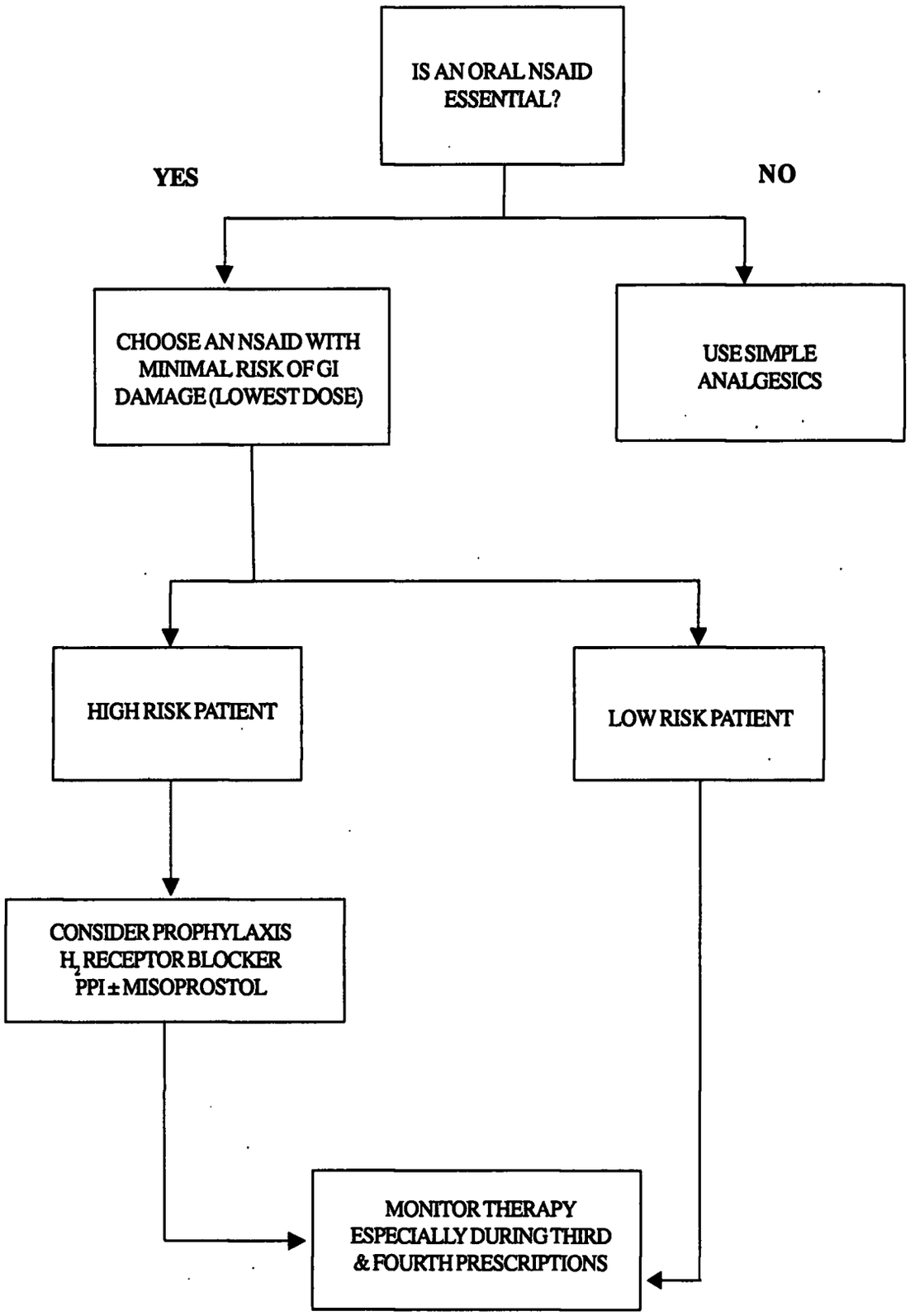
1. Improvement in medical education by the way of public lectures, seminars island-wide arranged by the appropriate bodies of medical professionals. Inclusion of these facts in undergraduate medical curricula.

2. Proper endoscopic evaluation of patients who developed dyspepsia during therapy or having the symptoms prior to therapy, including those who had evidence of upper GI damage. eg. malena or haematemesis.

