Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects. Results of a case-control study

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Aims The aim of the present study was to explore the level of risk associated with community use of non-steroidal anti-inflammatory drugs (NSAIDs).

Methods We carried out a matched case-control study of the relationship between recent use of NSAIDs and the presence of functional renal impairment present at the time of hospitalisation with a range of clinical problems. Cases ($n=110$) were consecutive patients admitted acutely to hospital who had serum creatinine levels greater than or equal to 0.15 mmol l^{-1} , which improved by 20% or more within the next 14 days, or prior to discharge from hospital. Controls ($n=189$) were subjects of the same sex and age (to within 5 years) as the cases, who were admitted to the same hospital, who had normal serum creatinine levels ($<0.12 \text{ mmol l}^{-1}$) throughout their hospital stay. Information on a number of study factors, including recent use of aspirin and other NSAIDs, was obtained by structured interview.

Results Overall, there was a weak association between consumption of NSAIDs (including non-prophylactic aspirin) and the development of functional renal impairment—adjusted odds ratios (OR) with use of NSAIDs in the previous week or in the previous month: OR 1.5 (95% CI 0.80, 2.9) and 1.8 (95% CI 0.97, 3.4) respectively. In subjects with a previous history of renal disease the adjusted OR was 6.6 (0.75, 57.8) and in those with a history of gout or hyperuricaemia the OR was 7.2 (1.3, 40.2). There was a weak positive relationship between the dose of drug consumed in the previous week and the odds of functional renal impairment. The relationship between risk and published figures for drug half-lives ($t_{1/2}$) was stronger. The odds ratio increased from 1.2 (95% CI 0.61, 2.4) with a $t_{1/2} \leq 4 \text{ h}$, to 4.8 (1.5, 15.8) with a $t_{1/2}$ of $\leq 12 \text{ h}$ ($P=0.012$, test for trend). This relationship remained statistically significant after adjustment for a number of clinical variables and the dose of drug ingested.

Conclusions NSAIDs are an important cause of functional renal impairment in subjects with renal disease or a history of gout or hyperuricemia. The half-life of the drug is more important than the ingested dose in determining the risk of this outcome. Long half-life drugs should be avoided in individuals who are at risk of developing renal impairment.

Keywords: non-steroidal anti-inflammatory drug, renal impairment, elderly

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a well known cause of renal failure. A number of renal syndromes have been described, but the most common is functional renal impairment of vascular origin [1]. Renal ischaemia is believed to be a consequence of the unopposed actions on the renal vasculature of the vasoconstrictor hormones angiotensin, noradrenaline and arginine vasopressin in patients who are physiologically 'stressed' as a result of serious underlying renal, hepatic, metabolic or cardiac disorders [2]. In these clinical states renal prostaglandins help

maintain renal blood flow. NSAIDs inhibit the synthesis of prostaglandins by the kidney and the loss of their vasodilator actions results in renal vasoconstriction [1, 3].

Although the physiological features of this syndrome have been extensively investigated in experimental studies there have been few controlled epidemiological investigations of renal disorders associated with NSAIDs [4–9]. Despite widespread concern regarding the risks of these drugs in the elderly they continue to be widely used, so even low relative risks of renal dysfunction could translate into a substantial burden of disease. The epidemiological studies that have been performed have tended to concentrate on chronic renal failure, or have relied on diagnoses of renal pathology to define cases for investigation [4]. There has been only one controlled epidemiological study of acute functional

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renal impairment [7, 8]. Most attempts to define risk factors for the development of renal impairment with NSAIDs have been uncontrolled case series and spurious associations are likely.

In the present study we used case-control methodology to explore the level of risk associated with community use of NSAIDs. We were interested in the clinical predisposing factors, and also wished to know to what extent the risk increased with the dose and the half-life of drugs that had been consumed prior to development of renal impairment.

Methods

We carried out a matched case-control study of the relationship between recent use of NSAIDs and transient renal impairment. The study was based in two general hospitals in the Hunter Region of New South Wales—the John Hunter Hospital and Newcastle Mater Hospital. These hospitals provide most of the acute care for a population of around 450 000. The study was approved by the ethics committees of the University of Newcastle and the Hunter Area Health Service, and all participants gave their informed consent. This study was run in parallel with a case-control study designed to explore the relationship between use of NSAIDs and the development of congestive heart failure.

