Steady-state pharmacokinetics of lithium in healthy volunteers receiving concomitant meloxicam

D. Türck,¹ G. Heinzel¹ & G. Luik²

¹Department of Pharmacokinetics and Drug Metabolism, Boehringer Ingelheim Pharma KG, D-88397 Biberach and der Riss, Germany and ²Human Pharmacology Centre, Boehringer Ingelheim KG, D-55216 Ingelheim am Rhein, Germany

Aims This open, controlled study investigated the effect of concomitant 15 mg oral meloxicam on the pharmacokinetics of lithium in healthy male volunteers.

Methods On days 1–14 lithium was coadministered with meloxicam to 16 volunteers; on days 10–14 lithium was administered in individualized dosage regimes to achieve stable lithium plasma concentrations in the lower therapeutic range of 0.3–0.7 mmol l⁻¹. A 12 h steady-state concentration profile for lithium was obtained at day 14, after which meloxicam was withdrawn. The lithium dose remained unchanged from day 15 to day 22, at which time a second lithium concentration profile was determined.

Results Lithium and meloxicam were well tolerated throughout the study and all 16 volunteers completed the study. Lithium predose concentrations ($C_{pre,ss}$) and area under the curve (AUC_{ss}) values both increased by 21% (paired *t*-test $P=0.0002$; 90% confidence intervals for test/reference ratios: 113–130% and 115–128%, respectively) when lithium was coadministered with meloxicam compared with values obtained for lithium alone. The geometric mean lithium $C_{pre,ss}$ was 0.65 mmol l⁻¹ when coadministered with meloxicam and 0.54 mmol l⁻¹ for lithium alone. Lithium $C_{max,ss}$ values were increased by 16% by coadministration of meloxicam, from 0.97 mmol l⁻¹ to 1.12 mmol l⁻¹. The total plasma clearance of lithium was lower with concomitant meloxicam administration (82.5% of value for lithium alone).

Conclusions Meloxicam (15 mg) moderately increased the plasma concentration of lithium in healthy volunteers, but by a magnitude thought to be of low clinical relevance. Nevertheless, lithium plasma concentrations should be closely monitored in patients receiving concomitant meloxicam and lithium therapy.

Keywords: interaction, lithium, meloxicam, NSAIDs, pharmacokinetics

Introduction

Lithium has been used in the treatment of unipolar and bipolar depression for the past 40 years, and, despite the introduction of alternative therapies, remains the treatment of choice for bipolar disorder [1]. Lithium is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring 0.5–3 h following an oral dose [1, 2] and its elimination half-life averages about 20–24 h

[1–3]. Steady-state concentrations are reached after 4–5 days. Lithium is nonprotein bound and after initial distribution into the extracellular fluid it accumulates in various tissues [2]. Over 95% of lithium is excreted unchanged through the kidneys, with 80% of the filtered lithium being reabsorbed in the proximal tubules [1, 2].

Lithium has a very narrow therapeutic range (about 0.5–1.2 mmol l⁻¹ under morning predose conditions [2, 5] or even lower), and a slight increase in serum concentrations may result in serious adverse effects [1, 5]. Interruptions in lithium treatment need to be avoided as they may provoke a relapse of the affective illness. Furthermore, the safety of combining lithium with other medications is a major concern as this can result in substantial elevations in lithium concentrations. Drugs that

Correspondence: Dr D. Türck, Department of Pharmacokinetics and Drug Metabolism, Boehringer Ingelheim Pharma KG, D-88397 Biberach an der Riss, Germany. Tel.: + 49 7351 54 4510; Fax: + 49 7351 54 2168.

Received 8 November 1999, accepted 4 May 2000.

affect the renal clearance of lithium, such as thiazide diuretics, can result in a significant increase in plasma lithium concentrations and hence lithium toxicity [2, 5]. Concomitant administration of most, but not all, non-steroidal anti-inflammatory drugs (NSAIDs) results in various degrees of elevated lithium concentrations (Table 1). For example, diclofenac treatment (50 mg three times daily) has resulted in a 26% increase in plasma lithium levels in normal volunteers [6], whereas concurrent aspirin therapy did not affect lithium plasma concentrations [7].

