Final Report

The impact of chronic non-steroidal anti-inflammatory drug use on the health of veterans.

Prepared for

Department of Veterans' Affairs

Prepared by

Department of Clinical Pharmacology
Flinders University

Submitted by

Quality Use of Medicines and Pharmacy Research Centre
Sansom Institute
University of South Australia
Division of Health Sciences
City East Campus
North Terrace
Adelaide SA 5000
Tel 08 8302 2288
Fax 08 8302 1472

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CONTACT PERSON

Ms Kathy Mott
Senior Project Manager and Development Officer
Quality Use of Medicines and Pharmacy Research Centre
Sansom Institute
School of Pharmacy and Medical Sciences
University of South Australia
GPO Box 2471
Adelaide SA 5000
Phone: (08) 8302 2403
Fax: (08) 8302 1087
Email: kathy.mott@unisa.edu.au

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CHIEF INVESTIGATORS

Department of Clinical Pharmacology, Flinders University:
Associate Professor Kathie Knights
Associate Professor Arduino Mangoni

ETHICS APPROVALS

UniSA Ethics Committee [Approved 4 December 2006, Protocol P252/06
DVA Human Research Ethics Committee [Approved 15 December 2006]
Flinders Clinical Research Ethics Committee [Approved 9 January 2007, protocol 103/067 period 12/02/2007-12/02/2010]

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BACKGROUND

The University of South Australia and Flinders University under Department of Veterans' Affairs Official Order no #2007/01/066 have been contracted to undertake research on the impact of chronic Non Steroidal Anti-inflammatory Drugs (NSAIDs) use on the health of veterans.

HYPOTHESIS

Chronic NSAID use is an independent contributing factor impacting on the health of Australian Veterans.

PROJECT AIMS

To undertake a preliminary study to evaluate an association between chronic NSAID use (including dose and chemical class) in the veteran population and: (1) all cause death, (2) rates of hospitalisation for acute myocardial infarction, (3) heart failure (4) acute ischaemic heart disease (5) cardiac arrest (6) intracerebral haemorrhage/cerebral infarction/stroke (7) paroxysmal tachycardia and other cardiac arrhythmias and (8) arterial embolism and thrombosis.

PROJECT METHODOLOGY

Matched Case-Control Study (retrospective)

Case Definition and Exclusion Criteria: We conducted a retrospective nested case-control study to examine the risk of exposure to NSAIDs and cardiovascular events. Our study population consisted of Australian war veterans, spouses and dependants aged 65 years and older on 1 Jan 2002 with current gold card status at 1 Jan 2000. Subjects were followed for events from 1/1/2002 until 30/06/2006. Potential cases and controls were excluded if they did not have complete hospital and prescribing data for the 2 years prior to their respective index date. Clients were also excluded if they had any of the outcomes of interest either as a primary diagnosis or co-morbidity in the 2 years prior to 1/1/2002. Additional exclusion criteria included diagnosis of malignant neoplasms (C00 to C96) at any time prior to or during the study period as a primary or secondary diagnosis, or treatment with antineoplastic agents in the 2 years prior to the start of the study period.

Cases were identified on the basis of a cardiovascular event or death. The cardiovascular events of interest were acute myocardial infarction (ICD-10 codes I21.0, I21.1, I21.2, I21.3, I21.4 or I21.9), acute myocardial infarction or other acute ischaemic heart diseases (I24.0, I24.1, I24.8, I24.9), cardiac arrest (I46.0, I46.1 or I46.9), paroxysmal tachycardia (I47.0, I47.1, I47.2 or I47.9) or other cardiac arrhythmias (I49.0, I49.1, I49.2 or I49.3), heart failure (I50.0, I50.1, I50.9), intracerebral haemorrhage or cerebral infarction (I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8 or I63.9), and arterial thrombosis and embolism (I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8 or I74.9). Deaths identified represented all-cause mortality as opposed to cause-specific mortality. Both public and private hospital admissions were used to identify events and co morbidities. Events and covariates were identified using hospital admission dates between 1 Jan 2000 and the index date. Pharmacy dispensing data were used to identify the number and type of medication supplies in the relevant period prior to the index date using the supply dates. The admission dates for Residential Aged Care (RAC) database were used to identify whether subjects had been in RAC for at least 6 months prior to their index date.