Case definition

We consulted renal physicians in the Newcastle area and reached agreement on the following definition of *functional renal impairment*: cases were consecutive patients admitted acutely to the study hospitals who had serum creatinine levels greater than or equal to 0.15 mmol l^{-1} , which improved by 20% or more within the next 14 days, or prior to discharge from hospital, whichever came first.

Case recruitment

We identified cases through computerised records containing routine biochemical investigations that are maintained by the Hunter Area Pathology Service. Three times weekly records were loaded into a relational database, which created a time series of plasma creatinine values for every patient admitted to the study hospitals. Potential cases were identified through the data-base. Patients who were initially too sick to be interviewed were followed up. If they remained unfit for interview their details were excluded from final analysis.

Selection and recruitment of controls

We tried to match two controls to each case. Controls were subjects of the same sex and age (to within 5 years) as the cases, who were admitted to the same hospital, who had normal serum creatinine levels ($<0.12 \text{ mmol l}^{-1}$) throughout their hospital stay. Controls were identified from the same data-base as the cases and the same exclusion criteria were applied.

Information gathering

The index day for cases and controls was the day of admission to hospital. Information on all drugs that had been used prior to the index day, past medical history (in particular prior diagnosis of renal disease, hypertension, cardiovascular disorders, hepatic disease and musculoskeletal disorders), demographic details, alcohol consumption and smoking history were obtained by structured interview. All interviews were conducted within 1 week of admission to hospital, and the great majority were within 4 days. The interviewers knew whether a subject was a case or control, but understood the importance of adhering strictly to the wording of the questionnaire. Each question could be repeated only once for clarification. We were particularly interested in the consumption of analgesic and anti-inflammatory medications. This information was obtained by a series of open questions enquiring about any drugs used for painful complaints. These were followed by more direct questions and presentation of 'flash' cards, listing in large type the proprietary and trade names of all relevant products on the Australian market. General practitioners attended by cases and controls were contacted to confirm the information on prescribed drug use obtained by interview. These methods had been used previously in a study of major gastrointestinal complications of NSAID treatment. In addition to the information obtained by interview we abstracted the following details from medical records and hospital computerised records: haematological and additional biochemical data, clinical notes regarding previous medical history and the primary diagnosis thought to be responsible for the hospital admission.

Statistical analysis

The anticipated prevalence of NSAIDs use in the controls was 20% [11]. We aimed to recruit 170 cases and 340 controls to detect an overall odds ratio (OR) of 2 associated with the use of NSAIDs with a power of 90% and type 1 error of 0.05 [12]. The odds ratio was assumed to be a valid estimate of the relative risk. Non-use of NSAIDs and aspirin was the reference for calculation of exposure odds ratios. Conditional logistic regression was used to calculate crude and adjusted odds ratios and their 95% confidence intervals. The mean daily dose of NSAIDs in the week prior to admission was used to assess dose response. This dose was standardised by using the manufacturer's recommended minimum daily maintenance dose for rheumatoid arthritis as one dose unit [11, 13]. The dose calculation excluded regular low-dose aspirin (regular daily dose of 100 to 300 mg) as this was likely to have been taken as prophylaxis against cardiovascular events, which were found to be associated with the study outcome. Published plasma half-life values for the drugs taken by subjects in the study were obtained from reference sources [14]. For the purpose of analysis drugs were categorised as short half-life $<4 \text{ h}$ (commonly used examples: ibuprofen, diclofenac, aspirin), $4\text{--}11.9 \text{ h}$ (indomethacin, sulindac, ketoprofen SR), and $\geq 12 \text{ h}$ (naproxen, piroxicam, tenoxicam).

We used multiple conditional logistic regression analysis to adjust for all variables that were statistically significantly

associated with renal impairment if their inclusion in the model affected the magnitude of the coefficients [15]. Multiple conditional logistic regression was used to assess interactions and relationships between drug doses and published plasma half-life values. The statistical computer package Stata (version 4.0) was used to analyse the data. All *P* values were two sided.

Results

Of the 164 cases of functional renal impairment identified, we were only able to use the data from 110. The remaining 54 were either too unwell to be interviewed or died soon after admission. Comparison of included and excluded cases showed that the latter were on average 2.6 years older. The sex distributions were similar and there were no significant differences in blood creatinine, urea and electrolyte levels (data not shown).

