An evaluation of the interaction of meloxicam with frusemide in patients with compensated chronic cardiac failure

F. O. Müller, M. V. Middle, R. Schall, J. Terblanché, H. K. L. Hundt & G. Groenewoud

FARMOVS Research Centre for Clinical Pharmacology and Drug Development, Department of Pharmacology, University of the Orange Free State, Bloemfontein, South Africa

Aims To evaluate the interaction of meloxicam with frusemide in patients with compensated cardiac failure.

Methods Nineteen patients with Grade II or III compensated chronic cardiac failure completed this randomized, double-blind, cross-over study. The patients received 40 mg frusemide day^{-1} for 7 days. Thereafter, patients received either 15 mg meloxicam plus 40 mg frusemide day^{-1}, or one placebo tablet plus 40 mg frusemide day^{-1} for 7 days. After a washout period of 7 days during which patients received 40 mg frusemide day^{-1} for 7 days, the patients were crossed over to the alternate treatment. The effect of concomitant ingestion of meloxicam and frusemide on frusemide-induced diuresis, urine and serum electrolytes, urinary frusemide excretion, and plasma frusemide pharmacokinetics was also determined.

Results The estimate (90% confidence interval) of the '(frusemide + meloxicam)/(frusemide alone)' mean ratio of the variables C_{max}, AUC_{ss} and C_{max}/AUC_{ss} for plasma frusemide were 121% (101% to 145%), 106% (96.4% to 117%), and 114% (98.3% to 132%), respectively. Similarly, the estimate (90% confidence interval) of the '(frusemide + meloxicam)/(frusemide alone)' of the mean ratio of the variable cumulative urinary frusemide excretion after multiple doses of frusemide were 123% (101% to 150%) for the period 0–8 h, and 122% (105% to 142%) for the period 0–24 h after drug administration on day 7. The estimate (90% confidence interval) of the '(frusemide + meloxicam)/(frusemide alone)' mean ratio of the pharmacodynamic variables cumulative sodium excretion was 105% (95.2% to 116%) for the period 0–8 h and 108% (96.5% to 121%) for the period 0–24 h after drug administration on day 7.

Conclusions Meloxicam may lead to slightly increased maximum concentrations of frusemide in plasma, as well as to slightly increased urinary excretion of frusemide, without affecting the pharmacodynamics of frusemide. Thus there is no clinically significant pharmacokinetic or pharmacodynamic interaction of meloxicam with frusemide following repeated co-administration of meloxicam and frusemide to patients with compensated chronic cardiac failure.

Keywords: frusemide, meloxicam, drug interaction, electrolytes

Introduction

Several non-steroidal anti-inflammatory drugs (NSAIDs), such as salicylates, indomethacin, ibuprofen, naproxen and sulindac, decrease the natriuretic response to loop diuretics like frusemide [1]. However, a pharmacodynamic interaction may not be present for all NSAIDs when given concomitantly with frusemide. Meloxicam is a new NSAID and its pharmacological profile is structurally specific and different from related compounds such as piroxicam. The enzyme cyclooxygenase (COX) exists in two isoforms, COX-1 and COX-2. COX-1 acts, for example in the cytoprotection of gastric mucosa, but COX-2 is associated with inflammation. Meloxicam is a relatively selective COX-2 inhibitor, sparing COX-1; this has been shown to reduce the incidence and severity of gastrointestinal adverse effects associated with most existing NSAIDs. Müller *et al.* [2] demonstrated that there is no clinically relevant influence of meloxicam on frusemide kinetics and dynamics in healthy volunteers. However, such an interaction cannot be excluded in patients with an ineffective circulatory volume. The aim of the present study, therefore, was to assess a possible interaction between meloxicam and frusemide in patients with compensated chronic cardiac failure.

Correspondence: Professor F. O. Müller, FARMOVS Research Centre for Clinical Pharmacology and Drug Development, University of the Orange Free State, PO Box 339 (66), Bloemfontein 9300, South Africa.