NSAIDs inhibit the cyclooxygenase (COX) enzyme, which results in inhibition of renal prostaglandin (PG) biosynthesis. The consequences of reduced levels of renal PGs include a decrease in renal plasma flow, retention of sodium and water, and hyperkalaemia. Two distinct isoforms of the COX enzyme have been shown to exist. COX-1 is thought to be responsible for synthesizing PGs for normal cell function and its inhibition is therefore also thought to result in the renal side-effects reported with NSAIDs. COX-2 is induced by exposure to inflammatory stimuli and seems to be constitutively expressed in the kidney and the brain [17], so it is hoped that selective inhibition of this isoform will control the inflammatory process without causing the unwanted gastrointestinal side-effects. The reduced renal blood flow associated with NSAIDs is possibly the reason for the elevated lithium levels observed with concomitant NSAID therapy. However, it is not known whether renal lithium excretion is dependent on COX-1 or COX-2-derived prostaglandins.

Meloxicam is a NSAID with preferential selectivity towards COX-2 relative to COX-1 [18–20]. It is effective in the treatment of osteoarthritis at a dose of 7.5 mg once daily and for rheumatoid arthritis at a dose of 15 mg once

daily [21]. Patients treated with lithium may also require treatment for arthritic pain. Meloxicam has been shown to have an improved toxicity profile compared with classical NSAIDs in a global analysis of clinical trials [22] and in two large-scale, 28-day studies, MELISSA (Meloxicam Large-scale International Study Safety Assessment) and SELECT (Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies) [23, 24]. The aim of this study was to investigate the effect of meloxicam on plasma lithium levels when administered concomitantly.

Methods

Patients

Sixteen healthy male Caucasian volunteers, aged between 24 and 42 years and weighing within 20% of normal range (Broca index), were enrolled in this open multiple-dose changeover trial. The study was conducted sequentially in two treatment phases, the first treatment phase days 1 through 14 in which lithium and meloxicam were administered concomitantly and a second treatment phase days 15 through 22 in which lithium was administered alone. The study was performed in accordance with the revised Declaration of Helsinki and after approval by an independent Ethics Committee. The following exclusion criteria were used: known or suspected hypersensitivity to the study medication; creatinine clearance $<80 \text{ ml min}^{-1}$ or any other clinically relevant laboratory abnormalities; acute or chronic infection; allergy (including drug allergies); thyroid dysfunction; >10 cigarettes/day; subjects receiving any medication within 2 weeks prior to study or 1 month if the drug half-life is $>24 \text{ h}$; participation in any clinical trial within the preceding 8 weeks. Volunteers had to

Table 1 Effect of concomitant NSAID administration on plasma lithium concentrations.

NSAID	Dose (mg day^{-1})	Patients (number)	Mean increase in serum lithium concentration	Reference
Aspirin	4000	Volunteers (5)	2%	Reimann <i>et al.</i> 1983 [7]
Sulindac	300	Patients (6)	0%	Ragheb & Powell, 1986 [8]
Ibuprofen	1600	Volunteers (11)	15%	Kristoff <i>et al.</i> 1986 [9]
	1800	Patients (9)	34%	Ragheb, 1987 [10]
Naproxen	750	Patients (7)	16%	Ragheb & Powell, 1986 [8]
Celecoxib	400	Volunteers (24)	17%	not yet published [29]
Flurbiprofen	200	Patients (11)	19%	Hughes <i>et al.</i> 1997 [11]
Lornoxicam	8	Volunteers (12)	20%	Ravic <i>et al.</i> 1993 [14]
Ketorolac	40	Volunteers (5)	21%	Cold <i>et al.</i> 1998 [12]
Indomethacin	150	Volunteers (5)	24%	Reimann <i>et al.</i> 1983 [7]
	150	Volunteers (4)	30%	Frölich <i>et al.</i> 1979 [13]
	150	Patients (3)	59%	Frölich <i>et al.</i> 1979 [13]
Diclofenac	150	Volunteers (5)	26%	Reimann & Frölich, 1981 [6]
Tenidap	120	Volunteers	39%	Apseloff <i>et al.</i> 1995 [15]

abstain from alcohol during the trial and the intake of methylxanthines (coffee, tea and other caffeine-containing beverages) was prohibited from day 12 up to 12 h after dosing on days 14 and 22.

