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Influence of meloxicam on furosemide pharmacokinetics and pharmacodynamics in healthy volunteers

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Abstract. Fifteen healthy male volunteers participated in an open, multiple-dose study to investigate a possible interaction between furosemide and meloxicam, a new non-steroidal anti-inflammatory agent (NSAID). The study comprised three treatment periods. First, furosemide (40 mg) was administered as a single oral daily dose for 3 days. A wash-out day was followed by the administration of meloxicam (15 mg) as a single oral daily dose for 10 days. Thereafter, meloxicam and furosemide were administered concomitantly at the same doses as described above, for 3 days. The effect of concomitant ingestion of meloxicam and furosemide on furosemide-induced diuresis, urine and serum electrolytes, and furosemide pharmacokinetics was determined, after both single and repeated administration of furosemide. Estimates of the "(furosemide + meloxicam)/(furosemide alone)" mean ratio of the variable AUC(0-∞) for plasma furosemide and the cumulative sodium excretion (0–8 h) were 97.4% (90% confidence interval 89.7–106%) and 88% (90% confidence interval 82–94%), respectively. The study results indicate that meloxicam does not affect the pharmacokinetics of furosemide in healthy volunteers, nor does it affect furosemide-induced diuresis or serum electrolytes. The cumulative urinary electrolyte excretion after concomitant administration of meloxicam and furosemide is somewhat lower than after administration of furosemide alone, in particular for the period 0–8 h after administration of furosemide. This effect of meloxicam on furosemide dynamics is small, and is probably not clinically relevant in healthy volunteers under the dosing regime studied.

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A number of non-steroidal anti-inflammatory drugs (NSAIDs), including the salicylates, indomethacin, ibuprofen, naproxen and sulindac, decrease the natriuretic response to loop diuretics [1]. Furosemide is a diuretic which inhibits the active reabsorption of chloride in the diluting segment of the loop of Henle, preventing the reabsorption of sodium. In addition, furosemide increases renal blood flow, thereby contributing to the overall natriuresis associated with the drug [2]. NSAIDs leave the tubular effect of loop diuretics predominantly intact, but the increase in renal blood flow produced by loop diuretics via enhanced prostaglandin release/production may be inhibited by NSAIDs due to inhibition of prostaglandin synthesis. The rationale for this mechanism is supported by the fact that NSAIDs do not affect the diuretic response to thiazide diuretics [1].

The clinical significance of such an interaction is increasingly recognized, especially in patients with rheumatoid arthritis or osteoarthritis who are likely to have impaired cardiac or renal function as a consequence of age, disease or concomitant medication. However, a pharmacodynamic interaction with furosemide may not be common to all NSAIDs. Indeed, Guentert et al. [3] showed no clinically significant interactions between tenoxicam and furosemide, although tenoxicam attenuated the natriuretic effect of furosemide in patients with mild heart failure. This effect is probably related to inhibition of renal prostaglandins [4].

Meloxicam is a new NSAID, the latest example of the enolic acid class of drugs. Meloxicam primarily inhibits cyclooxygenase 2, the cyclooxygenase isoenzyme which is found mainly in inflamed tissues. Since renal prostaglandin synthesis is catalysed by the cyclooxygenase 1 isoenzyme, a NSAID-like meloxicam with

relative specificity to the cyclooxygenase 2 isoenzyme should affect renal prostaglandin synthesis to a minor degree. This could lead to a reduced influence of such an NSAID on the natriuretic response to loop diuretics.

The aim of the present study, therefore, was to assess the effect of concomitant administration of meloxicam and furosemide on furosemide-induced diuresis, serum and urine electrolytes, and furosemide pharmacokinetics following both single and repeated administration of furosemide.

Material and methods

Study population

Fifteen healthy, non-smoking, male Caucasian volunteers, aged between 19 and 25 years [mean 21, standard deviation (SD) 1.5 years] and weighing between 61 and 94 kg (mean 76, SD 11 kg), entered the study and completed all treatment phases. All volunteers gave written informed consent. The study was approved by the ethics committee of the University of the Orange Free State and was conducted in accordance with the Declaration of Helsinki.