Methods

Study population

Nineteen patients (6 males and 13 females; mean age 65 years, range 50 to 74 years; mean weight 87 kg, range 67 to 109 kg) with a history of at least 3 months of Grade II

(18 patients) or Grade III (1 patient) compensated chronic cardiac failure according to the New York Heart Association Classification, who gave their informed consent, entered and completed the study. Prerequisites for entry were the use of an ACE-inhibitor and creatinine clearance values no more than 30% above or below the normal limits for a patients age, mass and sex. Patients were allowed to take concomitant medication not likely to influence trial outcome or compromise patient safety. All concomitant therapies had to be kept constant for the duration of the trial. The study was approved by the Ethics Committee of the University of the Orange Free State and by the Medicines Control Council of South Africa, and conformed with Good Clinical Practice guidelines [3, 4].

Study design

This was a single-centre, randomized, double-blind, placebo-controlled, cross-over study. Within 2 weeks of a screening visit, and after confirmation of eligibility, patients were randomized and included in the study. The study drugs were administered according to the following dosage scheme:
Days 1 to 7: run-in; 40 mg frusemide day^{-1}.
Days 8 to 14 and Days 22 to 28: randomized, cross-over treatment; 15 mg meloxicam plus 40 mg frusemide day^{-1} (test treatment) or one placebo tablet plus 40 mg frusemide day^{-1} (reference treatment).
Days 15 to 21: wash-out; 40 mg frusemide.

Study performance

For the duration of the study, patients visited the clinic for safety assessments and for administration of study drugs. The drugs were administered at approximately 08.00 h, following breakfast. Study medication was administered by medical personnel involved in this study so that compliance was assured; all patients received their medication according to the randomization plan. All patients included in the study had to be treated on 40 mg frusemide day^{-1} for at least 2 weeks before the start of the study. Concomitant medication not likely to influence the outcome of the trial, and not likely to compromise safety, was allowed. Throughout the study, patients followed their usual diet with the proviso that food with a high salt content was avoided. The only restriction on fluids was that at most 25 g alcohol (200 ml wine or 500 ml beer) and 300 mg caffeine (3 cups of coffee) per day was to be taken.

On the days preceding profile days and on profile days, no food or beverages containing alcohol or caffeine was allowed and standard meals were served at the clinic. The standard meals had an estimated daily potassium content of 2985 mg and a sodium content of 1545 mg. The estimated total daily energy content of the meals was 10 452 kJ.

Days 14 and 28 (day 7 of each treatment period) were pharmacodynamic and pharmacokinetic profile days. The patients were admitted to the clinic the night before the profile days to ensure an overnight fast of at least 12 h. On the profile days the patients remained at the clinic for 24 h for the collection of urine and blood samples. They remained recumbent for 4 h after drug administration, after which they were ambulant until they went to bed at 22.00 h.

Blood sampling

Venous blood samples were collected on profile days for the determination of serum electrolytes, uric acid, serum creatinine and plasma frusemide concentrations.

For determination of serum electrolytes and uric acid, 5 ml samples were collected before drug administration (0 h) and at 4, 8, 12 and 24 h after drug administration. For determination of serum creatinine, 5 ml samples were collected at 2, 6, 10, 12 and 18 h after drug administration. For determination of plasma frusemide concentrations 10 ml samples were collected before drug administration (0 h) and at 0.33, 0.66, 1, 1.33, 1.67, 2, 2.5, 3, 5, 8, and 16 h after drug administration.

Urine collection

Immediately before drug administration on profile days patients emptied their bladders completely. Urine collections were made 2-hourly for the first 8 h and one sample each for the 8 to 12 and 12 to 24 h periods.

Assays

Serum and urine electrolytes, as well as plasma and urine frusemide assays, were determined as described in Müller *et al.* [2].

Pharmacokinetic variables

Plasma To compare the rate and extent of absorption of frusemide following the two treatments, the following pharmacokinetic variables were calculated for each patient and treatment:

- The maximum concentration (C_{max}).
- The time to maximum concentration (t_{max}).
- The apparent terminal half-life ($t_{1/2.z}$).
- The area under the plasma frusemide concentration *vs* time curve [AUC(0, t_{last})], with extrapolation to 24 h, i.e. $AUC_{ss} = AUC(0, 24\ h)$.
- The ratio of C_{max} and AUC_{ss} (C_{max}/AUC_{ss}) [5, 6].

The variables AUC_{ss} [characteristic of the extent of absorption (bioavailability) of frusemide] and C_{max} were the primary characteristics for the assessment of a pharmacokinetic interaction.