Treatments

Meloxicam capsules (batch 41013, manufactured by Boehringer Ingelheim Pharma KG) were administered at a fixed dose of 15 mg once daily, the highest dose in clinical use, with concomitant lithium (536 mg lithium acetate [Quilonum retard[®], Smith Kline Beecham; batch 008562], 8.1 mmol) administered twice daily. The 15 mg meloxicam capsule was swallowed concomitantly with the lithium tablet in the morning with 150 ml of water after a standardized continental breakfast; the second lithium dose was administered 12 h after the morning dose. The lithium dose was titrated to achieve a morning predose lithium concentration between 0.3 and 0.7 mmol l⁻¹ on days 10–14. A 12 h steady-state concentration-time profile for lithium was obtained on day 14, after which meloxicam was withdrawn. The lithium dose remained then unchanged during days 15–22 and a second lithium concentration-time profile was determined on day 22.

This design was used in order to minimize the risk of adverse events associated with elevated lithium plasma concentrations. Meloxicam was expected to increase lithium plasma concentrations, as is the case with most other NSAIDs. This increase was avoided by titrating lithium under meloxicam medication, such that the subsequent withdrawal of meloxicam would then result in a decrease in lithium plasma concentrations. The extent of this decrease should reflect the expected increase in lithium levels had meloxicam been introduced to volunteers already receiving lithium. The relatively low dose of lithium should not have an impact on the extent of the interaction, because lithium shows linear pharmacokinetics in the therapeutic range [2]. The same design was used in a previous study with lornoxicam [14].

Analysis

Blood was sampled on the morning of each study day, and predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 h after the morning dose on days 14 and 22. The blood was collected in heparinized tubes, the plasma separated by centrifugation and stored frozen at -20°C until analysis. In addition, all urine was collected during the 12 h dosing interval on days 14 and 22. Lithium was quantified in plasma and urine using a validated atomic emission spectroscopy method (flame photometry). The assay was validated in the range 0.04–1.5 mmol l⁻¹ in plasma and 2.5–50 mmol l⁻¹ in urine. Prestudy interday variability (precision) during validation was 9.3%, 3.4% and 2.8% at

lithium plasma concentrations of 0.101, 0.504 and 1.01 mmol l⁻¹ with a deviation from theoretical values (accuracy) between -1.2 and +1.2%. Intraday variability at 0.05 mmol l⁻¹ was 9.0%. Respective precision values for urine were 9.6%, 2.1% and 1.6% for concentrations of 4.3, 21.6 and 43.2 mmol l⁻¹. The deviation from theoretical values ranged from -5.4 to +3.5%. Intraday variability at 4.0 mmol l⁻¹ was 2.0%.

Meloxicam was quantified in plasma by a specific high performance liquid chromatography (h.p.l.c.) method using ultraviolet detection at 365 nm. Plasma (0.1 ml; combined with an internal standard) was applied to columns filled with Perisorb[®] RP2. Proteins and other plasma constituents were removed by washing the column for 4 min at 1.5 ml min⁻¹ with water. Chromatographic separation was achieved on an analytical reversed-phase column (ODS Hypersil[®] 5 µm, 125 × 4.6 mm, 50°C) after column switching with eluent (methanol, tetrahydrofuran, 0.067 M potassium phosphate buffer pH 7.2[2460/252/1600 ml] containing 7.2 g cetyltrimethylammonium bromide) at 1.5 ml min⁻¹. The assay was validated for plasma in the range 0.05–10 µg ml⁻¹. Prestudy intraday variability in quality control samples was 3.8%, 2.1% and 2.2% for concentrations of 0.200, 1.20 and 6.16 µg ml⁻¹. Deviation from theory ranged from -0.2% to 2.7%. For interday variability during sample analysis refer to the results chapter.

Clinical pharmacology assessments

The primary pharmacokinetic assessment was the lithium predose plasma concentration ($C_{pre,ss}$) measured on day 14 (with concomitant meloxicam) and day 22 (without meloxicam). The predose concentration, $C_{pre,ss}$, corresponds to the concentration value obtained for clinical monitoring of lithium concentrations just prior to the next lithium dose, 12 h after the previous lithium dose. $C_{min,ss}$, the minimum plasma concentration, is the lowest concentration observed during a steady-state concentration profile. It differs from $C_{pre,ss}$ due to absorption lag times. The following pharmacokinetic parameters were also assessed: the maximum lithium plasma concentration at steady state ($C_{max,ss}$) and the time to reach this steady-state concentration ($t_{max,ss}$); the area under the concentration-time curve during a single constant dosing interval in steady state (AUC_{ss}); the average plasma concentration at steady state (C_{av}); the total plasma clearance (CL/F) and the peak-trough fluctuation (PTF) at steady state. The amount of lithium excreted unchanged in urine (A_e) was analysed, to compare the renal clearance (CL_r) of lithium with and without meloxicam. Elimination half-lives for lithium were not calculated because of the short observation period (12 h *vs* an elimination half-life of 20–24 h [1–3]). Attainment of lithium steady-state

