

TOLERABILITY OF ASPIRIN AND PREDICTORS FOR WITHDRAWAL IN ELDERLY PATIENTS

CC Mok. MRCP (UK), FHKAM (Med)

Senior Medical Officer

YK Kwan. MRCP (UK), FHKAM (Med)

Senior Medical Officer

Department of Geriatrics, Tuen Mun Hospital, Tsing Choon Koon Road, New Territories, Hong Kong

J HK Geriatr Soc 2002; 11:11-15

Correspondence to: Dr. CC Mok

E mail: ccmok@netvigator.com

Summary

Aspirin has been proven to reduce risk of thrombotic cardiovascular events such as ischemic stroke and myocardial infarction. However, side effects are not uncommon with gastrointestinal side effects and haemorrhagic complications being the commonest causes of its withdrawal from treatment. A retrospective review was performed to study the tolerability of aspirin in elderly patients and predictors for drug withdrawal. Between 1995 and 1999, 285 consecutive patients aged over 60 who were started on aspirin and followed up in the Geriatrics outpatient clinic of Tuen Mun Hospital were recruited for study. Case notes were reviewed and the end-point was reached when aspirin had to be discontinued because of toxicities. Four patients in whom aspirin was stopped because of frailty or non-compliance were excluded. Of the remaining 281 patients, there were 165 females (58.7%) and 116 males (41.3%). The mean age at entry was 76.2 ± 7.0 (range 60-92) years. The mean duration of aspirin therapy was 17.0 ± 14 (range 1-50) months and the mean dosage was 111 ± 39 (range 80-300) mg. The cumulative probabilities of aspirin withdrawal at 12, 24 and 36 months were 13.1%, 17.5% and 23.8%, respectively. At the time of analysis, aspirin was stopped in 42 (15.0%) patients and the main reasons were endoscopically documented peptic ulceration (21/42, 50%) with or without gastrointestinal bleeding, gastritis (4/42, 9.5%), dyspepsia with normal endoscopy (3/42, 7%) and dyspepsia but patients refused an endoscopy (10/42, 23.8%). Univariate analysis revealed that an albumen level of 35 g/L ($p=0.002$), hemoglobin 11.0 g/dL ($p=0.004$), previous history of peptic ulcer or dyspepsia ($p=0.007$) and concomitant non-steroid anti-inflammatory drug (NSAID) use ($p=0.003$) were predictive factors for aspirin withdrawal. Multivariate analysis using the Cox proportional hazard model revealed history of peptic ulcer or dyspepsia (HR 5.4 [2.1-14.4], $p=0.007$) was independent risk factors for aspirin withdrawal. Extra caution should be given when aspirin is going

to be commenced in this subset of elderly patients.

Keywords: acetylsalicylic acid, peptic ulcer disease, risk factors, geriatric

Introduction

Aspirin (acetylsalicylic acid) is the commonest anti-platelet agent used in clinical practice. Aspirin has proven benefit in the secondary prevention of a number of occlusive vascular disorders such as unstable angina, myocardial infarction, transient ischemic attack (TIA) and stroke¹. In the first report of the Antiplatelet Trialists' Collaboration (ATC)¹, it was concluded that antiplatelet therapy, particularly with aspirin, reduced the risk of death from cardiovascular causes by about one-sixth and the risk of nonfatal myocardial infarction and stroke by approximately one-third in patients with unstable angina or a history of myocardial infarction, TIA or stroke. Moreover, there is evidence from recent studies that aspirin is also beneficial in the primary prevention of thromboembolism in patients at risk. In the Early Treatment Diabetic Retinopathy Study², 3711 patients with diabetes (49% with a history of cardiovascular disease) were given either aspirin (650 mg daily) or placebo and followed for an average of five years, treatment with aspirin was associated with a significant reduction in myocardial infarction (28%, $p = 0.01$) and important cardiovascular events (18%, $p = 0.05$). Results from the Thrombosis Prevention Trial³, which involved more than 1200 subjects, showed that treatment with low dose aspirin (75mg /day) reduced the incidence of both fatal and non-fatal cardiovascular events in men who had risk factors for cardiovascular disease. Aspirin has also been shown to be useful in the primary prevention of arterial thromboembolism in patients with non-rheumatic atrial fibrillation⁴. A recent prospective study indicated that women who take aspirin have a slightly reduced risk of first time large-artery ischemic stroke and the risk reduction is greater in older, hypertensive and smoking subjects⁵.