C_{max} and t_{max} were read directly from the observed concentrations. $t_{1/2.z}$ was calculated from the adjustment of a single exponential function to the terminal phase of the plasma concentration *vs* time profile [7]. AUC(0, t_{last}) was calculated according to the linear trapezoidal rule from the 0 h to the last quantifiable concentration after drug administration, and extrapolated to $AUC_{ss} = AUC(0, 24\ h)$ by adding $[C(t_{last})\text{-}C(24\ h)]/z$, where z is the terminal rate constant, $C(t_{last})$ is the last quantifiable concentration, and $C(24\ h)$ is the predicted concentration value at 24 h. C_{max}/AUC_{ss} was calculated by dividing C_{max} by AUC_{ss}.

Urine The fractional urinary excretions (Ae_{ur}) were calculated and cumulated for each patient.

Pharmacodynamic variables

Serum The following variables were recorded for each blood sampling time of each patient and treatment: electrolytes (chloride, potassium and sodium), uric acid and creatinine.

The AUC(0, 24 h) of the electrolyte *vs* time curves were calculated according to the linear trapezoidal rule. The average electrolyte concentrations were calculated as: C_{av} = AUC(0, 24 h)/24 h.

Urine The following variables were recorded for each urine collection of each patient and treatment: volume; electrolyte excretion (chloride, potassium and sodium); and creatinine. The primary variable for the assessment of a pharmacodynamic interaction between frusemide and meloxicam was the cumulative urine and sodium excretion on Days 14 and 28 for the periods 0 to 8 h and 0 to 24 h after drug administration.

Statistical analysis of interaction between meloxicam and frusemide

The analysis of a possible interaction between frusemide and meloxicam can be treated as an equivalence problem [8]. The administration of frusemide and placebo serves as the reference situation, and the concomitant administration of frusemide and meloxicam serves as the test situation.

The test treatment was compared with the reference treatment with respect to the pharmacokinetic variables C_{max}, $t_{1/2.z}$, AUC(0, t_{last}) and AUC_{ss}, using an analysis of variance with subject and treatment effects after a logarithmic transformation of the data. Point estimates and 90% confidence intervals (CI) for the 'test/reference' mean ratios of those variables were calculated [9]. Equivalence of the test treatment and the reference treatment was assessed on the basis of those CI, in relation to the bioequivalence ranges of 70% to 143% for C_{max}, and 80% to 125% for AUC).

Similarly, the test treatment was compared with the reference treatment with respect to the following pharmacodynamic variables: cumulative urine volumes [(0–8 h) and (0–24 h)], cumulative urinary frusemide excretion [(0–8 h) and (0–24 h)], cumulative urinary electrolyte excretion [chloride (0–8 h) and (0–24 h), potassium (0–8 h) and (0–24 h), sodium (0–8 h) and (0–24 h)], average serum electrolytes (chloride, potassium, sodium), average serum uric acid and creatinine clearance. Point estimates and 90% Cl for the 'test/reference' mean ratios of those variables were calculated. Equivalence of the test and reference treatment was assessed on the basis of the CI in relation to the conventional equivalence range of 80% to 125%.

Sample size calculation

In a previous study [2], the intra-individual coefficient of variation (CV) of the pharmacokinetic and pharmacodynamic variables was 20% or less. Given that the intra-individual CV for the cumulative sodium excretion is 20%, and the true mean difference of these variables between the reference (frusemide alone) and test (frusemide and meloxicam) treatments is at most 5%, one needs 20 patients to demonstrate lack of interaction (90% CI for the 'test/reference' mean ratio lies within the conventional equivalence range of 80% to 125%) with a power of 80% [10].

Results

Concomitant therapies

Table 1 lists medication taken by patients for the treatment of symptoms relating to cardiac indications. The dosage of concomitant medication was kept constant for each patient for the duration of the study period. Each patient thus served as his/her own control.

Pharmacokinetic results

The geometric means, geometric standard deviations and ranges of the pharmacokinetic variables for plasma frusemide and cumulative urinary frusemide excretion are summarized in Table 2. Figure 1 is a log-linear plot showing plasma frusemide concentrations. The cumulative urinary frusemide excretion is shown in Figure 2.

Estimates (90% CI) of the 'test/reference' mean ratio of the variables C_{max}, AUC_{ss} and C_{max}/AUC_{ss} for plasma frusemide were 121% (101% to 145%), 106% (96.4% to 117%), and 114% (98.3% to 132%), respectively.