Study design

This was an open, multiple-dose study, comprising three treatment periods, and extending over 21 days. The study started with a run-in period of 4 days during which no medication was administered (days −3 to 0). A period of 3 days followed during which furosemide was administered orally as a single daily dose of 40 mg (days 1–3). Thereafter, a single wash-out day (day 4) was followed by a period of 10 days during which meloxicam was administered as a single daily dose of 15 mg (days 5–14). On days 15–17, furosemide and meloxicam were administered concomitantly at the same doses as described above. All medication was administered to the volunteers at 08:00 h. Days 1 and 3, and 15 and 17 were pharmacokinetic and pharmacodynamic profile days.Baseline pharmacodynamic measurements were taken on days 0 and 14.

Study performance

Volunteers were not allowed to take any medication 14 days prior to and during the study, or ingest alcohol and caffeine-containing food and beverages 24 h prior to and during profile days.

Volunteers reported to the clinic at 07:00 h on days 0, 3, 14 and 17 of the study after an overnight fast of at least 10 h. On profile days the volunteers remained at the clinic for 24 h for the collection of urine and blood samples. On days preceding profile and baseline measurement days (days –1, 2, 13 and 16), volunteers reported to the clinic at 07:00, 13:00 and 18:00 h, where standardized meals were served. At 08:00 h, furosemide (day 2), meloxicam (day 13) or both drugs (day 16) were administered. Fluid intake was not standardized on these days except that the ingestion of beverages containing alcohol or caffeine was not permitted. On the remaining non-profile days, volunteers reported to the clinic at 08:00 h to receive their medication (days 4–12) and followed a regular diet but were instructed not to ingest food with a high salt content or add additional salt to their food. Fluid intake was not restricted except that at most 25 g alcohol (200 ml wine or 500 ml beer) and 300 mg caffeine (three cups of coffee)/day were allowed.

Blood sampling

Venous blood samples (10 ml) were collected on profile and baseline days according to the following time schedule: before drug administration (0 h) and at 4, 8 and 24 h after drug administration for the determination of serum electrolytes and uric acid. In addition, venous blood samples (5 ml each) were collected at 2, 6, 12 and 16 h after drug administration for the determination of serum creatinine. On days 3 and 17, venous blood samples (10 ml each) were collected according to the following time schedule: before drug administration (0 h) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10, 12 and 16 h after drug administration for the determination of plasma furosemide concentrations. Additional venous blood samples (10 ml) were collected on days 12, 13 and 14 before drug administration at 08:00 h for the determination of meloxicam trough concentrations.

Urine collection

Immediately before drug administration on profile and baseline days volunteers emptied their bladders completely. In order to replace fluid and electrolyte losses regularly, urine collections were made hourly for the first 4 h (0–4 h), 2-hourly for the following 4 h (4–8 h) and one collective sample throughout the 8- to 24-h period. The volume of each sample was measured and isovolumetric oral replacement was done with "half-strength Darrow's with glucose 5% injection" solution flavoured with Oros orange base concentrate (20 ml/200 ml).

Pharmacokinetic variables

The following pharmacokinetic variables were calculated: maximum concentration (C_{max}); time to maximum concentration (t_{max}); the terminal half-life ($t_{½,z}$); area under the plasma concentration vs time data pairs [AUC(0-t_{last})]; area under the plasma concentration vs time data pairs, with extrapolation to infinity [AUC(0-∞)]; and cumulative urinary furosemide excretion (Ae_{ur}). The variables C_{max} and AUC were the primary measures of the rate and extent of absorption of furosemide, respectively.

C_{max} and t_{max} were read directly from the observed concentrations. $t_{½,z}$ was calculated from the adjustment of a single or double exponential function to the terminal phase of the plasma concentration vs time profile. AUC(0-t_{last}) was calculated according to the linear trapezoidal rule, and extrapolated to infinity [AUC(0-∞)] using the terminal rate constant.

