Renal tolerability of three commonly employed non-steroidal anti-inflammatory drugs in elderly patients with osteoarthritis

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Abstract

Objective

The primary endpoint of this study was to compare the renal tolerability of amtolmetin guacyl (AMG), diclofenac and rofecoxib in elderly patients with symptomatic osteoarthritis (OA). The assessment of efficacy was the secondary endpoint.

Methods

90 patients who satisfied the American College of Rheumatology classification criteria for hand, hip or knee OA were randomly assigned to 3 treatment groups receiving either: AMG 1200 mg over the first 3 days and and 600 mg/day thereafter; diclofenac 150 mg/day; or rofecoxib 25 mg/day for 2 weeks. At baseline and after therapy patients were clinically assessed by the same examiner who was unaware of the treatment arm assignement. Serum and urinary parameters of renal function and the outcome measures of efficacy were evaluated before (t_0) and after therapy (t_1).

Results

Diclofenac produced a significant reduction in creatinine clearance ($t_0 = 88.93 \pm 11.59$; $t_1 = 75.90 \pm 16.32$; p: < 0.001) and in the daily urine volume ($t_0 = 1337.93 \pm 202.07$; $t_1 = 1027.59 \pm 249.14$; p: < 0.001). In the same treatment group a significant increase in serum creatinine, blood urea nitrogen, uric acid and potassium were observed. Rofecoxib treated patients showed a significant increase in body weight ($t_0 = 75.31 \pm 4.26$; $t_1 = 76.54 \pm 4.84$; p: < 0.001), systolic blood pressure ($t_0 = 144 \pm 10.86$; $t_1 = 154 \pm 11.8$; $p < 0.001$), diastolic blood pressure ($t_0 = 80 \pm 6.05$; $t_1 = 89 \pm 7.66$; $p < 0.001$) and serum sodium ($t_0 = 138.73 \pm 1.28$; $t_1 = 140.12 \pm 1.80$; $p < 0.005$) associated with a significant decrease in the daily urine volume ($t_0 = 1294.64 \pm 205.21$; $t_1 = 1115.48 \pm 238.47$; $p < 0.001$) and creatinine clearance ($t_0 = 86.73 \pm 8.14$; $t_1 = 83.15 \pm 7.96$; $p < 0.01$). No significant changes in the clinical and humoral parameters were recorded in AMG treated patients. Diclofenac was more efficacious than the other 2 drugs ($p < 0.001$). No differences were observed between AMG and rofecoxib. Side effects related to altered kidney function were significantly higher in the rofecoxib group ($p < 0.005$).

Conclusion

Diclofenac mainly impaired blood renal flow and the glomerular filtration rate, while rofecoxib negatively influenced the renal sodium-water exchange. AMG demonstrated a renal sparing effect, although the exact mechanism is unclear.

Key words

Renal tolerability, NSAIDs, amtolmetin guacyl, diclofenac, rofecoxib, creatinine clearance, malleolar edema.

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Introduction

Symptomatic osteoathritis (OA) represents the most frequent rheumatic disorder. Its frequency increases with age in people older than 60 (1). Owing to their analgesic and anti-inflammatory effects, non-steroidal anti-inflammatory drugs (NSAIDs) are widely employed in the treatment of OA (2). Their use in the management of OA has been recommended in a recent paper by the American College of Rheumatology Subcommittee on OA guidelines (3).

The pharmacological activity of NSAIDs is principally mediated by the inhibition of cyclooxygenase (COX) with suppression of proinflammatory and pain-enhancing prostaglandin (PG) synthesis (4). It is well known that PG synthesis blockade is responsible for the gastrointestinal and renal adverse effects of NSAIDs (5, 6). Several alterations in renal function are related to NSAID inhibition of the PG pathway: fluid and electrolyte disturbances, acute reduction of the glomerular filtrate through a reduction in the blood renal flow, nephrotic syndrome with interstitial nephritis, and papillary necrosis (7). After NSAID assumption, these effects may occur rapidly and are reversible over 2-7 days after the discontinuation of therapy (7, 8). Predisposing conditions to the renal toxicity of NSAIDs are all disorders associated with reduced renal perfusion (7). Considering age-associated changes in renal function, the prevalence of comorbid conditions, and the taking of drugs which cause reduced renal blood flow, older individuals are at greater risk of NSAID-related adverse renal events (9, 10).