Estimates (90% CI) of the 'test/reference' mean ratio of the variable cumulative urinary frusemide excretion were 123% (101% to 150%) for the period 0–8 h, and 122% (105% to 142%) for the period 0–24 h after drug administration.

Pharmacodynamic results

Summaries of the following pharmacodynamic results for the various collection intervals are presented: urinary electrolyte excretion (chloride, potassium and sodium) and cumulative urine volumes (Table 3); serum electrolytes, average creatinine clearance and serum uric acid (Table 4).

The estimates (90% CI) of the 'test/reference' mean ratio of the variable cumulative sodium excretion (primary variable for the assessment of an interaction) were 105% (95.2% to 116%) for the period 0–8 h, and 108% (96.5% to 121%) for the period 0–24 h after drug administration.

Safety results

There were no clinically significant changes in laboratory variables, body mass, blood pressure, heart rate or R-R interval (ECG) during the study period. Two adverse events, heartburn and worsening of symptoms of heart failure (paroxysmal nocturnal dyspnoea and ankle oedema) were recorded during treatment with meloxicam and frusemide. Both adverse events were mild in intensity and were deemed possibly related to the study medication. Arthritic pains (moderate intensity), heartburn (mild intensity), and extrasystoles (mild intensity) were recorded during treatment with placebo and frusemide. During treatment with frusemide alone (run-in and wash-out periods) a mild headache was also reported. The relation of these adverse events to the study medication were deemed to be doubtful. Thirteen

Table 1 Concomitant medication used by patients during the study period for the treatment of heart disease and related symptoms.

Active ingredient	*Indication*	*Number of patients*	*Total daily dosage (mg)*
Acebutolol	Hypertension	1	200
Aspirin	Blood coagulation	7	150–300
Captopril	Hypertension/Cardiac failure	5	25–100
Clopamide	Hypertension/Cardiac failure	1	5
Digoxin†	Cardiac failure	7	0.25
Diltiazem	Ischaemic heart disease	1	60
Ergocristine	Hypertension/Cardiac failure	1	0.5
Indapamide	Hypertension/Cardiac failure	1	2.5
Isosorbide dinitrate	Ischaemic heart disease/Cardiac failure	2	40
Nifedipine	Ischaemic heart disease/Hypertension	1	30
Quinapril	Hypertension/Cardiac failure	2	5-10
Ramipril	Cardiac failure	4	2.5–10
Reserpine	Hypertension/Cardiac failure	1	0.1
Spirinolactone	Cadiac failure	1	50
Verapamil	Dysrhythmlas	2	80–120

†Drug level was checked weekly. Dosage was decreased in patients with levels >2 ng ml^{-1}.

Table 2 Summary of plasma and urine pharmacokinetics of frusemide. ($n=19$; Dose: 40 mg frusemide daily for duration of trial + [1 placebo tablet or 1×15 mg meloxicam tablet] for 7 days).

		Frusemide + placebo (Reference)			*Frusemide + meloxicam (Test)*					
		Geometric			*Geometric*			*Mean ratio*	*90% confidence*	*Intra-individual*
Variable		*Mean*	*s.d.*	*Range*	*Mean*	*s.d.*	*Range*	*(%)**	*interval (%)†*	*CV (%)*
C_{max}	(ng ml^{-1})	1124	1.83	316–2342	1367	1.36	783–2505	121	101–145	33
t_{max}‡	(h)	1.67		1.00–5.00	1.67		0.67-3.00	−0.08	−0.46–0.34	
AUC(0, t_{last})	(ng ml^{-1} h)	3963	1.55	1980–9211	4127	1.35	229–6979	104	93.3–116	19
AUC_{ss}	(ng ml^{-1} h)	4135	1.54	2130–9571	4398	1.35	2465–8673	106	96.4–117	17
C_{max}/AUC_{ss}	l h^{-1})	0.27	1.38	0.12–0.39	0.31	1.34	0.18–0.52	114	98.3–132	27
$t_{(1/2)z}$	(h)	2.07	1.53	1.29–6.27	1.95	1.46	0.98–6.03	93.9	83.1–106	22
Ae_{ur}(0–8 h)	(mg)	8.74	1.63	2.95–21.5	10.8§	1.80	3.67–28.8	123	101–150	35
Ae_{ur}(0–24 h)	(mg)	11.4	1.58	4.29–23.9	13.9§	1.64	4.34–32.8	122	105–142	27

*Estimate of 'test/reference' mean ratio from analysis of variance of log-transformed data.