Characteristics of cases and controls

Table 1 shows the characteristics of cases and controls. Despite matching the cases were slightly older than the controls, and subsequent analyses adjusted for this age difference. Cases were more likely than controls to have a past history of malignancy, hypertension, heart disease, renal/urinary tract disease and gout/hyperuricemia.

Primary reasons for admission to hospital differed between the groups. Renal and urinary tract diagnoses were mentioned in 23% of cases compared with 3% of controls. Differences also existed for electrolyte and acid base

disturbances (10% of cases, 0% of controls), gastrointestinal disease (16% of cases and 10% of controls), fractures/trauma (18% of cases and 8% of controls) and neurological and psychiatric disorders (9% of cases and 4% of controls).

The median plasma creatinine concentration on admission was 0.19 mmol l⁻¹ in cases, compared with 0.09 mmol l⁻¹ in controls. The corresponding values for plasma urea concentrations were 18.4 mmol l⁻¹ in cases and 6.3 mmol l⁻¹ in controls. The average fall in plasma creatinine in the cases was 0.06 mmol l⁻¹ (32% of the mean admission concentration). In comparison the average fall in plasma creatinine in the controls was 0.01 mmol l⁻¹ (11% of the mean admission concentration). Blood urea concentrations were approximately three times higher in cases than in control patients. Sodium and potassium levels were quite similar.

Drug consumption by cases and controls

There was a higher use of drugs for cardiovascular disorders by cases than by control subjects (Table 2). The differences were modest in the cases of calcium channel blocking drugs and β -adrenoceptor blockers. It is likely that these differences reflect the high prevalence of cardiovascular disorders amongst the cases. The differences were substantial in the case of ACE inhibitors and high ceiling diuretics. This probably indicates a causal association between these agents and functional renal impairment. However the study was not designed to explore these relationships in detail.

Use of non-steroidal anti-inflammatory drugs

Cases were more likely to have been taking prophylactic aspirin (100 to 300 mg daily) than controls (Table 3). Use of aspirin in higher doses was similar among cases and controls. Consumption of non-aspirin non steroidal anti-inflammatory drugs was greater in cases compared with

Table 1 Characteristics of cases and controls at the time of admission to hospital.

	Cases (n = 110)	Controls (n = 189)
Males	61 (55.5)	104 (55.0)
Age in years	76.6 (s.d. 7.4)	75.1 (s.d. 7.2)
Smoking status		
Current smokers	15 (14.2)	32 (17.5)
Ex-smokers	43 (40.6)	72 (39.3)
Never smoked	48 (45.3)	79 (43.2)
Alcohol intake (> 5 drinks/week)	20 (18.2)	48 (25.4)
Past medical history of:		
Malignant disease	19 (17.3)	24 (12.7)
Psychiatric disease	3 (2.7)	4 (2.1)
Diabetes mellitus	18 (16.4)	29 (15.3)
Hypertension	55 (50.0)	63 (33.3)
Heart disease	51 (46.4)	49 (25.9)
Other arterial disease	9 (8.2)	12 (6.4)
Respiratory disease	11 (10.0)	29 (15.3)
Gastrointestinal disease	16 (14.6)	26 (13.8)
Renal/Urinary disease	50 (45.5)	25 (13.2)
Musculoskeletal disorders (other than gout)	21 (19.1)	31 (16.4)
Gout/hyperuricemia	29 (26.4)	26 (13.8)

Percentages are shown in parentheses for categorical variables. The number of cases was 110 and the number of controls 189. Information was missing for some variables.

Table 2 The use of drugs by cases and controls.

	Cases (n = 110)	Controls (n = 189)
Calcium channel blockers		
Vascular action	7 (6.4)	11 (5.8)
Mixed vascular/cardiac	5 (4.6)	13 (6.9)
Cardiac action	10 (9.1)	10 (5.3)
ACE inhibitors	37 (33.6)	38 (20.1)
β -adrenoceptor blockers		
Selective β_1 -blockers	13 (11.8)	11 (5.8)
Nonselective β_1 -blockers	6 (5.5)	2 (1.1)
Topical eye preparations	2 (1.8)	4 (2.1)
Diuretics		
Thiazides/others	29 (26.4)	39 (20.6)
High ceiling diuretics	38 (34.6)	16 (8.5)
Indapamide	6 (5.5)	8 (4.2)
Spironolactone	5 (4.6)	3 (1.6)
Oral steroids	8 (7.3)	13 (6.9)
Insulin/oral hypoglycaemics	11 (10.0)	21 (11.1)
Drugs for gastrointestinal symptoms	28 (25.5)	42 (22.2)

Table 3 The use of NSAIDs and aspirin by cases and control.