concentrations was determined by analysis of $C_{pre,ss}$ values of lithium on days 12, 13 and 14. Geometric mean of $C_{pre,ss}$ values of lithium were 0.650, 0.654 and 0.654 mmol l^{-1} , respectively.

Safety assessments

Volunteers were interviewed by study staff on each study day and were requested to report adverse events spontaneously elicited by an unspecific question throughout the study, including time of onset, duration and severity. Additionally, the investigator evaluated the adverse events as mild, moderate or severe. Haematology, clinical chemistry and urinalysis were performed at the screening visit, before drug administration on days 1, 14 and 22, and at the end of study evaluation.

Statistics

Geometric means instead of arithmetic means were selected for descriptive statistics because of the lognormal distribution of drug plasma concentrations and pharmacokinetic parameters. The bioequivalence approach was used to determine whether an interaction had occurred between meloxicam and lithium [25]. Lithium $C_{pre,ss}$ on days 14 and 22 were also tested for differences by means of a paired *t*-test. Ninety percent confidence intervals were calculated for the ratio of the geometric mean lithium pharmacokinetic parameters determined on days 14 (with meloxicam) and 22 (without meloxicam). To establish bioequivalence, the calculated confidence interval had to fall within an acceptance limit of 80–125%. The point estimate (the averaged test/reference ratio) gives an impression about the extent of change due to the interaction. This statistical method is equivalent to the one-sided *t*-test procedure [26] and allows the statement that two parameters are equal, if 90% confidence intervals are inside the acceptance limit of 80–125%. The parameters are different if 100% (unity) is not included in the confidence interval. A sample of 12 volunteers was considered necessary for this approach; a total of 16 volunteers participated in the study to ensure 12 evaluable volunteers.

Results

Patients

All 16 volunteers completed the study and were included in the analysis. The mean (s.d.) age of the volunteers was 31 (6) years (Table 2). All volunteers received once-daily meloxicam 15 mg for 14 days and lithium for 22 days. Eight subjects were titrated to receive 24.3 mmol lithium (three tablets) as the final daily dose and the remaining

Table 2 Demographic data of the volunteers.

Characteristic	Value
Mean age (s.d.) (years)	31 (6)
Range (years)	24–42
Mean height (s.d.) (cm)	179 (5)
Mean weight (s.d.) (kg)	83 (6)
Broca index ^a (s.d.)	+4.2 (7.5)

^aBroca index = (weight $\times$ 100/height–100)–100, with weight in kg and height in cm.

eight subjects were titrated to 32.4 mmol (four tablets) daily.

Assay validation

The atomic emission spectroscopy method of measuring lithium during daily sample analysis showed a interday variability (at three different concentrations: 0.101, 0.498, 1.02 mmol l^{-1}) within 11.1% in plasma and within 2.1% in urine quality control samples (4.45, 21.6, 40.9 mmol l^{-1}), while accuracy (deviation from theory) was within $\pm 3.9\%$ for plasma and $\pm 6.7\%$ for urine in quality control samples during sample analysis. The limit of quantification of meloxicam, as determined by h.p.l.c., was 0.05 $\mu\text{g ml}^{-1}$; interday variability was within $\pm 5.3\%$, and the assay accuracy was within $\pm 2.3\%$ in quality-control samples (0.20, 1.20, 6.16 $\mu\text{g ml}^{-1}$).

Pharmacokinetics

The geometric mean plasma concentrations determined on days 14 (with meloxicam) and 22 (without meloxicam) are shown in Figure 1. The difference in $C_{pre,ss}$ between lithium administration alone, measured on day 22, compared with lithium and meloxicam administration, measured on day 14, was statistically significant

Figure 1 Geometric mean lithium plasma concentrations with meloxicam (●, day 14) and without meloxicam (○, day 22).