†90% Conventional Cl for the 'test/reference' mean ratio from analysis of variance of log-transformed data.

‡Medians, ranges and non-parametric point estimate of the 'test-reference' median difference, and corresponding confidence interval.

§$n=18$.

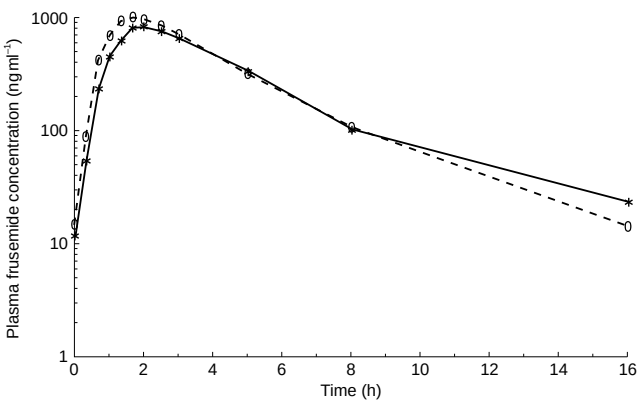

Figure 1 Log-linear plot of plasma frusemide concentrations for the duration of the trial for the frusemide/placebo (—) and frusemide/meloxicam (---) study groups.

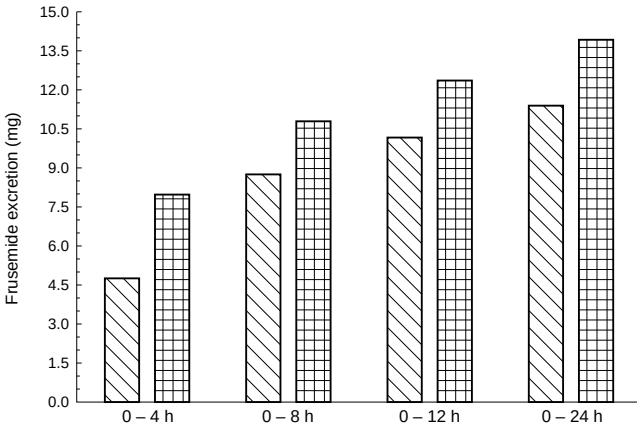

Figure 2 Histograms of the cumulative urinary frusemide excretion in the frusemide/placebo (▨) and frusemide/meloxicam (▦) study groups.

Table 3 Cumulative urinary electrolyte excretion (mmol) and cumulative urine volumes (ml). ($n = 19$; Dose: 40 mg frusemide daily for duration of trial + [1 placebo tablet or 1 × 15 mg meloxicam tablet] for 7 days).

		Frusemide + placebo (Reference)			*Frusemide + meloxicam (Test)*					
		Geometric			*Geometric*			*Mean ratio*	*90% confidence*	*Intra-individual*
Variable	*Period*	*Mean*	*s.d.*	*Range*	*Mean*	*s.d.*	*Range*	*(%)**	*interval (%)†*	*CV (%)*
Sodium	0–8 h	149	1.34	66.3–224	155‡	1.41	67.4–292	105	95.2–116	17
	0–24 h	182	1.39	70.6–280	195‡	1.40	114–336	108	96.5–121	20
Chloride	0–8 h	164	1.31	82.8–239	171‡	1.37	75.2–290	105	96.9–114	14
	0–24 h	182	1.34	85.8–275	192‡	1.37	89.5–304	107	97.2–118	17
Potassium	0–8 h	33.7	1.38	20.3–78.6	30.5‡	1.50	12.6–59.3	90.6	77.9–105	26
	0–24 h	59.1	1.43	23.8–121	55.8‡	1.39	27.0–92.9	94.8	83.0–108	23
Urine volumes	0–8 h	1482	1.22	943–1980	1506	1.34	782–2690	102	93.3–111	16
	0–24 h	1974	1.26	1087–2874	2035	1.33	1284-3404	103	94.5–113	16

*Estimate of 'test/reference' mean ratio from analysis of variance of log-transformed data.

†90% Conventional Cl for the 'test/reference' mean ratio from analysis of variance of log-transformed data.

‡$n = 18$.