Two isoforms of COX, i.e. COX-1 and COX-2, have been recently identified (11, 12). COX-1 is constitutively expressed in most tissues and plays an essential role, especially in normal gastrointestinal, renal and platelet physiology (12). COX-2, commonly termed "inducible", is transiently expressed in response to inflammatory mediators (12). Traditional NSAIDs inhibit both COX-1 and COX-2, whereas a new class of NSAIDs, rofecoxib and celecoxib, selectively inhibit COX-2 and are characterized by a reduced risk of adverse gastrointestinal events (13, 14). However, COX-2 is constitutively present in the kidney in the absence of inflammation (15) and exerts an important function in renal hemodynamics and in the regulation of sodium and water excretion (16).

Amtolmetin guacyl (AMG) is an NSAID that is not selective for COX-2; it is characterized by good efficacy and gastric tolerability in the treatment of OA (17). The pharmacological characteristics and the mechanism of action of AMG have recently been reviewed (18). The drug is widely employed in Italy. No data are available on its renal tolerability in humans.

The primary objective of this three-arm, randomized, single blinded study was to compare the renal tolerability of AMG diclofenac and rofecoxib in elderly patients with active OA. The secondary endpoint was to assess the efficacy of these three NSAIDs in the treatment of symptomatic OA.

Patients and methods

Patients

The patients studied had symptomatic hand, hip or knee OA. Inclusion criteria consisted of consecutive patients seen over a 6-month period, aged between 60 and 80 years, who met the American College of Rheumatology classification criteria for hand, hip and knee OA (19-21). All gave their informed consent for participation.

Exclusion criteria included patients who appeared unreliable or uncooperative in the self-evaluation of symptoms; the presence of severe cardiovascular, hepatic and renal disorders, gastrointestinal bleeding or peptic ulcer, or a history of hypersensitivity to NSAIDs; concomitant drugs such as antihistamines, antibiotics, other NSAIDs, corticosteroids, mucolytics, anticoagulants, antiplatelets or other potentially nephrotoxic drugs; pregnancy or lactation; and previous abnormalities in renal function (serum creatinine >1.5 mg/dl; creatinine clearance < 50 ml/min)

The difference in creatinine clearance values before and after treatment, evaluated by covariance analysis, constituted the primary outcome measure. The

inclusion of 30 patients in each treatment arm was determined to yield 80% power with a 5% level of significance to detect a 20% reduction in creatinine clearance values. Therefore 90 patients were recruited. Each dropout was replaced by the next eligible patient, who was assigned to the same treatment arm.

Treatment

Patients were randomly assigned to one of the following treatment arms: AMG tablets 600 mg twice daily for the first 3 days and followed by 600 mg/day for the rest of the study; diclofenac tablets 50 mg three times daily; and rofecoxib tablets (25 mg) 1 per day. These are the dosages recommended by the manufactures and by the Italian Ministry of Health for the treatment of OA. No restrictions were imposed on the patients' normal diet. The duration of therapy for each arm was 2 weeks and the drugs were taken soon after meals.

Assessment of renal tolerability

At baseline and after 2 weeks the following clinical and humoral parameters were evaluated in each patient: body weight, systolic and diastolic blood pressure, presence of peripheral edema, blood urea nitrogen (BUN), serum creatinine, serum sodium, potassium and chlorum, serum uric acid, daily urine volume, and creatinine clearance. All biochemical examinations were carried out at the same laboratory. Since sodium intake was not being controlled in this study, 24-hour urinary sodium excretion was not considered to be a reliable parameter and was not monitored.

Assessment of efficacy

Clinical evaluation of the patients was performed at baseline and after 2 weeks, each time by the same examiner who was unaware of the patient's treatment. The efficacy of therapy was evaluated by patient self-assessment measures including the current global level of pain and global disease activity and the physician's assessment of global disease activity. The assessment measures were made using a 100 mm visual analogue scale (VAS).

Table I. Demographic and clinical characteristics of the 90 patients randomized to 3 treatment arms.

	AMG	Diclofenac	Rofecoxib	p
Females/Males	18/12	19/11	18/12	ns
Age (years; mean ± SD)	73.27 ± 6.24	71.06 ± 5.83	72.42 ± 6.36	ns
Joint involved				
Knee	12	14	11	ns
Hip	7	6	7	ns
Hand	11	10	12	ns
10-year age group				
60-69	7	10	8	ns
70-79	23	20	22	ns

Laboratory examinations including a complete blood cell count and liver function tests were performed at baseline and after 2 weeks.