Pharmacodynamic variables

Urine

The following variables were recorded: urine volume, urinary electrolyte excretion (potassium and sodium) and urine creatinine. The primary variable for the assessment of a pharmacodynamic interaction between furosemide and meloxicam was the cumulative sodium excretion on days 1, 3, 15 and 17 for the first 8 h after drug administration.

The average creatinine clearance for a profile day was calculated as the weighted average of the fractional creatinine clearances determined for each sampling interval, where the weights were given by the length of the sampling intervals corresponding to each fractional creatinine clearance value.

Serum

The following variables were recorded: serum electrolytes (sodium and potassium), serum uric acid and serum creatinine. The

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

Drug assay method

Serum and urine electrolytes were determined on a Synchron EL-ISE (Beckman) electrolyte system and serum uric acid on a Cobas Mira S (Roche Diagnostics) random access analyser.

Plasma furosemide assay

To 1 ml plasma was added 50 µl internal standard solution (100 µgml^{-1} piretanide in methanol), 0.5 ml phosphate buffer (0.2 M, pH 7) and 3 ml diethyl ether. After vortexing for 30 s and centrifuging for 10 min at 1250 *g*, the aqueous phase was frozen and the ether layer discarded by decantation. Next 0.5 ml 0.1 M HCl and 3 ml diethyl ether were added to the aqueous phase and the mixture vortexed for 30 s, centrifuged for 10 min at 1250 *g* and the organic layer transferred to a 5-ml glass ampoule. After evaporation of the ether under a stream of nitrogen at 40°C, the residue was reconstituted in 140 µl mobile phase, transferred to a microfuge tube, centrifuged for 5 min at 12 000 *g* and 90 µl injected onto the high-performance liquid chromatography (HPLC) column using a Spectra-Physics model 8780 XR autosampler. The analytical column used was a Waters Radial Pak, Novapak C18, 4 µ, 100 × 8 mm cartridge held in an RCM 8 × 10 compression unit and protected by an Upchurch 20 × 2 mm precolumn dry-filled with Perisorb RP-18 packing (30–40 µ).

The mobile phase consisted of acetonitrile: water: 0.1 M, pH 2.6 citric acid phosphate buffer (prepared by mixing 900 ml 0.1 M citric acid with 100 ml 0.2 M disodium hydrogen phosphate) (700 + 550 + 550) and was pumped at a flow-rate of 2.4 mlmin^{-1} at ambient temperature with a Shimadzu model LC-6A pump. The effluent was monitored with a Kratos Spectroflow 980 programmable fluorescence detector set at an excitation wavelength of 349 nm with a 418 nm emission cut-off filter, and chromatograms recorded on a Spectra-Physics model SP4290 integrator. Furosemide eluted at a retention time of about 3.2 min and the internal standard at about 6.0 min.

Urine furosemide assay

To 100 µl urine (centrifuged) in the autosampler injection vial was added 100 µl internal standard solution (3.33 µgml^{-1} piretanide in acetonitrile: water, 4:1) and the vial vortexed briefly. Using a Spectra-Physics model 8775 autosampler, 20 µl was injected onto the HPLC column. The analytical column used was a Waters Radial Pak, Novapak C18, 4 µ, 100 × 8-mm cartridge held in an RCM 8 × 10 compression unit and protected by a Waters Guard Pak, with a Novapak C18 precolumn.

The mobile phase consisted of acetonitrile: water: 0.1 M, pH 2.6 citric acid/phosphate buffer (prepared by mixing 900 ml 0.1 M citric acid with 100 ml 0.2 M disodium hydrogen phosphate) (700 + 550 + 550) and was pumped at a flow-rate of 2.4 mlmin^{-1} at ambient temperature with a Spectra-Physics model SP8810 pump. The effluent was monitored with a Kratos Spectroflow 980 programmable fluorescence detector set at an excitation wavelength of 349 nm with a 418 nm cut-off emission filter, and chromatograms recorded on a Spectra-Physics model SP4290 integrator. During the first 2 min the eluent was diverted to bypass the detector. Furosemide eluted at a retention time of about 2.8 min and the internal standard at about 5.4 min.