Statistical analyses

An Incidence density sampling approach was used for each outcome with up to 20 controls selected for each case. All subjects were eligible for selection as a control (including subjects who later became cases), provided that the subject had been free of the condition of interest up to and including the index date for the case they were being matched with. Subjects could also be used as controls on multiple occasions. The odds ratios obtained from logistic regression are considered a good approximation to relative risk in the setting of incidence density sampling. Controls were matched with cases on age (within 2 years), sex and State of residence and given the same index date as the case. Conditional logistic regression was performed to estimate the effect of various levels of exposure (0, 1-4, 5-9, 10-19, 20 or more prescription supplies in the past 2 years) for each NSAID of interest and also for total NSAID usage with the risk of various cardiovascular events. We also examined the associations between cardiovascular events and the use of any COX-2 inhibitor, the combined use of either Celecoxib, Lumiracoxib or Rofecoxib, and the use of NSAIDs divided into three categories of CV-risk based on *in vitro* data:

1. High Risk: mefenamic acid, diclofenac potassium and diclofenac sodium
2. Moderate Risk: naproxen, naproxen sodium, tiaprofenic acid, ketoprofen and indomethacin
3. Low Risk: diflunisal and ibuprofen

Both crude and adjusted effect estimates were obtained. Models were adjusted for age (to nearest year), residential aged care status (in RAC for at least 6 months prior to index date), public or private hospital admissions at any time prior to the index date for diabetes, obesity, dementia, hypertension, IHD, respiratory disease, liver disease, rheumatoid arthritis or renal disease, and the use of salicylic acid and derivatives or medications for the following conditions: obesity, diabetes, thrombosis, cardiovascular disease, dementia and obstructive airways diseases within 4 months prior to the index date. All analyses were performed using Stata (version 10) (StataCorp, TX, USA).

PROJECT ACTIVITY

The majority of the analyses on all defined outcomes have been completed. Descriptive analyses have been used to report age, gender, concomitant medicines and medical conditions and other relevant covariates as previously stated

RESULTS

Study 1: Association between NSAID use in the veteran population and: (1) all cause death and (2) rates of hospitalisation for acute myocardial infarction, acute ischaemic heart disease and arterial embolism and thrombosis

Baseline characteristics of the cases and controls for the acute myocardial infarction (AMI) cohort, acute ischaemic heart disease (IHD) cohort, arterial embolism and thrombosis (AE & T) cohort and death cohort are shown in table 1.

Table 1	**AMI Cohort**		**Acute IHD Cohort**		**AE & T Cohort**		**Death Cohort**	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
N	10,132	202,125	10,390	207,269	743	14,793	54,588	1,083,341
Person-years of follow up	22,578	450,069	23,065	459,776	1,550	30,833	121,696	2,413,660
Male (%)	67.9	67.9	68.1	68.1	66.8	66.7	66.3	66.4
Age (years) (mean ± SD)	80.6 ± 4.8	80.6 ± 4.8	80.5 ± 4.8	80.5 ± 4.8	79.9 ± 4.6	79.8 ± 4.6	82.0 ± 5.3	81.9 ± 5.1
Morbidities (%)								
Diabetes	15.5	8.6	15.5	8.5	13.9	8.5	12.0	7.4
Obesity	1.0	0.5	1.0	0.5	1.5	0.6	0.9	0.5
Dementia	4.2	3.8	4.2	3.8	3.8	3.5	10.3	2.8
Hypertension	24.9	17.0	25.2	16.7	30.1	17.7	42.6	53.5
IHD	25.3	12.4	25.7	12.4	28.1	13.5	31.7	36.8
Respiratory diseases	12.2	7.0	12.2	7.1	11.7	7.2	12.6	4.9
Liver disease	0.2	0.1	0.2	0.1	0.0	0.1	0.5	0.1
Rheumatoid arthritis	0.2	0.1	02	0.15	0.0	0.1	0.7	0.1
Renal failure	7.6	2.9	7.6	2.9	8.6	2.8	10.2	2.5
Medications (%)								
Anti-obesity preparations	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Drugs used in diabetes	14.0	7.9	13.9	8.0	12.0	8.5	10.5	7.7
Anti-thrombotic agents	43.1	35.3	43.2	35.2	54.6	35.1	41.8	36.3
Cardiovascular system drugs	81.4	70.4	81.6	70.3	84.0	71.0	72.7	70.6
Salicylic acid and derivatives	15.3	12.1	15.5	11.9	18.2	12.2	14.8	12.4
Anti-dementia drugs	1.6	2.1	1.6	2.1	1.2	2.1	2.8	2.1
Obstructive airway disease agents	2.7	16.3	22.6	16.3	21.8	16.5	27.4	15.9
NSAIDs (used in last 2 years) (%)								
No NSAIDs	52.57	54.02	52.35	53.78	51.14	52.58	59.46	55.26
Any NSAID	17.80	16.99	17.88	17.07	17.77	18.11	14.59	16.13
Any COX-2 inhibitor	38.30	36.47	38.51	36.57	39.43	37.56	32.26	35.58
Specific NSAIDs (used in last 2 years) (%)								
Diclofenac	5.99	7.79	7.64	7.79	8.48	7.95	6.16	7.39
Naproxen	2.81	2.66	3.23	2.96	2.96	3.24	2.55	2.65