All side effects were carefully recorded in the patient's chart. In the case of any adverse events related to the study drug, patients were withdrawn from the study and all manifestations were carefully recorded on the data collection form and in the appropriate chart of the Italian Ministry of Health.

Statistical analysis

Statistical analysis was done using the SPSS statistical package (SPSS Inc., Chicago). Continuous variables were compared among the three treatment groups by variance analysis, while the chi-square test was used for nominal variables. Covariance analysis was used to asses the creatinine clearance values. Multiple comparisons among the three groups were carried out by the least significance differences method. Efficacy variables for each group were analysed by the Wilcoxon test for paired data and comparisons among the 3 groups by the Kruskal-Wallis test. The incidence of adverse events was calculated by the chi-square test.

Results

A total of 96 patients were considered suitable candidates for the study. Six patients – 1 in the AMG group, 1 in the diclofenac group, and 4 in the rofecoxib group – withdrew from the study during the first week of treatment due to intolerance or other adverse events. Therefore, 90 OA patients (35 men and 55 women) were recruited and randomly assigned to the AMG, diclofenac and rofecoxib treatment arms. Each treatment group consisted of 30 patients with no significant differences with regard to sex and age distribution. The demographic and clinical characteristics of the 90 patients are summarised in Table I. The baseline and after treatment parameters are summarised in Table II.

The intra-group statistical analysis demonstrated that, unlike AMG, both diclofenac and rofecoxib significantly impaired renal function. In particular, diclofenac reduced renal blood flow as expressed by a significant increase in serum creatinine, potassium, uric acid and BUN and by a reduction in the 24-hour urine volume and creatinine clearance. Figures 1 and 2 show the most significant effects of AMG, diclofenac and rofecoxib on renal function.

The significant increase in body weight and in both the systolic and diastolic blood pressure and serum sodium, associated with a reduction in diuresis and to a lesser extent in creatinine clearance, indicate that rofecoxib negatively affected renal function, mainly through increased salt and water retention. As reported below, this mechanism seems to be confirmed by the 4 patients who withdrew from the study because of the acute development of marked peripheral edema and rapid weight gain.

AMG treated patients did not show any significant impairment of renal function.

Covariance analysis for multiple comparisons demonstrated a significant reduction in creatinine clearance in the diclofenac group compared with both the AMG and rofecoxib groups (p >

Table II. Clinical and humoral parameters of renal function in 90 patients treated with AMG, diclofenac or rofecoxib at baseline (t_0) and after 2-week therapy (t_1)

Parameter	t_0 AMG	t_1 AMG	P	t_0 Diclofenac	t_1 Diclofenac	P	t_0 Rofecoxib	t_1 Rofecoxib	p
Body weight (kg)	76.23 ± 5.3	76.31 ± 5.4	ns	74.65 ± 6.2	74.71 ± 7.3	ns	75.31 ± 4.26	76.54 ± 4.84	<0.001
SBP (mm/Hg)	146 ± 10.81	146 ± 10.86	ns	144 ± 7.94	146 ± 7.45	ns	144 ± 10.86	154 ± 11.81	<0.001
DBP (mm/Hg)	84 ± 6.11	84 ± 6.75	ns	85 ± 5.63	86 ± 6.23	ns	80 ± 6.05	89 ± 7.66	<0.001
BUN	40.69 ± 3.12	41.02 ± 3.13	ns	39.52 ± 2.67	45.93 ± 5.57	<0.001	39.96 ± 2.69	40.32 ± 2.62	ns
Creatinine	1.12 ± 0.11	1.16 ± 0.13	ns	1.04 ± 0.08	1.29 ± 0.17	<0.001	1.06 ± 0.10	1.12 ± 0.09	ns
Sodium (mEq/l)	138.62 ± 1.51	138.72 ± 1.25	ns	138.69 ± 1.51	138.83 ± 1.49	ns	138.73 ± 1.28	140.12 ± 1.80	<0.005
Potassium (mEq/l)	3.94 ± 0.19	4.12 ± 0.18	ns	3.97 ± 0.21	4.64 ± 0.51	<0.001	3.89 ± 0.17	3.99 ± 0.25	ns
Chlorum (mEq/l)	100.85 ± 1.26	101.19 ± 0.80	ns	101.20 ± 1.00	101.52 ± 1.98	ns	101.17 ± 0.87	101.08 ± 1.28	ns
Uric acid (mg/dl)	4.14 ± 0.54	4.30 ± 0.56	ns	4.11 ± 0.67	5.41 ± 1.08	<0.001	4.10 ± 0.61	4.66 ± 0.97	<0.05
24 hr urine (ml) vol.	1231.03 ± 175.97	1211.93 ± 217.39	ns	1337.93 ± 202.07	1027.59 ± 249.14	<0.001	1294.64 ± 205.21	1115.48 ± 238.47	<0.001
Creatinine clearance (ml/min)	83.96 ± 11.44	83.45 ± 12.61	ns	88.93 ± 11.59	75.90 ± 16.32	<0.001	86.73 ± 8.14	83.15 ± 7.96	<0.01

Table III. Measures of efficacy in the 3 treatment groups at baseline and after treatment.