Statistical analysis of interaction between meloxicam and furosemide

The analysis of a possible interaction between furosemide and meloxicam can be treated as an equivalence problem [5]. The administration of furosemide alone serves as the reference treatment, and the concomitant administration of furosemide and meloxicam serves as the test treatment.

The test treatment was compared with the reference treatment with respect to the pharmacokinetic variables C_{max}, $t_{½,z}$, AUC(0-t_{last}) and AUC(0-∞) using an analysis of variance with subject and treatment effects after a logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "test/reference" mean ratios of those variables were calculated [6]. Equivalence of the test treatment and the reference treatment was assessed on the basis of those confidence intervals, in relation to the bioequivalence ranges of 70–143% for C_{max}, and 80–125% for AUC(0-∞).

Similarly, the test treatment was compared with the reference treatment with respect to the following pharmacokinetic and pharmacodynamic variables: cumulative urine volumes, cumulative urinary furosemide excretion, cumulative urinary electrolyte excretion, serum electrolytes, serum uric acid and average creatinine clearance.

In each case a comparison of the data collected on day 1 (furosemide alone; reference) and day 15 (furosemide + meloxicam; test) allowed the assessment of an interaction of meloxicam with furosemide following a single dose of furosemide; a comparison of the data collected on day 3 (furosemide alone; reference) and day 17 (furosemide + meloxicam; test) allowed the assessment of an interaction following repeated doses of furosemide.

Results

Safety

None of the volunteers withdrew or was withdrawn from the study. A total of 11 adverse events were recorded, all ranging from mild to moderate: headaches, dizziness, abdominal cramps and diarrhoea. Three volunteers experienced mild diarrhoea (two volunteers while both on meloxicam plus furosemide, and while on meloxicam alone, and one volunteer while on meloxicam plus furosemide). No serious or unexpected adverse events were observed or reported. There were no clinically significant changes in vital signs, clinical chemistry and haematological variables of volunteers during the study.

Pharmacokinetics

The pharmacokinetic data for furosemide are summarized in Table 1. Estimates of the "test/reference" mean ratio of the variables C_{max} and AUC(0-∞) for plasma furosemide were 88.6% (90% CI 70.3–112%) and 97.4% (90% CI 89.7–106%), respectively. The estimates of the "test/reference" mean ratio of the variable cumulative urinary furosemide excretion (Ae_{ur}) were 105% (90% CI 93–118%) for the period 0–8 h, and 106% (90% CI 97–115%) for the period 0–24 h.

Meloxicam trough concentrations on day 12 ranged from 0.89 to 3.52 µg/ml (mean 1.88, SD 0.77). The

Table 1 Summary of pharmacokinetic parameters derived for furosemide

Pharmacokinetic parameter	Furosemide[a] (n = 15)			Furosemide + meloxicam[b] (n = 15)			Mean ratio (%)[c]	90% Confidence interval (%)[d]
	Geometric mean	(SD)	Range	Geometric mean	(SD)	Range		
C_{max} (mg·l^{-1})	1311	(1.54)	492–2670	1160	(1.43)	510–2100	88.6	70.3–112
t_{max} (h)	[1.20	(46.7)	0.75–2.50	1.42	(31.8)	0.75–2.25][e]		
AUC(0-t_{last}) (mg·h/l)	2750	(1.24)	1820–3790	2680	(1.24)	1660–3610	97.1	88.6–107
AUC(0-∞) (mg·h/l)	2920	(1.22)	1940–4080	2850	(1.21)	2040–3740	97.4	89.7–106
Ae_{ur}(0–8 h) (mg)	16.2	(1.24)	12.0–25.1	17.0	(1.29)	11.0–27.1	105	93.4–118
Ae_{ur}(0–24 h) (mg)	18.5	(1.20)	13.7–27.3	19.5	(1.23)	13.1–29.1	106	97.2–115