Ibuprofen	2.67	2.76	2.90	2.85	2.83	2.93	2.75	2.72
Meloxicam	6.70	6.43	6.69	6.37	7.94	6.13	4.85	6.16

Preliminary review of the data for Study 1 indicates

- The adjusted relative risk of AMI in users of any NSAIDs within the last 2 years was 1.00 (95% CI, 0.96-1.04) and any COX-2 inhibitor 1.02 (95% CI, 0.97-1.06). However, an increased number of prescriptions 11-19 and 20+ was associated with an increase in relative risk 1.08 (95% CI, 1.01-1.15, 1.10 (95% CI, 1.01-1.19), respectively
- The adjusted relative risk of acute IHD in users of any NSAIDs within the last 2 years was 1.00 (95% CI, 0.96-1.04) and any COX-2 inhibitor 1.02 (95% CI, 0.98-1.06). However, an increased number of prescriptions 20+ was associated with an increase in relative risk 1.10 (95% CI, 1.02-1.19).
- The adjusted relative risk of arterial embolism and thrombosis in users of any NSAIDs within the last 2 years was 0.99 (95% CI, 0.86-1.16) and any COX-2 inhibitor 1.00 (95% CI, 0.86-1.17) with no evidence of increased risk with multiple prescriptions.
- The adjusted relative risk of all cause death in users of any NSAIDs within the last 2 years was 0.87 (95% CI, 0.85-0.90) and any COX-2 inhibitor 0.88 (95% CI, 0.86-0.91) with an inverse relationship with the number of prescriptions e.g. 1-4 prescriptions 0.93 (95% CI, 0.90-0.97) and 20+ prescriptions 0.74 (95% CI, 0.69-0.79).

Study 2: Association between NSAID use in the veteran population and rates of hospitalisation for heart failure, cardiac arrest and paroxysmal tachycardia and other cardiac arrhythmias.

- The adjusted relative risk of heart failure in users of any NSAIDs within the last 2 years was 0.95 (95% CI, 0.92-0.98) and any COX-2 inhibitor 0.95 (95% CI, 0.92-0.98).
- The adjusted relative risk of cardiac arrest in users of any NSAIDs within the last 2 years was 0.87 (95% CI, 0.78-0.97) and any COX-2 inhibitor 0.89 (95% CI, 0.79-0.99).
- The adjusted relative risk of paroxysmal tachycardia and other cardiac arrhythmias in users of any NSAIDs within the last 2 years was 0.95 (95% CI, 0.89-1.02) and any COX-2 inhibitor 0.97 (95% CI, 0.90-1.04).
- There was no evidence of a relationship with increasing number of prescriptions for any of the outcomes in Study 2

Study 3: Association between NSAID use in the veteran population and rates of hospitalisation for ischaemic or haemorrhagic stroke

- The adjusted relative risk estimates indicate that NSAIDs use within the last two years is not an increased risk factor for either ischaemic or haemorrhagic stroke

SUMMARY

The data from Study 1 supports current published evidence of a decreased risk of all-cause mortality following NSAID exposure[1]. Interestingly our data shows an inverse relationship between all-cause mortality and increasing number of prescriptions with both diclofenac and meloxicam. However, further analyses of individual NSAIDs including diclofenac, naproxen, ibuprofen mefenamic acid and meloxicam are in progress to gain further verifiable data on the relative risk of the outcomes of interest. In addition, the preliminary results of Study 3 support current published data that NSAIDs are not a risk factor for ischaemic or haemorrhagic stroke[2].

[1] Lee, TA, Bartle B and Weiss KB. Impact of NSAIDs on mortality and the effect of pre-existing coronary artery disease in US Veterans *Am. J. Medicine* 2007; 120: 98.e9-98.e16.

[2] Bak, S, Andersen M, Tsiropoulos, I, Garcia Rodriguez, LA, Hallas, J, Christensen ,K and Gaist, D. Risk of stroke associated with nonsteroidal anti-inflammatory drugs. *Stroke* 2003; 34: 379-386.

FINANCIALS

Financials removed for publication.