Measure	t_0 AMG	t_1 AMG	p	t_0 Diclofenac	t_1 Diclofenac	p	t_0 Rofecoxib	t_1 Rofecoxib	p
VAS pain	63.97 ± 6.03	48.97 ± 8.70	< 0.001	64.14 ± 6.95	41.72 ± 9.38	< 0.001	64.62 ± 7.86	48.46 ± 8.46	< 0.001
Patient GDA	61.38 ± 6.39	44.66 ± 9.15	< 0.001	60.69 ± 6.51	37.76 ± 9.22	< 0.001	60.58 ± 6.98	44.04 ± 8.49	< 0.001
Physician GDA	55.69 ± 6.08	38.62 ± 10.68	< 0.001	56.55 ± 5.19	32.24 ± 9.12	< 0.001	56.92 ± 6.71	37.69 ± 8.97	< 0.001

0.001). No differences were observed between the AMG and rofecoxib groups with respect to this parameter.

Efficacy

The results in terms of efficacy are shown in Table III. All 3 drugs significantly improved the measures of pain, and the patient's and physician's global assessment of disease activity. Multiple comparison analysis showed that diclofenac significantly reduced pain, and the patient's and physician's global disease activity scores compared to both the AMG and rofecoxib groups ($p < 0.001$). No significant differences were found between the AMG and rofecoxib groups.

Side effects and adverse events

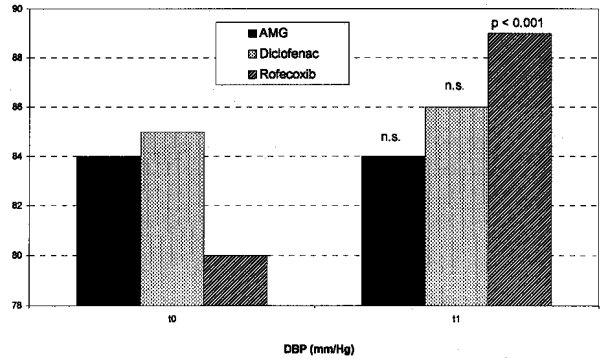
The side effects and adverse events were calculated based on the 96 patients originally enrolled. One of the 31 (3.2%) patients in the AMG group withdrew from the study because of the onset of diarrhea after 5 days, and 1 patient out of the 31 (3.2%) treated with diclofenac dropped out due to gastric intolerance after 7 days of treatment. In rofecoxib group 4/34 (11.7%) patients withdrew because of marked renal side effects. These patients developed marked peripheral subcutaneous edema with weight gains of 6, 4, 5 and 6 kgs, respectively, and hypertension over the first week of treatment. These signs rapidly remitted over 4-5 days after interruption of the drug. Statistical analysis of the dropout rate showed no significant difference among the 3 groups ($p = 0.255$).

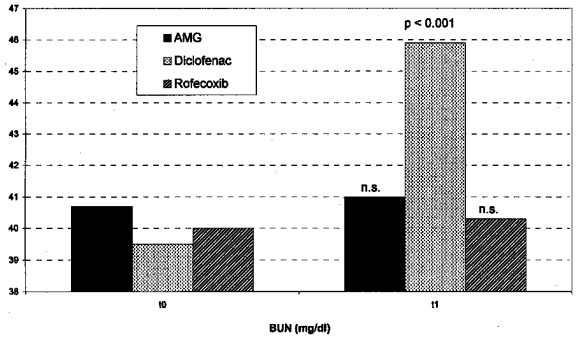
Side effects not causing withdrawal from the study were observed in all 3 treatment groups and are listed below. In the diclofenac group 8/30 (26.6%) patients experienced gastric pain. Of the rofecoxib treated patients 10/30 (33.3%) developed side effects: oliguria and mild malleolar edema associated with 1 to 3 kg weight gains in 6 (20%) and hypertension in 4/30 (16.6%). Side effects were recorded in 5/30 (16.6%) of the AMG treated patients; 1 patient experienced gastric pain and 4 abdominal pain.