	Cases (%) (n = 110)	Controls (%) (n = 189)	Unadjusted OR (95% C.I.)	Adjusted OR§ (95% C.I.)
Prophylactic aspirin				
Use in the past week	22 (20.0)	29 (15.3)	1.4 (0.79, 2.6)	1.1 (0.50, 2.2)
Non-prophylactic aspirin				
Use in the past month	10 (9.1)	16 (8.5)	1.1 (0.48, 2.5)	1.6 (0.58, 4.7)
Use in the past week	7 (6.4)	13 (6.9)	0.96 (0.37, 2.5)	1.3 (0.39, 4.1)
Non aspirin NSAID				
Use in the past month	36 (32.7)	31 (16.4)	2.5 (1.4, 4.4)	2.0 (0.98, 3.9)
Use in the past week	32 (29.1)	29 (15.3)	2.3 (1.3, 4.0)	1.5 (0.80, 2.8)
Any NSAID (excluding prophylactic aspirin)				
Use in the past month	43 (39.1)	45 (23.8)	2.1 (1.3, 3.7)	1.8 (0.97, 3.4)
Use in the past week	38 (34.6)	40 (21.2)	2.0 (1.2, 3.5)	1.5 (0.80, 2.9)

§The odds ratios are adjusted for age in years, a history of gout, a past history of heart disease and a past history of renal disease.

controls and the unadjusted odds ratio with use in the week prior to hospitalisation was approximately 2.

Inclusion of a number of variables resulted in a statistically significant improvement in the fit of the statistical model, as judged by changes in deviance. The variables were: a previous history of heart disease, renal disease and gout/hyperuricaemia. Age was also included in the model because it remained an important determinant of the odds of renal impairment despite matching.

Adjustment resulted in a decrease in the odds ratios with use of NSAIDs in the last week or month (Table 3). Use of non-aspirin NSAIDs, or any NSAIDs (including non-prophylactic aspirin), was associated with an approximate 1.5 times increase in the odds of developing reversible renal impairment. However this was not statistically significant at the 5% level.

Investigation of risk factors

Possible effect modification by a history of renal disease, heart disease, gout/hyperuricaemia, chronic liver disease, age and sex, were explored by including interaction terms into the multiple regression model. There was evidence of a statistically significant interaction only with a history of gout/hyperuricaemia ($\chi^2_{1df}=6.72$, $P=0.010$), and with a history of renal disease ($\chi^2_{1df}=5.35$, $P=0.021$).

Table 4 shows the odds ratios associated with the use of NSAIDs in subgroups of patients with gout/hyperuricaemia and renal disease. Note that the confidence intervals are wide due to the small number of patients in the various

subgroups. However the data suggest that these disorders are risk factors for the development renal impairment after ingestion of NSAIDs.

Dose-response relationship

There was evidence of a positive relationship between the dose of drug and the odds of functional renal impairment ($P=0.054$; Table 5). However the slope was not steep and the relationship was not statistically significant after adjusting for age and a previous history of cardiac disease. Examination of dose-response relationships in sub-groups was hampered by small numbers, but the relationship approached statistical significance in the case of subjects with gout/hyperuricaemia.

The relationship to half life of NSAIDs

The odds ratio tended to increase with the half-life of the non-steroidal anti-inflammatory drug used in the week prior to admission (Table 6). The test for log-linear trend was statistically significant in the univariate analysis ($P=0.012$). We simultaneously adjusted these analyses for dose by entering this as a continuous variable, and the relationship between drug half-life and the odds ratio remained statistically significant (test for log linear trend, $p=0.032$). In contrast, when half-life was entered as a continuous variable the relationship between dose and the odds ratio for renal impairment was non-significant (Table 5).

Table 4 The effect of use of non steroidal anti-inflammatory drugs according to previous history of renal disease and gout/hyperuricaemia.