Figure 2 % change in $C_{pre,ss}$ for individual volunteers when lithium was coadministered with meloxicam compared with lithium alone.

($P=0.0002$) based on a paired t -test. In individual volunteers the effect of concomitant meloxicam on $C_{pre,ss}$ ranged from -9% to $+59\%$ (Figure 2). Concomitant administration of meloxicam increased the $C_{pre,ss}$ of lithium by 21% (90% CI for the test/reference ratio: 113–130%; Table 3) of the value observed for lithium alone. The maximum plasma lithium concentration, $C_{max,ss}$, increased by 16% when meloxicam was administered concomitantly with lithium (90% CI: 109–123%) compared with lithium alone. However, the time to

Figure 3 Geometric mean renal clearance of lithium with meloxicam (day 14) and without meloxicam (day 22).

achieve $C_{max,ss}$ of lithium, $t_{max,ss}$, was similar for the combined treatment and lithium alone. The AUC_{ss} and C_{av} were both 21% higher when lithium was administered concomitantly with meloxicam (90% CI: 115–128% for both parameters).

The total plasma clearance of lithium was 18% lower with concomitant meloxicam administration (90% CI: 78–87%). In addition, the peak-trough fluctuation (PTF) decreased with concomitant meloxicam by 25% of the PTF with lithium alone (90% CI: 70–80%). This was because the $C_{min,ss}$ increased more with concomitant meloxicam administration than the $C_{max,ss}$. The amount of lithium excreted by the kidney was unchanged by the concomitant administration of meloxicam, but the administration of meloxicam decreased renal clearance by 21% (90% CI: 73, 86%) (Figure 3). Meloxicam predose

Table 3 Pharmacokinetic parameters for lithium with (day 14) and without (day 22) meloxicam coadministration.

Parameter	Without meloxicam		With meloxicam		Point estimate # (%)	Confidence interval (90%) (%)
	<i>gmean</i>	% <i>gCV</i>	<i>gmean</i>	% <i>gCV</i>		
$C_{pre,ss}$ (mmol l ⁻¹)	0.54	19.5	0.65	16.5	121	113–130
$C_{max,ss}$ (mmol l ⁻¹)	0.97	19.5	1.12	13.8	116	109–123
AUC_{ss} (mmol l ⁻¹ h)	7.75	15.9	9.40	15.5	121	115–128
$t_{max,ss}$ (h)	1.5 ^a	0.5–3 ^b	1.5 ^a	1–2.5 ^b	94	82–100
C_{av} (mmol l ⁻¹)	0.66	15.9	0.78	15.5	121	115–128
$C_{min,ss}$ (mmol l ⁻¹)	0.35	22.2	0.55	21.1	160	148–172
CL/F (ml min ⁻¹)	30.2	10.1	24.9	16.3	82	78–87
PTF (%)	96.0	16.6	71.8	21.4	75	70–80
A_e (mmol)	14.0	25.6	13.5	18.5	96	89–104
A_e (% of dose)	100.0	12.6	96.2	11.1	96	89–104
CL_r	30.2	17.7	23.9	20.9	79	73–86
$C_{pre,ss}$ (μg ml ⁻¹) for meloxicam	–	–	0.998	45.6	–	–

the average of the individual test/reference ratios in percent *gmean* = geometric mean; *gCV* = geometric coefficient of variance ^a median, ^b range $C_{pre,ss}$: drug plasma concentration just prior to the next dose in steady state, $C_{max,ss}$: steady state maximum drug plasma concentration, AUC_{ss} : steady state area under the drug plasma concentration–time curve, $t_{max,ss}$: time to achieve $C_{max,ss}$, $C_{min,ss}$: minimum drug plasma concentration during a steady state interval, CL/F : apparent oral clearance, PTF: peak-trough fluctuation, A_e : Amount of drug (lithium) excreted in urine during a steady state dose interval, CL_r : renal drug (lithium) clearance.

concentrations were similar to the those observed in previous multiple dose studies [27].