3. Periodic evaluation by a consultant or a senior registrar to assess the necessity of continuation of the therapy.

Minimizing NSAID damage

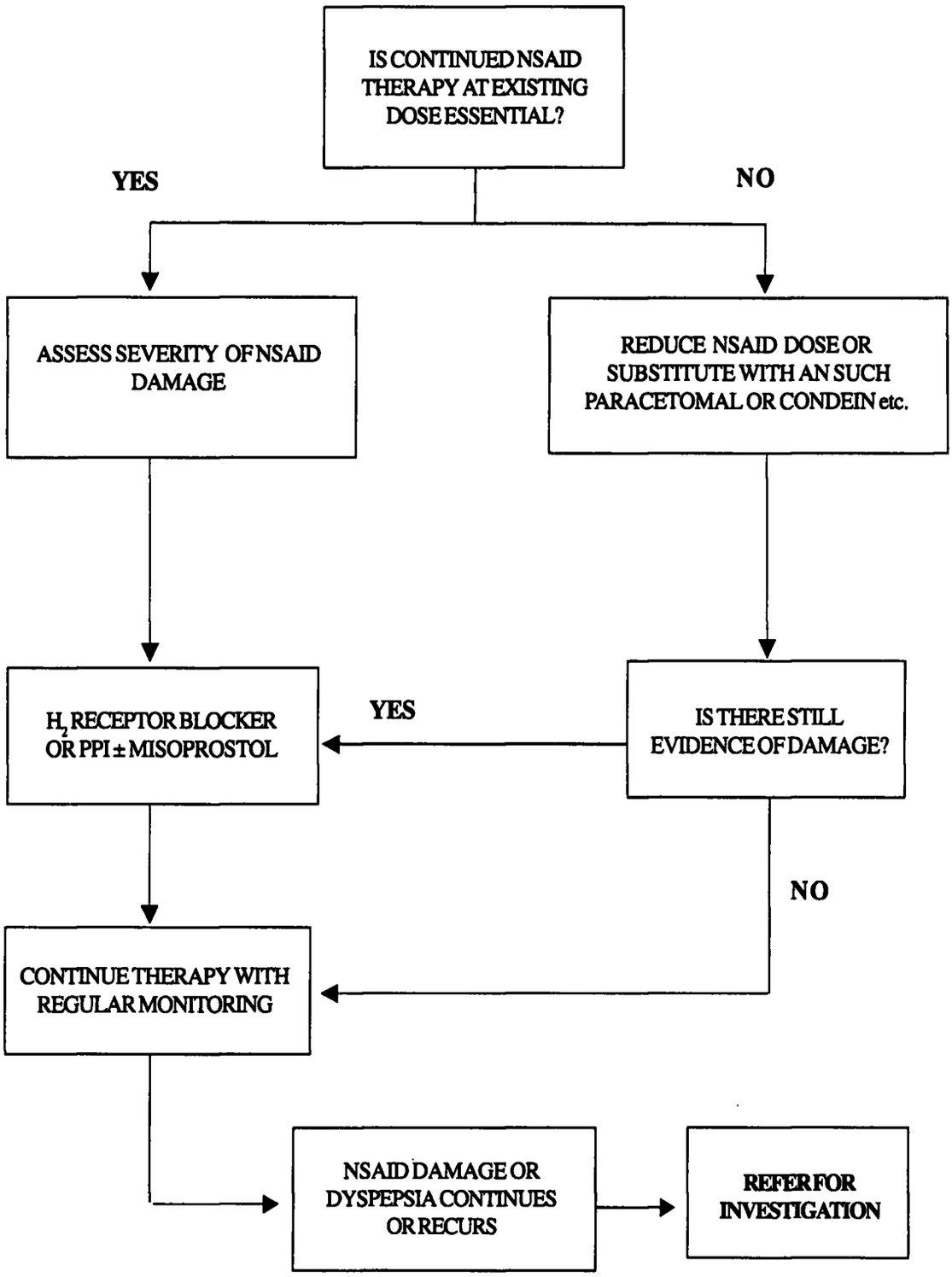
Patients presenting with an arthritic condition



High risk patients; elderly, previous peptic ulcer, high dose NSAID, steroid use, other underlying disease

Minimizing NSAID damage

Clinical evidence of NSAID damage or dyspepsia



High risk patients; elderly, previous peptic ulcer, high dose NSAID, steroid use, other underlying disease

4. Prescription of other modes of alternative treatment mentioned in the text where appropriate.
5. Patient education to improve the awareness of NSAID related GI hazards in order to report early to avoid self medication and combination therapy.
6. To follow the following guidelines, when prescribing NSAID.
   (a) Firmly establish the fact that the patient needs a NSAIDs.
   (b) In single doses NSAIDs have analgesic activity comparable to that of paracetomol and can therefore be taken on demand for mild and intermittent pain or as supplement to regular treatment.
   (c) In regular doses they have both long lasting analgesic and anti-inflammatory properties and the differences in the above activity between different NSAIDs are small, but there is a considerable variation in individual patient response. About 60% of patients will respond to any NSAID. Among the rest those who do not respond to one may well respond to another which has higher GI side effects.
   (d) Use the doses found to be safer in clinical trials. eg. Ibuprofen up to 1200mg daily.
   (e) There is no rationale in combining NSAIDs, which only increase the GI hazards. The combination with paracetamol or opiate analgesics is often effective, more appropriate and will give adequate pain control in individual cases.
   (f) As the main differences between NSAIDs are in the incidence and type of side effects before prescription the prescriber should weigh the efficacy against possible side effects.
   (g) Evaluate any dyspeptic symptoms before or during treatment endoscopically avoiding blind treatment.
   (h) Identify the high risk groups prior to therapy.
   (i) Follow the following flow charts in routine practice.

Ongoing clinical research:

The following questions remain, still to be answered.

i. What is the mechanism of adaptation and why does this break down?
ii. Is the acute damage which almost invariably seem on endoscopy of NSAID users relevant to the eventual development of ulcers?
iii. Does topical use of NSAIDs avoid GI damage?
iv. How relevant is the presence of Helicobacter pylori to the risk of NSAID induced damage, and what effect would eradication of this organism have on a recurrence?

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