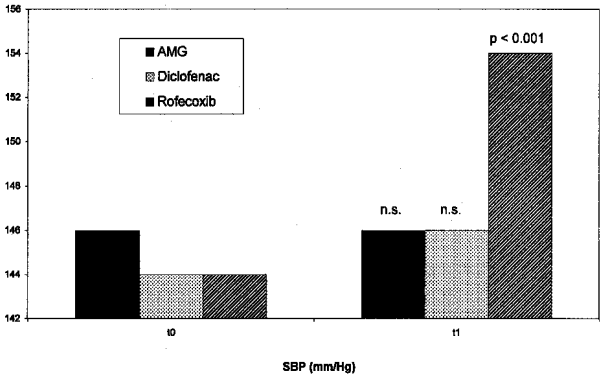
Statistical analysis did not show any significant difference among the 3 groups with respect to the total numer of side effects. However, all 10 patients treated with rofecoxib experienced side effects (mild malleolar edema, body weight gain and hypertension) related to impaired renal function. No patients had such manifestations in the other two treatment groups with a significant statistical difference ($p < 0.005$).

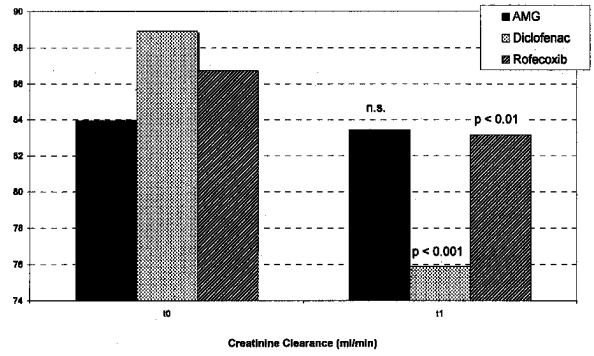
Discussion

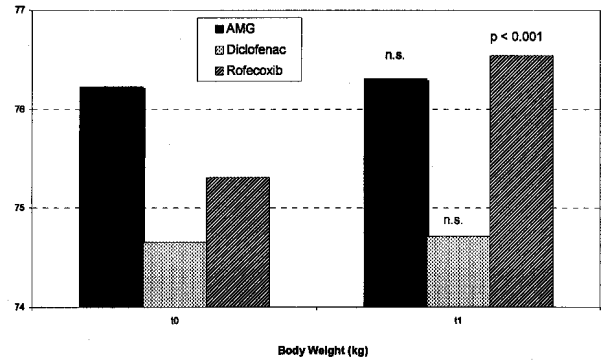
Gastrointestinal and renal side effects represent a well-known complication of NSAID therapy, especially in the elderly (9, 10). To reduce gastrointestinal side effects and adverse events, the use of COX-2 specific inhibitors or non-selective NSAIDs plus misoprostol or a proton pump inhibitor have been recommended (3). However, COX-2 specific inhibitors probably do not offer advantages in terms of renal toxicity with respect to traditional NSAIDs (22, 23). Indeed, COX-2 is a critical enzyme for sodium excretion and renin release and its inhibition produces sodium retention, hyperkaliemia and water intoxication (24). In clinical practice these effects are responsible for the development of peripheral edema and hypertension (25). For traditional non-selective NSAIDs, co-therapy with misoprostol is useful to prevent











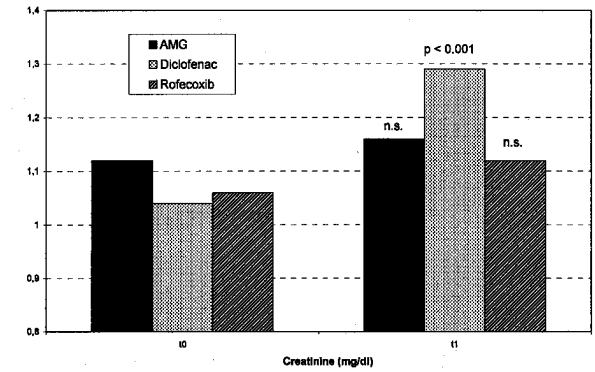


Fig. 1. The effects of AMG, diclofenac and rofecoxib on blood pressure and body weight.