[a]Once daily furosemide 40 mg for 3 days (days 1, 2 and 3 of the study)
[b]Once daily meloxicam 15 mg for 13 days (days 5–17) and furosemide 40 mg on days 15–17
[c]Geometric mean of individual "test/reference" ratios
[d]90% conventional confidence interval for the "test/reference" mean ratio after logarithmic transformation of the data
[e]Arithmetic mean and coefficient of variation (CV%)

Table 2 Cumulative urinary electrolyte excretion (mmol) and cumulative urine volumes (ml)

	Day	Period	Furosemide[a] (n = 15)			Furosemide + meloxicam[b] (n = 15)			Mean ratio (%)[c]	90% confidence interval (%)[d]
			Geometric mean	(SD)	Range	Geometric mean	(SD)	Range		
Potassium excretion	Day 1/15[e]	0–8 h	59.9	(1.19)	41.8–75.1	50.2	(1.19)	39.1–64.8	83.7	79.1–88.5
		0–24 h	96.9	(1.17)	75.8–128	89.1	(1.21)	71.8–138	92.0	85.8–98.6
	Day3/17[f]	0–8 h	56.1	(1.18)	38.4–79.9	43.5	(1.30)	24.7–62.5	77.5	70.2–85.5
		0–24 h	99.1	(1.21)	70.0–146	83.2	(1.23)	63.6–118	84.0	78.4–90.0
Sodium excretion	Day 1/15[e]	0–8 h	251	(1.22)	180–403	220	(1.24)	165–391	87.7	82.1–93.7
		0–24 h	330	(1.21)	241–491	318	(1.19)	252–509	96.6	91.0–103
	Day 3/17[f]	0–8 h	184	(1.24)	131–264	171	(1.30)	108–247	93.1	82.9–104
Urine volumes	Day 1/15[e]	0–8 h	2470	(1.24)	1550–4220	2510	(1.27)	1810–4820	102	95.2–109
		0–24 h	3260	(1.24)	2010–5300	3270	(1.26)	2500–5900	100	94.0–107
	Day 3/17[f]	0–8 h	1850	(1.30)	1230–2840	1840	(1.37)	1070–3510	99.4	89.3–111
		0–24 h	2530	(1.26)	1760–3720	2540	(1.33)	1650–4700	101	92.5–109

[a]Once daily furosemide 40 mg on days 1, 2 and 3 of the first study phase (furosemide alone)
[b]Once daily meloxicam 15 mg for 13 days (days 5–17) and furosemide 40 mg on days 15–17
[c]Geometric mean of individual "test/reference" ratios
[d]90% conventional confidence interval for the "test/reference" mean ratio after logarithmic transformation of the data
[e]After a single dose of furosemide
[f]After multiple doses of furosemide

corresponding values for days 13 and 14 were 0.99–4.16 μgml^{-1} (mean 1.92, SD 0.91), and 0.84–3.24 μgml^{-1} (mean 1.63, SD 0.79), respectively.

Pharmacodynamics

Summaries of the following pharmacodynamic results for the various collection intervals are presented: cumulative urine volumes and urinary electrolyte excretion (Table 2); serum electrolytes, serum uric acid and average creatinine clearance (Table 3). The estimates of the "test/reference" mean ratio of the variable cumulative sodium excretion (primary variable for the assessment of an interaction) after a single dose of furosemide were 88% (90% CI 82–94%) for the period 0–8 h, and 97% (90% CI 91–103%) for the period 0–24 h after drug administration. After multiple doses of furosemide, estimates of the "test/reference" mean ratio of the variable cumulative sodium excretion were 93% (90% CI 83–104%) for the period 0–8 h, and 103% (90% CI 93–114%) for the period 0–24 h after drug administration.