	Cases (n/Total)	Controls (n/Total)	OR* (95% C.I.)	P value
No previous renal disease or gout/hyperuricaemia	6/43	33/143	0.57 (0.20, 1.6)	0.3
Previous renal disease, but no gout/hyperuricaemia	14/38	2/20	6.6 (0.8, 57.9)	0.089
Gout/hyperuricaemia, but no previous renal disease	8/17	4/21	7.1 (1.3, 39.7)	0.027
Previous renal disease and gout/hyperuricaemia	4/12	0/5	82.2 (4.1, 1661.1)	0.004

*Adjusted odds ratios were calculated from conditional logistic regression models. Adjustment was made for a previous history of heart disease and age in years.

Table 5 The relationship between the odds of functional renal impairment and the average daily dose of NSAIDs used in the week prior to admission (in standard dose units).

Dose of NSAIDs#	Cases (%)	Controls (%)	Univariate* OR (95% C.I.)	Multivariate§ OR (95% C.I.)	Adjusted for half-life** OR (95% C.I.)
No NSAIDs	72 (65.5)	149 (78.8)	1	1	1
0–0.63	10 (9.1)	13 (6.9)	1.7 (0.70, 4.0)	1.2 (0.42, 3.6)	1.2 (0.41, 3.8)
0.63–1	6 (5.5)	7 (3.7)	2.0 (0.67, 6.2)	1.9 (0.51, 7.1)	1.7 (0.42, 6.9)
≥1	22 (20.0)	20 (10.6)	2.3 (1.2, 4.5)	1.6 (0.71, 3.5)	1.2 (0.50, 2.8)

*Test for log linear trend, $P=0.054$.

§Adjusted for age in years, a history of gout, a past history of heart disease and a past history of renal disease. Test for log linear trend, $P=0.27$.

**Adjusted for drug half-life as well as the factor unclined in the multivariate analysis. Test for log linear trend $P>0.50$.

#Standard dose units (see Methods section).

Table 6 The relationship between the odds of functional renal impairment and the half life of the NSAIDs.

Half-life of NSAIDs	Cases (%)	Controls (%)	Univariate* OR (95% C.I.)	Multivariate§ OR (95% C.I.)	Adjusted for dose** OR (95% C.I.)
No NSAIDs	72 (65.5)	149 (78.8)	1	1	1
≤4 h	16 (14.6)	28 (14.8)	1.2 (0.61, 2.4)	1.1 (0.50, 2.5)	1.3 (0.48, 3.6)
4–12 h	13 (11.8)	9 (4.8)	2.8 (1.17, 6.8)	2.1 (0.77, 5.9)	2.8 (0.66, 12.0)
≥12 h	10 (9.1)	4 (2.1)	4.8 (1.5, 15.8)	2.9 (0.72, 11.6)	3.8 (0.68, 21.0)

*Test for log linear trend, $P=0.012$.

§These odds ratios are adjusted for age in years, a history of gout, a past history of heart disease and a past history of renal disease. Test for log linear trend, $P=0.043$.

**Adjusted for dose (as a continuous variable) as well as the factors included in the multivariate analysis. Test for log linear trend $P=0.032$.

Discussion

The main findings of this study were that there was a weak overall association between recent use of NSAIDs and development of functional renal impairment but two risk factors—a previous history of renal disease or a previous history of gout/hyperuricaemia—were important independent risk factors. The dose of drug was not an important determinant of the outcome in this study, but there was a strong relationship between the half-life value for the drug and the risk of developing functional renal impairment. This relationship persisted after adjustment for ingested dose.

The overall results of this study may appear to conflict with confident assertions regarding a high level of risk of renal impairment induced by NSAIDs [5]. It is important to consider a number of factors that may explain this apparent discrepancy. First, most of the literature on this topic has been uncontrolled. As use of NSAIDs is extremely common in most communities, spurious associations with individual cases of renal impairment are likely. In this situation controlled studies are necessary to provide unconfounded estimates of the strength of the association. In this study, most of the risk appeared to be concentrated in identifiable subgroups, particularly those with a prior history of renal disease or gout. In such subjects, the estimated relative risks were high and would translate into a substantial excess risk. Because we have not highlighted other risk factors in this study it should not be assumed they do not exist. We set fairly strict statistical criteria when examining the results for interactions. Other factors such as cardiac disease and

diabetes may be important but may have been missed in the study because of inadequate statistical power.