Because of the well-proven efficacy of aspirin in the secondary prevention of cardiovascular and cerebrovascular disorders, this antiplatelet agent is routinely prescribed for all patients who are admitted to our hospital because of vascular events, unless definite contraindications are evident. As a substantial proportion of acute admissions to the medical and geriatric wards are patients with cerebrovascular accident (CVA), transient ischemic attack (TIA) and ischemic heart disease (IHD), aspirin is one of the most commonly prescribed drugs in our unit. A previous small local study reported that the withdrawal rate of aspirin, administered at a dosage of 300mg/day, in elderly patients with cerebrovascular accident was 42% at 12 months and the chief reason for drug withdrawal was gastrointestinal toxicities⁶. As the relatively high incidence of aspirin gastropathy in that study could be partially related to the aspirin dosage, a lower dose of aspirin (75-160mg/day) is being employed in our unit for the treatment or secondary prophylaxis of acute vascular events in these few years. This lower dose aspirin regimen appears to be well tolerated in our elderly patients. The current study was undertaken to examine the tolerability of aspirin in the elderly population in terms of withdrawal rate over time. Statistical analysis was performed to determine the risk factors for aspirin side effects, in particular, the gastrointestinal (GI) toxicities.

Patients and methods

Between January 1995 and December 1999, consecutive patients who were started on aspirin for various indications and were followed in the Geriatrics outpatient clinic of Tuen Mun Hospital were included for study. Exclusion criteria were as follows: (1) information regarding aspirin commencement was incomplete; (2) aspirin was started more than 3 months before first clinic attendance. The records of patients who met the inclusion criteria were reviewed and the following information was obtained: demographic data; indications for aspirin; laboratory results at aspirin commencement such as serum albumen level, liver and renal function; hemoglobin; number of active medical diagnoses; number and nature of concomitant drugs being taken by patients like other antiplatelet agents; non-steroidal anti-inflammatory agents (NSAIDs) and antisecretory drugs (eg. proton pump inhibitors, H₂ antagonists); and past history of gastrointestinal (GI) problems such as dyspepsia and peptic ulcer disease (with or without complications).

Record of the recruited patients were reviewed till the end-point was reached when aspirin had to be stopped by the attending specialists because of side effects / up to date of the study. Patients in whom aspirin was discontinued voluntarily because of poor drug compliance were excluded from our study. Time zero was the time of aspirin commencement and the time interval between the start of aspirin and the time of data analysis or endpoint was taken for the subsequent life table analysis.

Statistical analysis

Unless otherwise stated, all the values in this study were expressed as mean \pm SD (standard deviation). For the comparison of categorical data between two groups, the Chi-square test was used while for the comparison of the continuous data, the Students' t-test was employed. When the data did not follow a normal distribution or when equal variance could not be assumed, the Mann Whitney U test was used instead. The Kaplan-Meier life table analysis was employed to study the cumulative percentage of patients who remained taking aspirin over time. Univariate analysis for predictors for aspirin withdrawal was performed by both the Chi-square and the non-parametric log rank tests. Cox proportional hazard model was adopted to study multivariately the independent predictor variables for aspirin withdrawal in our cohort of patients. As multiple comparisons were performed, Bonferroni's correction for multiple subgroup analyses was performed with statistical significance defined as a 2-tailed p-value less than 0.01. All the data were computed using the SPSS program (version 9.0, Windows 98).

Results

One thousand three hundred and thirteen consecutive records were screened. Two hundred and eighty-five patients who met the inclusion criteria were recruited for study. The main indications for aspirin were ischemic heart disease (myocardial infarction or unstable angina) (147 of 285, 51.6%) and stroke / transient ischemic attack (TIA) (135 of 285, 47.4%). Four patients in whom aspirin was stopped because of frailty or non-compliance were excluded from analysis. Of the remaining 281 patients, there were 165 women (58.7%) and 116 men (41.3%). The mean age at entry was 76.2 ± 7.0 (range 60-92) years. The mean duration of aspirin therapy was 17.0 ± 14 (range 1-50) months and the mean dosage was 111 ± 39 (range 80-300) mg.

The cumulative probabilities of aspirin withdrawal at 12, 24 and 36 months were 13.1%, 17.5% and 23.8%, respectively. At the time of analysis, aspirin was stopped in 42 (15.0%) patients and the main reasons were endoscopically documented peptic ulceration (21/42, 50%) with or without gastrointestinal bleeding, gastritis (4/42, 9.5%), dyspepsia with normal endoscopy (3/42, 7%), dyspepsia but patients refused an endoscopy (10/42, 23.8%), allergic skin rash (2/42, 4.7%) and intracerebral hemorrhage (2/42, 4.7%). It is noteworthy that of the 25 patients with aspirin-induced ulcer / gastritis, 11 (44%) did not have any preceding dyspeptic symptoms.