Discussion

The 90% confidence intervals for the "test/reference" mean ratios of the pharmacokinetic variables C_{max} and AUC fall within the bioequivalence ranges 70–143% for C_{max} and 80–125% for AUC(0-∞). The urinary excretion of furosemide is similar for both regimens

Table 3 Serum electrolytes C_{av} (0–24 h)(mmol/l), serum uric acid C_{av}(0–24 h)(mmol/l) and average creatinine clearance (ml/min)

		Furosemide[a] (n = 15)			Furosemide + meloxicam[b] (n = 15)				
		Geometric mean	(SD)	Range	Geometric mean	(SD)	Range	Mean ratio (%)[c]	90% confidence interval(%)[d]
Serum sodium	Day 1/15[e]	141	(1.01)	138–143	139	(1.01)	136–142	99.1	98.6–99.5
	Day 3/17[f]	140	(1.01)	138–141	134	(1.02)	132–141	96.1	95.5–96.7
Serum potassium	Day 1/15[e]	4.16	(1.04)	3.88–4.43	4.14	(1.04)	3.99–4.52	99.6	97.7–102
	Day 3/17[f]	3.90	(1.03)	3.72–4.10	4.00	(1.06)	3.72–4.40	103	100–105
Serum uric acid	Day 1/15[e]	0.34	(1.19)	0.25–0.43	0.32	(1.11)	0.27–0.36	94.8	89.0–101
	Day 3/17[f]	0.38	(1.18)	0.29–0.48	0.38	(1.15)	0.30–0.46	99.7	97.5–102
Average creatinine clearance	Day 1/15[e]	120	(1.13)	100–150	118	(1.10)	94.3–130	98.2	92.4–104
	Day 3/17[f]	108	(1.13)	84.1–132	111	(1.19)	73.0–145	103	94.9–111

[a] Once daily furosemide 40 mg on days 1, 2 and 3 of the first study phase (furosemide alone)
[b] Once daily meloxicam 15 mg for 13 days (days 5–17) and furosemide 40 mg on days 15–17
[c] Geometric mean of individual "test/reference" ratios
[d] 90% conventional confidence interval for the "test/reference" mean ratio after logarithmic transformation of the data
[e] After a single dose of furosemide
[f] After multiple doses of furosemide

(Table 1), confirming that meloxicam does not affect the pharmacokinetic profile of furosemide.

The concentrations of serum electrolytes and serum uric acid, and the average creatinine clearance were similar for the two treatments after both single and multiple doses of furosemide (Table 3). In addition, the cumulative urine volumes were similar for the two treatments (Table 2).

The urinary electrolyte excretions are generally somewhat lower following concomitant administration of meloxicam and furosemide compared with furosemide alone (Table 2). For example, the "test/reference" mean ratio of the variable cumulative sodium excretion (0–8 h) after a single dose of furosemide was 88% (90% CI 82–94%). The observed mean decrease in electrolyte excretion is generally between 5% and 10%, and the confidence intervals for the mean ratios indicate that the mean decreases are unlikely to be more than 20% (a possible exception is potassium following multiple doses of furosemide; cumulative excretion 0–8 h). Thus we observe an effect of meloxicam on urinary electrolyte excretion. The statistical analysis (see the confidence intervals in Table 2) indicates that this effect is unlikely to be due to chance, but it is also unlikely to be clinically relevant in healthy volunteers under the dosing regimen studied.

In patients with impaired renal function, however, renal prostaglandin synthesis is more important for maintenance of renal blood flow than in healthy volunteers, so that in patients the effects of meloxicam on furosemide pharmacodynamics could be enhanced.

The study results indicate that meloxicam does not affect the pharmacokinetics of furosemide in healthy volunteers. The cumulative urinary electrolyte excretion after concomitant administration of meloxicam and furosemide is somewhat lower than after administration of furosemide alone, in particular for the period 0–8 h after administration of furosemide. This effect of meloxicam on furosemide dynamics is small, and is probably not clinically relevant in healthy volunteers. However, a possibly more significant interaction in a clinical situation with patients deserves further study.

Many arthritic patients have impaired cardiac or renal function as a consequence of age or disease. The absence of an interaction between meloxicam and furosemide in such patients would be an important element in the safety profile of this new NSAID. A study to investigate this question in patients with impaired cardiac function is currently in progress.

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