The result of our unadjusted analysis for exposure to NSAIDs in the past month (OR 2.5, 95% CI 1.4, 4.4) was similar to that recorded by Evans *et al.* using the Tayside record-linkage system: OR for exposure in the past 90 days 2.2 (1.5, 3.3) [7]. However in our study adjustment for confounding weakened the association. Evans *et al.* relied on recorded prescriptions rather than reported consumption of NSAIDs and collected no information directly on clinical factors that were potential confounders.

We found only a weak relationship between the ingested dose of NSAIDs and the risk of development of renal impairment. This contrasts with the stronger relationship found by Perez Gutthaus *et al.* [8]. In a case-control study involving 28 subjects with more severe degrees of renal impairment these workers found an odds ratio for development of renal failure of 9.8 with high doses. Exploring dosage in epidemiological studies of NSAIDs is difficult because of the varying potencies of the different drugs. In this study we used a dose standardisation approach that has been used by others, and also by us in previous work [11, 13]. This is an arbitrary standardisation that may tend to obscure true dose response relationships. However, using this approach we have been able to show a fairly strong relationship between the ingested dose and the development of major gastrointestinal complications [11]. The weak dose-response seen in the present study may be due to the narrow range of doses that had been ingested in the week prior to admission to hospital. Few subjects had a daily dose in

excess of one standard unit and this contrasts with the findings of a previous study we conducted of gastrointestinal complications [11]. However, it should be noted that the dose effect disappeared entirely after simultaneous adjustment for drug half-life, and we believe that the latter is a more important determinant of the risk of renal impairment during therapy with NSAIDs.

The present study does not allow us to explain the apparently strong relationship between drug half-life and risk. However, it was not due to confounding by dose as it remained after simultaneous adjustment for the latter. Also, it was not due to confounding by the presence of the risk factors that were examined in this study. In our view, the most likely explanation is that long half-life drugs produce sustained inhibition of renal cyclo-oxygenase, and the kidneys are not provided with a sufficient recovery period during each dosing interval. The potential of long half-life drugs to cause renal dysfunction has been commented on previously [5].

There are a number of limitations to this study which must be considered in interpreting the results. First, the outcome used to define cases included subjects with a fairly minor degree of renal impairment which are of uncertain clinical significance. An effect of this is that differences between cases and controls were small. Despite this, there were clear differences with respect to past history, presenting complaints, the prevalence of risk factors for renal impairment and half-lives of the NSAIDs that had been consumed prior to admission to hospital. Although the relatively mild degree of renal impairment may have led to some bias to the null, the study was capable of answering a number of important questions. It is more difficult to comment on the clinical significance of the findings as the degree of renal impairment experienced by the cases means that this can only be used as a surrogate marker.

It can be argued that case-control methodology is sub-optimal for exploring this type of clinical problem. It is quite possible that the episode of renal impairment documented in the cases was but one episode in a fluctuating course. Many other diseases were present in these subjects and the prevalence of these disorders may have led to interventions that changed their use of NSAIDs. As with the severity of disease used to define cases, we believe that these factors may have caused some bias to the null, and may have rendered some of our estimates conservative.

There is an increasing awareness of the dangers of use of NSAIDs by elderly subjects. For instance in Australia, the use of these drugs by elderly subjects fell by around 40% during the 1990s [16]. However, there is also evidence of a shift in prescribing habits from short-acting to long-acting drugs as these have been marketed and promoted heavily by pharmaceutical manufacturers in recent years [16]. There is substantial variability in the risk of serious gastrointestinal bleeding with individual NSAIDs [17]. Taken together, these findings suggest that we should direct prescribing initially to lower risk drugs, which generally have short half-lives, and only use high risk compounds if there is an inadequate clinical response to the first line strategy. In the sub-groups identified here, particularly those with a history of renal disease and those with a history of gout or hyperuricaemia, long half-life drugs should be avoided altogether.

This study was supported by a grant from the National Health and Medical Research Council of Australia and from Pfizer Pharmaceuticals (Australia) Pty Limited.

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(Received 14 November 1996,
accepted 18 March, 1997)