Table 1 shows the clinical characteristics of those patients who had aspirin withdrawal when compared with those who continued to take aspirin. The aspirin withdrawal group of patients was older at study entry but the difference was not significant. The mean serum albumen level was lower in the withdrawal group and the proportion of patients who had a serum albumen level of less than 35g/dL was significantly higher in this group (27% vs 13%, $p=0.03$; OR 2.0 [1.1-3.7]). Those who had aspirin discontinued during follow-up were more likely to have a previous history of gastrointestinal (GI) problems such as dyspepsia and documented ulcer disease (36% vs 16%, $p<0.001$; OR = 2.7 [1.6-

4.7]), concomitant chronic NSAID therapy at time of aspirin commencement (21% vs 9%, $p<0.001$; OR = 4.0 [2.3-7.0]) and a hemoglobin of less than 11g/dL at entry (24% vs 10%, $p=0.008$; OR 2.3 [1.3-4.3]). Univariate analysis using the non-parametric log rank test revealed that an albumen level of 35g/L ($p=0.002$), hemoglobin 11.0 g/dL ($p=0.004$), previous history of peptic ulcer or dyspepsia ($p=0.007$) and concomitant non-steroid anti-inflammatory drug (NSAID) use ($p=0.003$) were predictive factors for aspirin withdrawal.

Figure 1 (a-c) shows the probability of patients remaining on aspirin therapy over time with regard to the hemoglobin level, history of GI problem and concurrent NSAID use at study entry. Multivariate analysis using the Cox proportional hazard model demonstrated that history of peptic ulcer or dyspepsia (hazard ratio 5.4 [2.1-14.4], $p=0.007$) being independent risk factors for aspirin withdrawal. Age > 80 years (hazard ratio 2.6 [1.1-5.9], $p=0.03$), serum creatinine level > 120 $\mu\text{mol/L}$ (hazard ratio 3.4 [1.2-9.5], $p=0.02$), hemoglobin 11g/dL (hazard ratio 2.7 [1.1-6.4], $p=0.03$) and concomitant NSAID use (hazard ratio 2.9 [1.1-8.1], $p=0.04$) might also be risk factors for aspirin withdrawal, yet they did not reach statistical significance with Bonferroni's correction with the $p<0.01$ criterion.

Table 1: Clinical characteristics of our cohort of patients in relationship to aspirin withdrawal during follow-up

| | Patients continued with aspirin N = 239 | Patients in whom aspirin was stopped N = 42 | P |
|--|---|---|----------------|
| Age (years) | 75.9 \pm 7.0 | 77.7 \pm 6.8 | 0.13 |
| Proportion of patients > 80 yrs of age (%) | 60 (25) | 14 (33) | 0.26 |
| Female sex (%) | 136 (57) | 29 (69) | 0.14 |
| Daily aspirin dose (mg) | 110 \pm 9 | 114 \pm 36 | 0.53 |
| No. of drugs apart from aspirin | 2.5 \pm 1.4 (range 0-7) | 2.7 \pm 1.5 (range 0-7) | 0.35 |
| No. of active medical diagnosis | 1.9 \pm 1.1 (range 0-5) | 2.3 \pm 1.1 (range 0-5) | 0.03 |
| History of dyspepsia / ulcer (%) | 36 (15) | 16 (38) | < 0.001 |
| Use of GI prophylactic agents (%) | 31 (13) | 9 (21) | 0.15 |
| Laboratory results at study entry | | | |
| Hemoglobin (g/dL) | 13.1 \pm 1.6 | 12.5 \pm 1.9 | 0.06 |
| Proportion < 11 g/dL (%) | 23 (10) | 10 (24) | 0.008 |
| Serum albumen (g/dL) | 40.0 \pm 4.2 | 37.2 \pm 5.4 | 0.01 |
| Proportion < 35 g/dL (%) | 31 (13) | 11 (27) | 0.03 |
| Serum creatinine ($\mu\text{mol/L}$) | 102 \pm 31 | 105 \pm 43 | 0.64 |
| Proportion > 120 $\mu\text{mol/L}$ (%) | 53 (22) | 8 (19) | 0.65 |
| Concomitant drugs (%) | | | |
| Anti-platelet agents | 9 (4) | 2 (5) | 1.00 |
| Corticosteroids | 10 (4) | 3 (2) | 0.90 |
| NSAIDs | 9 (4) | 9 (21) | < 0.001 |