Safety

Lithium and meloxicam were well tolerated during this trial. Five volunteers reported six adverse events when receiving lithium and meloxicam, compared with three volunteers (who reported four adverse events) when receiving lithium alone (Table 4). All of these events were classified as mild or moderate. The adverse events were all deemed to be related to either lithium or meloxicam, except for headache. Headache was reported by three subjects, all under lithium alone and was deemed not to be drug related. There were no adverse events leading to withdrawal from the study. No clinically relevant changes were observed in laboratory variables or other safety variables.

Discussion

This study indicates a moderate potential for interaction between lithium and a concomitantly administered once daily 15 mg dose of meloxicam (the recommended dose for patients with RA). A 21% elevation of lithium plasma concentrations was observed during meloxicam coadministration compared with when lithium was given alone.

The 21% elevation in lithium plasma concentrations observed during concomitant meloxicam administration is of a similar magnitude to increases observed with equi-effective or lower doses of other NSAIDs in healthy volunteers: flurbiprofen 19% [11], diclofenac 26% [6] and ketorolac 21% [12]. Lornoxicam and tenidap raised lithium concentrations by on average 20% and 39%, respectively, despite the use of relatively low analgesic

doses [14]. Ibuprofen (1800 mg day^{-1}) raised lithium concentrations by an average of 34% in elderly patients [10], but by only 15% in healthy volunteers following a dose of 1600 mg day^{-1} [9]. Similarly, indomethacin (150 mg day^{-1}) raised lithium levels by 59% in psychiatric patients but only by 24–30% in healthy volunteers [7, 13]. Elevations of lithium plasma concentration in the range of $\leq 25\%$ are generally considered to be of low therapeutic relevance [5].

The slightly greater increase in $C_{\text{pre,ss}}$ and AUC_{ss} in comparison with $C_{\text{max,ss}}$ is compatible with reduced lithium clearance. This reduced lithium clearance is thought to be accompanied by a slightly longer elimination half-life as there is no evidence for an alteration in the volume of distribution for lithium. This is not surprising considering that lithium is entirely excreted by the kidney and NSAIDs are known to affect renal function. It is possible that a decrease in renal function which may not be detected by a change in, for example, creatinine clearance may affect the renal clearance of lithium and hence the lithium plasma concentration.

There is little evidence to suggest that the relatively small elevation of lithium concentrations caused by concomitant meloxicam administration, compared with that induced by some other NSAIDs, is associated with the greater preferential selectivity of meloxicam for COX-2 relative to COX-1. In fact, the results with sulindac [8] and aspirin [7] contradict the hypothesis that the interaction of NSAIDs on lithium excretion is dependent on COX-2. Aspirin, for example, is considered to be a classical COX-1 inhibitor and concomitant administration had no effect on lithium plasma concentrations or lithium urinary excretion [7]. Recent data showed that the COX-2 selective inhibitor celecoxib also has an effect on renal blood flow and on glomerular filtration rate at least in salt-

Table 4 Number of reported adverse events.

<i>Adverse event</i>	<i>Lithium alone</i>	<i>Lithium with meloxicam</i>	<i>Investigators assessment</i>
Headache	3 (Vol. 4, 5, 15)	–	Not drug related
Increase in bodyweight (>2 kg)	–	2 (Vol. 2, 8)	Drug related (lithium)
Increased feeling of thirst	–	1 (Vol. 14)	Drug related (lithium)
Polyuria	–	1 (Vol. 5)	Drug related (lithium)
Subclinical hypothyroidism	1 (Vol. 5)	–	Drug related (lithium)
Flatulence	–	1 (Vol. 10)	Drug related (meloxicam)
Pressure in the upper abdominal region	–	1 (Vol. 10)	Drug related (meloxicam)

depleted volunteers [28]. A yet unpublished study [29] indicated a 17% elevation of the lithium AUC during concomitant celecoxib treatment.