Table 4 Serum electrolytes [C_{av}(0–24 h)], average creatinine clearance and serum uric acid [C_{av}(0-24 h)]. ($n = 19$; dose 40 mg frusemide daily for duration of trial + [1 placebo tablet or 1 × 15 mg meloxicam tablet] for 7 days).

		Frusemide + placebo (Reference)			*Frusemide + meloxicam (Test)*					
		Geometric			*Geometric*			*Mean ratio*	*90% confidence*	*Intra-individual*
Variable	*Period*	*Mean*	*s.d*	*Range*	*Mean*	*s.d*	*Range*	*(%)**	*interval (%)†*	*CV (%)*
Serum electrolyts										
Sodium	(mmol l^{-1})	139	1.01	136-142	140	1.01	137–145	101	100–101	1
Chloride	(mmol l^{-1})	104	1.02	98–109	105	1.02	101–111	101	101–102	1
Potassium	(mmol l^{-1})	3.95	1.12	2.73–4.58	4.10	1.07	3.61–4.53	104	100–108	6
Creatinine clearance	(mmol l^{-1})	73.0	1.66	19.9–141	73.5	1.43	39.2–137	101	88.0–115	24
Uric acid	(mmol l^{-1})	0.36	1.27	0.22–0.59	0.35	1.21	0.23–0.47	96.5	92.5–101	7

*Estimate of 'test/reference' mean ratio from analysis of variance of log-transformed data.

†90% Conventional Cl for the 'test/reference' mean ratio from analysis of variance of log-tranformed data.

patients recorded no adverse events, and no serious or severe adverse events were recorded. The concomitant administration of meloxicam and frusemide was well tolerated. No serious adverse events were recorded, and in general the adverse events were related to the underlying pathological conditions.

Discussion

The CI for the 'test/reference' mean ratios of the pharmacodynamic variables fall within the equivalence range of 80% to 125% (with the exception of the variable potassium whose CI for the 'test/reference' mean ratio extends slightly over the lower bound of the equivalence range (80%)).

The average concentrations of serum electrolytes and serum uric acid, and the creatinine clearance are similar for the two treatments (Table 4).

The cumulative urine volumes are similar for the two treatments. The cumulative urinary sodium excretion (primary variable) is similar for the two treatments, as is the excretion of chloride. The potassium excretion for the period 0–8 h is about 10% lower for the treatment meloxicam + frusemide compared with frusemide alone, and the CI for the mean ratio extends slightly over the lower bound of the equivalence range. However, the cumulative potassium excretion for the period 0–24 h is similar for the two treatments. This suggests that there is no pharmacodynamic interaction of frusemide with meloxicam following repeated co-administration of meloxicam and frusemide to patients with compensated chronic cardiac failure.

The 90% CI for the 'test/reference' mean ratio of the pharmacokinetic variable AUC_{ss} (as primary measure of the extent of absorption of frusemide) falls within the conventional equivalence range of 80% to 125%. The 90% CI for the test/reference mean ratio of the pharmacokinetic variable C_{max} extends slightly over the upper limit of the conventional equivalence range of 70% to 143%. The urinary excretion of frusemide for 0–8 h and 0–24 h is somewhat higher after concomitant administration of meloxicam and frusemide compared with administration of frusemide alone. In summary, the concomitant administration of meloxicam and frusemide has no effect on the extent of absorption of frusemide. The maximum concentrations of frusemide may be slightly increased, as may be the urinary excretion of frusemide, but this does not seem to have a significant effect on frusemide pharmacodynamics.

Treatment with NSAIDs is associated with several syndromes of renal pathology. These include a reduction of renal blood flow, altered intrarenal distribution of blood, reduced renin release and altered tubular function [11]. Some of these effects may result in reversible or irreversible renal failure [12], loss of blood pressure control in hypertensive patients or adverse drug interactions. The maintenance of stable renal function depends on the ability of a kidney to produce adequate amounts of the vasodilator prostaglandins, mediated by COX-1 action. This suggests that selective COX-2 inhibitors may help to reduce NSAID-related renal toxicity, a problem which is particularly troublesome in the elderly population who have the greatest need for such therapy.

Meloxicam appears to be a selective COX-2 inhibitor, sparing the physiologically important COX-1 isoform [13]. This observation may explain why no interaction between meloxicam and frusemide was observed in the present study, and why control of compensated chronic cardiac failure was not compromised by meloxicam.

Conclusion

These results suggest safe and uncomplicated combined use of these therapeutic agents in such patients.

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