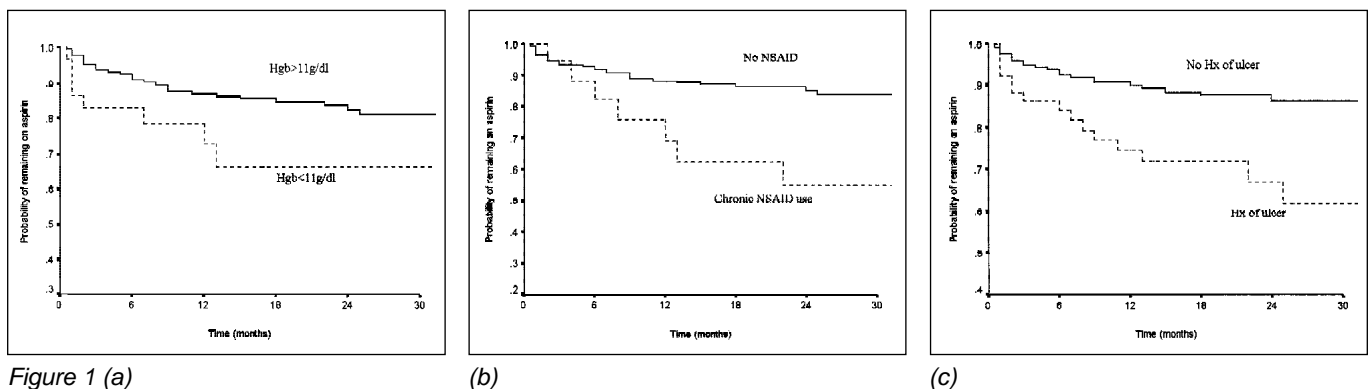


Figure 1 (a)

(b)

(c)

Figure 1 : Probability of patients remaining on aspirin with time in our cohort of elderly out-patients in regard to: (a) hemoglobin level; (b) concurrent NSAID use; (c) previous GI history

Discussion

This study examined the tolerability and withdrawal rate of aspirin in a cohort of elderly patients and the clinical predictors for aspirin withdrawal. Consistent with our anecdotal experience, we have shown that aspirin was quite well tolerated in the elderly and the withdrawal rate was only 14% at 2 years. The commonest reason for aspirin discontinuation in our cohort of patients was GI side effects and it was noteworthy that a significant proportion of patients with aspirin-induced GI complications did not have preceding symptoms of GI upset. As more than two-thirds of our patients were receiving a daily aspirin dose of 100mg or less, the low overall withdrawal rate was probably related to this low dose regimen. Because of the relative small size of our cohort, bias during patient selection into the study cohort may occur and we attempted to minimize this by recruiting consecutive patients within a specified time period and in whom aspirin was commenced not more than 3 months before first clinic attendance. However, involvement of patients who are followed up in the outpatient clinics only may miss a certain proportion of patients who had more severe vascular events and either died, remained in hospital or followed up by the community geriatric assessment team (CGAT). This may cause an underestimation of the GI events related to aspirin therapy. Moreover, the relatively short period of follow-up in our study may also cause an apparently low incidence of aspirin gastropathy. For these reasons, a prospective study of the incidence of aspirin toxicities in a large number of patients with ischemic stroke is going on in our unit.

Aspirin is a potent inhibitor of prostaglandin synthesis through its irreversible acetylation of cyclooxygenase. The inactivation of the

cyclooxygenase enzyme results in the inhibition of thromboxane A₂ formation by the platelets, which prevents their aggregation and adhesion. This anti-platelet action of aspirin is the basis for its efficacy in the prophylaxis of various vascular occlusive diseases. However, inhibition of cyclooxygenase also leads to the reduction in the production of other prostaglandins that are important in mucosal protection of the GI tract and regulation of the renal blood flow. Prostaglandins are important cytoprotective agents in the GI tract because they increase mucus secretion, bicarbonate secretion and mucosal blood flow⁷. In addition, they stabilize mucosal mast cells and lysosomal membranes, and inhibit free radical production and enzyme release by the neutrophils⁸. Inhibition of the E and I series of prostaglandins by aspirin is one of the major mechanisms for mucosal injury in the stomach and the duodenum. Moreover, aspirin is also capable of breaking the gastric mucosal barrier by non-prostaglandin-dependent mechanisms, leading to a reduction in mucosal potential difference and back diffusion of hydrogen ions⁷.