The clinical relevance of any elevation of lithium concentration is also dependent on the individual as there is interpatient variation in the baseline concentration of lithium after a standard dose and in susceptibility to lithium toxicity. Interindividual variation in the effect of meloxicam coadministration on lithium plasma levels was evident in this study and has been observed in studies with other NSAIDs. For example, naproxen (750 mg day⁻¹) increased lithium concentrations by on average 16%, but this ranged from 0 to 41.9% in individuals [8]. Case studies of lithium toxicity after NSAID coadministration have been reported, including several reports of interactions with piroxicam [30–33]. In one case, a 64-year-old man on lithium carbonate (1000 mg), with a serum lithium level within the therapeutic range (0.5–1.2 mmol l⁻¹), was prescribed piroxicam (20 mg) for OA of the knee. Four months later he was admitted to hospital with ataxia, muscle twitching, poor limb coordination, slurred speech and confusion. Lithium toxicity was diagnosed and his serum lithium level was found to be 2.4 mmol l⁻¹ [32]. The reported elevations in lithium concentrations in these case studies were generally high compared with the therapeutic range of 0.6–1.5 mmol l⁻¹ [2, 4, 5]. For example, an elevation in serum lithium levels from 0.99 mmol l⁻¹ to 2.84 mmol l⁻¹ followed administration of ibuprofen (1200 mg) [34].

Moderate toxicity, roughly correlated with serum lithium concentrations of 2.0–2.5 mmol l⁻¹, includes confusion, dysarthria, nystagmus, ataxia, myoclonic twitches and ECG changes [5]. The reported adverse events in this study are those commonly observed with either lithium or meloxicam when given alone. Increases in body weight, hypothyroidism, polyuria and thirst are well known adverse events of lithium treatment [1]. Flatulence and pressure in the upper abdominal region were reported with coadministration of meloxicam.

In conclusion, meloxicam 15 mg, the highest recommended dose (e.g. for rheumatoid arthritis), increases the plasma concentration of lithium by a magnitude that is thought to be of low clinical relevance. In addition, it would be expected that the lower meloxicam dose of 7.5 mg (recommended as the starting dose for osteoarthritis) would result in a smaller interaction with lithium. Nevertheless, plasma concentrations of lithium should be closely monitored in patients receiving both meloxicam and lithium due to the narrow therapeutic range of lithium. It should also be noted that any additional treatments that a patient might be taking could affect the interaction results. In addition, this study was only conducted on a small number of healthy volunteers, and

does not rule out clinically relevant interactions occurring in the general population.

References

- 1 Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med* 1994; **331**: 591–598.
- 2 Ward ME, Musa MN, Bailey L. Clinical pharmacokinetics of lithium. *J Clin Pharmacol* 1994; **34**: 280.
- 3 Thornhill DP. The biological disposition and kinetics of lithium. *Biopharm Drug Dispos* 1981; **2**: 305–322.
- 4 Goodnick PJ, Fieve RR, Meltzer HL, Dunner DL. Lithium elimination half-life and duration of therapy. *Clin Pharmacol Ther* 1981; **29**: 47–50.
- 5 Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin Pharmacokin* 1995; **29**: 172–191.
- 6 Reimann IW, Frölich JC. Effects of diclofenac on lithium kinetics. *Clin Pharmacol Ther* 1981; **30**: 348–352.
- 7 Reimann IW, Diener U, Frölich JC. Indomethacin but not aspirin increases plasma lithium ion levels. *Arch Gen Psychiatry* 1983; **40**: 283–286.
- 8 Ragheb M, Powell AL. Lithium interaction with sulindac and naproxen. *J Clin Psychopharmacol* 1986; **6**: 150–154.
- 9 Kristoff CA, Hayes PE, Barr WH, Small RE, Townsend RJ, Ettigi PG. Effect of ibuprofen on lithium plasma and red blood cell concentrations. *Clin Pharm* 1986; **5**: 51–55.
- 10 Ragheb M. Ibuprofen can increase serum lithium levels in lithium-treated patients. *J Clin Psychiatry* 1987; **48**: 161–163.
- 11 Hughes BM, Small RE, Brink D, McKenzie ND. The effect of flurbiprofen on steady-state plasma lithium levels. *Pharmacotherapy* 1997; **17**: 113–120.
- 12 Cold JA, ZumBrunnen TL, Simpson MA, Augustin BG, Awad E, Jann MW. Increased lithium serum and red blood cell concentrations during ketorolac coadministration. *J Clin Psychopharmacol* 1998; **18**: 33–37.
- 13 Frölich JC, Leftwich R, Ragheb M, Oates JA, Reimann I, Buchanan D. Indomethacin increases plasma lithium. *Br Med J* 1979; **1**: 1115–1116.
- 14 Ravic M, Salas-Herrera I, Johnston A, Turner P, Foley K, Rosenow D. Influence of lornoxicam a new non-steroidal anti-inflammatory drug on lithium pharmacokinetics. *Human Psychopharmacol* 1993; **8**: 289–292.
- 15 Apseloff G, Wilner KD, Von Deutsch DA, Gerber N. Tenidap sodium decreases renal clearance and increases steady-state concentrations of lithium in healthy volunteers. *Br J Clin Pharmacol* 1995; **39**: 25–28.
- 16 Aronoff GR. Therapeutic implications associated with renal studies of nabumetone. *J Rheumatol* 1992; **19** (Suppl 36): 25–31.
- 17 Harris RC, McKenna JA, Akai Y, Jacobson HR, Dubois RN, Breyer MD. Cyclooxygenase-2 is associated with the macula densa of rat kidney and increases with salt restriction. *J Clin Invest* 1994; **94**: 2504–2510.
- 18 Churchill L, Graham AG, Shih C-K, *et al.* Selective inhibition of human cyclo-oxygenase-2 by meloxicam. *Inflammopharmacol* 1996; **4**: 125–135.
- 19 Stichtenoth DO, Wagner B, Frölich JC. Effects of meloxicam and indomethacin on cyclooxygenase pathways in healthy volunteers. *J Invest Med* 1997; **45**: 44–49.
- 20 Patrignani P, Panara MR, Santini G, *et al.* Differential