Fig. 2. The effects of AMG, diclofenac and rofecoxib on BUN, creatinine clearance and creatinine.

gastrointestinal but not renal side effects (9). It must be emphasized that most studies of the safety of either traditional NSAIDs and selective COX-2 inhibitors have prevalently focused on gastrointestinal tolerability.

In recent years a new NSAID called AMG has been approved in Italy for the treatment of OA. In short-term studies, this drug has been shown to have better gastrointestinal tolerability than traditional NSAIDs both in experimental animals and in humans (15,26, 27). However, long-term controlled studies are required to confirm the safety of AMG with regard to the entire spectrum of adverse gastrointestinal events. The gastro-sparing effect of the drug has been explained by the demonstration of its stimulatory action on inducible nitric oxide synthase (NOS) activity. The consequent increased levels of nitric oxide (NO) in the gastric mucosa may balance the gastrolesive effects on PG inhibition (26). No data are available on the renal toxicity of AMG in humans.

In this randomized, single blinded study we compared the renal toxicity of AMG, diclofenac and rofecoxib in elderly patients with symptomatic OA. The results indicate that both diclofenac and rofecoxib impair the renal function.

As was to be expected given their different pharmacological properties, these two drugs affected the kidney in different ways. In keeping with other reports (8, 28), diclofenac caused a significant reduction in creatinine clearance associated with significant increases in serum creatinine, BUN and potassium, indicating an impairment of renal hemodynamics with reductions in the renal blood flow and glomerular filtra-

tion rate linked to non-selective COX inhibition.

Confirming recent observations (25) rofecoxib, which selectively inhibits COX-2, resulted in a significant increase in body weight, blood pressure and serum sodium, and a reduction in the 24-hour urine volume. These data indicate that the drug prevalently affects the sodium-water exchange mechanism in the body and are in keeping with the demostration that COX-2 is constitutively expressed by the kidney and represents the critical enzyme for sodium excretion and renin release (22, 29). Analysis of adverse events not causing withdrawal from the study, including the occurrence of malleolar edema, weight gain and hypertension, seems to confirm the negative role of COX-2 inhibition in renal salt and water retention. These events also occurred in the 4 patients who dropped out in the rofecoxib treatment group. Our results are in agreement with two recently published papers which assessed the renal safety of rofecoxib (25, 30). In a recent paper, Whelton *et al.* (31) found a significant reduction in the glomerular filtration rate induced by celecoxib. The lower selectivity ratio for COX-2 inhibition of celecoxib with respect to rofecoxib (32) may explain the different results observed in our study.

Unlike the other two NSAIDs, in our study AMG did not alter significantly the clinical and humoral parameters of kidney function. We can only put forward suppositions to explain this renal sparing effect of AMG. Experimental studies on rats showed that AMG stimulates the activity of inducible NOS with a consequent increase in NO which protects the gastric mucosa and counteracts the negative effect of COX inhibition (33).

Experimental studies have demonstrated that NO plays a major role in regulating the renal blood flow, inducing an increase in the glomerular filtration rate (34). NO seems to act synergically with PG in the regulation of the renal blood flow, and renal function impairment due to COX inhibition by NSAIDs is significantly reduced in the presence of elevated levels of NO (35). No data are available on the NO production enhancement exerted by AMG in the kidney. However, this hypothetical action may explain the renal sparing effect of the drug.

As regards the secondary endpoint of the study, AMG, diclofenac and rofecoxib significantly improved the clinical parameters currently used to assess the efficacy of treatment in patients with OA. Multivariate analysis showed that diclofenac was significantly more efficacious than the other 2 drugs. No differences were observed between AMG and rofecoxib.

In conclusion, the results of this study indicate that both traditional non-selective NSAIDs and selective COX-2 inhibitors such as diclofenac and rofecoxib negatively influence renal function over a short-term period of therapy in elderly subjects with symptomatic OA. Diclofenac reduces the glomerular filtration rate and rofecoxib causes sodium retention due to the inhibition of COX-2. Although the underlying mechanism is unclear, in our clinical series AMG did not show any significant impairment of renal function. Indeed, AMG did not influence the glomerular filtration rate nor water-sodium exchange mechanisms. The three drugs showed good therapeutic efficacy, resulting in a significant reduction of the clinical parameters of OA activity. Diclofenac proved significantly more efficacious than the other two NSAIDs.

In view of our results, the balance between therapeutic efficacy and gastrointestinal and renal safety should be kept in mind by clinicians when choosing an NSAID for the treatment of OA, which occurs in the elderly and requires a prolonged therapeutic course.

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