Among the various side effects of aspirin, GI toxicity deserves most concern because it is associated with significant morbidity and mortality. The relative risks (RR) for the occurrence of gastric and duodenal ulcers in chronic aspirin users were estimated to be 4.7 and 1.2, respectively and the relative risk for GI bleeding was 3.3 for aspirin users⁹. In the Thrombosis Prevention Trial (TPT)³ and the Hypertension Optimal Treatment (HOT) study¹⁰, the incidence of major GI bleeding was reported to be 0.74 and 2.16 per 1000 patient-years, respectively. In both trials, non-fatal major GI bleeding was shown to be significantly more common in aspirin users than placebo. The risk of aspirin-induced GI bleeding appears to be dose dependent. Weil et al¹¹ demonstrated that the odd

ratios for GI bleeding were 2.3 for 75mg, 3.2 for 150mg, and 3.9 for 300mg of daily aspirin at least 5 days per week. We were unable to show that the dosage of aspirin was a significant predictor for aspirin withdrawal. This is probably because of the fact that more than two-thirds of our patients were receiving an aspirin dosage of 160mg /day or less and the dosage effect is therefore difficult to be demonstrated. Moreover, the number of patients who actually developed GI bleeding was too small and a type II statistical error is inevitable.

A number of epidemiological studies have proposed additional factors that may increase the risk of adverse GI events induced by the NSAIDs¹². These include increasing age, previous history of peptic ulcer / gastrointestinal bleeding, high NSAID dose and concomitant use of steroid, anticoagulants or other NSAIDs. The reasons why advancing age is associated with an increased risk of NSAID-induced gastropathy are not fully understood. Comorbidity, polypharmacy, altered pharmacokinetics associated with advancing age and age-dependent decline in gastric and duodenal prostaglandin concentrations have been implicated. The results from our study are in keeping with previous studies in that increasing age and previous history of GI disorders were shown to be multivariate predictors for aspirin related GI side effects. Because of the small number of patients who were receiving concomitant drugs such as non-aspirin NSAIDs, anticoagulants or corticosteroids, the contribution of these drugs in aggravating the risk of aspirin related GI toxicities in our cohort could not be determined.

Given the knowledge that increasing age, past history of GI problems, renal impairment and concomitant NSAID use are independent predictors for aspirin related toxicities, extra caution should be given when aspirin is to be commenced in this subgroup of elderly patients. Concomitant NSAIDs should better be avoided and a careful history

concerning previous GI disorders should be taken. Prophylaxis with agents like misoprostol, high dose H₂-receptor antagonists and proton-pump inhibitors should be considered in subjects at higher risk of aspirin-induced gastropathy.

References

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy - I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *Br Med J* 1994;**308**:81-106
2. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. *J Am Med Asso* 1992;**268**:1292-1300
3. Thrombosis prevention trial: randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998;**351**:233-241
4. Hellemons BS, Langenberg M, Lodder J et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomized controlled trial comparing two intensities of coumarin with aspirin. *Br Med J* 1999;**319**:958-964
5. Iso H, Hennekens CH, Stampfer MJ et al. Prospective study of aspirin use and risk of stroke in women. *Stroke* 1999;**30**:1764-1771
6. Mok CK, Lum CM. Aspirin 300mg per day - Can the elderly tolerate? *J HK Geri Soc* 1991;**2**:32-34
7. Haekey CJ. Review article: aspirin and gastrointestinal bleeding. *Aliment Pharmacol Ther* 1994;**8**:141-146
8. Levi S, Smith-Shaw C. Non-steroidal anti-inflammatory drugs: how do they damage the gut? *Br J Rheumatol* 1994;**33**:605-612
9. Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers: facts and figures multiply, but do they add up? *Br Med J* 1990;**300**:278-284
10. Hansson L, Zanchetti A, Carruthers S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. *Lancet* 1998;**351**:1755-1762
11. Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *Br Med J* 1995;**310**:827-830
12. McCarthy D. Nonsteroidal anti-inflammatory drug-related gastrointestinal toxicity: definitions and epidemiology. *Am J Med* 1998;**105**(5A):3S-9S

LEARNING POINTS

1. **With a mean follow up of 17 months, 15.0% of patients previously receiving aspirin were withdraw from treatment. Cumulative probabilities of aspirin withdrawal at 12, 24, 36 months were 3.1%, 17.5% and 23.8% respectively.**
2. **The main reason for aspirin withdraw was peptic ulceration with or without gastrointestinal bleeding.**
3. **Univariate analysis revealed that an albumen of $\leq 35\text{g/L}$, haemoglobin $\leq 11.0\text{g/dL}$, previous history of peptic ulcer or dyspepsia and concomitant NSAID use were predictive factors for aspirin withdrawal.**