- inhibition of the cyclooxygenase activity of prostaglandin endoperoxidase synthase isozymes *in vitro* and *ex vivo* in man. *Prostaglandins Leukot Essent Fatty Acids* 1996; **55** (Suppl 1): abs P115.
- 21 Barner A. Review of clinical trials and benefit/risk ratio of meloxicam. *Scand J Rheumatol* 1996; **25** (Suppl 102): 29–37.
- 22 Distel M, Mueller C, Bluhmki E, Fries J. Safety of meloxicam: a global analysis of clinical trials. *Br J Rheumatol* 1996; **35** (Suppl 1): 68–77.
- 23 Dequeker J, Hawkey C, Kahan A, Steinbrück K, Alegre C, Baumelou E. Improvement in gastrointestinal tolerability of the selective COX-2 inhibitor, meloxicam, compared with piroxicam: results of the safety and efficacy large scale evaluation of COX inhibiting therapies (SELECT) trial in osteoarthritis. *Br J Rheumatol* 1998; **37**: 946–951.
- 24 Hawkey C, Kahan A, Steinbrück K, Alegre C, Baumelou E, Bégaud B. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. *Br J Rheumatol* 1998; **37**: 937–945.
- 25 Steinijans VW, Hartmann M, Huber R, Redke HW. Lack of pharmacokinetic interactions as an equivalence approach. *Int J Clin Pharmacol Ther Toxicol* 1991; **29**: 323–328.
- 26 Schuirman DJ. A comparison of the two-one sided tests procedure and the power approach for assessing the bioequivalence of average bioequivalence. *J Pharmacokin Biopharm* year?; **15**: 657–680.
- 27 Türk D, Busch U, Heinzel G, Narjes H. Clinical pharmacokinetics of meloxicam. *Arzneim -Forsch* 1997; **47**: 253–258.
- 28 Rossat J, Maillard M, Nussberger J, Brunner HR, Burnier M. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt depleted subjects. *Clin Pharmacol Ther* 1999; **66**: 76–84.
- 29 Lee Su-Chih. Celebrex (celecoxib) capsules. NDA 20998: Clinical pharmacology / biopharmaceutics review, page 41. (<http://www.fda.gov/cder/foi/nda/98/20998.htm>), 1999.
- 30 Harrison TM, Davies DW, Norris CM. Lithium carbonate and piroxicam. *Br J Psychiatry* 1986; **149**: 124–125.
- 31 Kerry RJ, Owen G, Michaelson S. Possible toxic interaction between lithium and piroxicam. *Lancet* 1983; **i**: 418–419.
- 32 Nadarajah J, Stein GS. Piroxicam induced lithium toxicity. *Ann Rheum Dis* 1985; **44**: 502.
- 33 Waldbridge DG, Bazire SR. An interaction between lithium carbonate and piroxicam presenting as lithium toxicity. *Br J Psychiatry* 1985; **147**: 206–207.
- 34 Bailey EC, Stewart JT, McElroy RA. Ibuprofen-induced lithium toxicity. *South Med J* 1989; **82**: 1197.