Lithium Interaction With the Cyclooxygenase 2 Inhibitors Rofecoxib and Celecoxib and Other Nonsteroidal Anti-Inflammatory Drugs

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to increase serum lithium concentrations. We sought to determine whether NSAIDs that selectively inhibit cyclooxygenase (COX) 2 also elevate serum lithium concentrations.

Method: The U.S. Food and Drug Administration's Adverse Event Reporting System (AERS) database was searched in January 2003 for reports of interactions between lithium and rofecoxib or celecoxib, the selective COX-2 inhibitors marketed in the United States. Additionally, a literature search was performed using PubMed with the MeSH terms *anti-inflammatory agents, nonsteroidal* and *lithium*. Reports of interactions between NSAIDs and lithium were selected for review based on titles of retrieved citations.

Results: Eighteen cases of increased serum lithium concentrations after the addition of one of the COX-2 inhibitors to stable lithium therapy were retrieved from AERS, 13 with rofecoxib and 5 with celecoxib. Serum lithium concentration increases of up to 99% and 448% with concomitant celecoxib and rofecoxib use, respectively, were reported. Thirty-six English-language literature articles report interactions between lithium and various NSAIDs. Although some articles report no effect or decreased serum lithium concentrations with concomitant aspirin or sulindac, increased serum lithium concentration reports exist for aspirin, sulindac, and 14 other NSAIDs, including celecoxib and rofecoxib.

Conclusion: Clinicians should consider NSAID use in the differential diagnosis of lithium toxicity, monitor patients' serum lithium concentrations during the initiation or discontinuation of NSAID therapy, and be aware that the selective COX-2 inhibitors can increase serum lithium concentrations leading to toxicity.

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Lithium toxicity in patients receiving various nonsteroidal anti-inflammatory drugs (NSAIDs) has been reported in the medical literature. Also, small pharmacokinetic studies have demonstrated increased serum lithium concentrations with concomitant use of some NSAIDs. These interactions are of clinical significance because lithium toxicity is closely related to serum lithium concentration and can occur at concentrations that are close to therapeutic.[1] We report the U.S. Food and Drug Administration (FDA)'s postmarketing experience with lithium concentrations in patients treated with 2 new NSAIDs, the selective cyclooxygenase 2 (COX-2) inhibitors rofecoxib and celecoxib, and we review the English-language literature on lithium-NSAID interaction.

METHOD

In order to investigate any possible interaction between lithium and the COX-2 NSAIDs, the FDA's Adverse Event Reporting System (AERS) database (Rockville, Md.) was searched in January 2003 for reports of adverse events occurring in patients taking both lithium and either rofecoxib or celecoxib. AERS contains adverse event reports submitted directly by clinicians and patients to the FDA through the MedWatch system, and by drug manufacturers as required by law.[2] All reporting is ultimately voluntary and spontaneous, as neither patients nor health care professionals are required to report either to the FDA or to the manufacturer any adverse events suspected to be related to drug products. Because reporting is

Table 1. Celecoxib/Lithium Interaction: Cases From the U.S. Food and Drug Administration's Adverse Event Reporting System

Demographics, Baseline Lithium Dose, Concentration, Duration	Celecoxib Dose and Duration	Lithium Concentration, % Increase With Celecoxib	Symptoms	Treatment and Outcome
Female, 53 y 1350 mg/d Concentration unknown Duration unknown	Dose unknown Duration 3 mo as needed, 1 wk regular dosing	2.47 mEq/L	Nausea, vomiting, tremor, weakness	Hospitalize, interrupt lithium, discontinue celecoxib. Resume lithium at 1350 mg/d. Recovered.
Female, 59 y 450 mg/d "Normal" concentration 1.2 (no units) Duration 13 y	200 mg/d for 1 to 6 mo (duration unclear)	2.1 (no units) 75% increase	Ataxia, dysarthria, tremors	Interrupt lithium, discontinue celecoxib. Resume lithium at 450 mg/d. Final lithium concentration 0.8 (no units).
Male, 51 y 1200 mg/d for 3 mo preceding celecoxib use Concentration 1.33 (no units) 8 mo total lithium use	400 mg/d for 10 d	2.65 (no units) 99% increase	Lethargy	Hospitalize, interrupt lithium, discontinue celecoxib. Resume lithium at 1200 mg/d. Final lithium concentration 1.16 (no units).
Male, 38 y 900 mg/d Concentration 0.9 mmol/L Duration unknown	200 mg/d for 1 mo to event onset	1.4 mmol/L 56% increase	Tremors, upset stomach, flu-like symptoms	Lithium reduced to 600 mg/d. Final lithium concentration 0.7 mmol/L. Unclear if celecoxib was continued. Recovered.
Female, 58 y Dose unknown Concentration unknown Duration unknown	800 mg/d for 8 d (prescribed 200 mg/d)	"High"	Abdominal pain, vomiting, dizziness, low blood pressure, trouble breathing	Hospitalize, dialyze, discontinue celecoxib. Recovered with unspecified sequelae.

voluntary, only a small fraction of actual adverse drug events are reported to the FDA. Also, unless the reporter can be reached for additional information, reports often lack information required for complete analysis, such as data on concomitant drug use or medical history. However, in spite of its limitations, AERS remains a first-line tool for identifying previously unknown adverse drug events. AERS reports are not readily available to the public, but redacted copies may be requested through the FDA's Freedom of Information office found on the FDA Web site (http://www.fda.gov/opacom/backgrounders/foiahand.html).

PubMed was searched on January 14, 2003, using the MeSH terms *anti-inflammatory agents*, *nonsteroidal* and *lithium*. English-language case reports or studies concerning interactions between lithium and NSAIDs were retrieved based on a review of titles of all citations identified by the search. Appropriate references used in selected papers were also reviewed. PubMed was also searched separately for reports of interactions between lithium and the COX-2 inhibitors.

RESULTS

FDA Postmarketing Adverse Event Reporting System Database Review

Eighteen cases of increased serum lithium concentrations after the addition of one of the COX-2 inhibitors to stable lithium therapy were retrieved from the AERS, 13 with rofecoxib and 5 with celecoxib. Because serum lithium concentrations that were stable increased after the addition of one of the COX-2 inhibitors, a possible association between the NSAID and the serum lithium concentration increase is suggested. In 3 of the celecoxib and 2 of the rofecoxib cases, serum lithium concentrations returned to baseline after the NSAID was discontinued and lithium dosing was resumed at baseline dosing, thus strengthening the association. In the celecoxib cases, serum lithium concentration increases ranged from 56% to 99% and reported adverse events included tremor, nausea, vomiting, upset stomach, weakness, ataxia, dysarthria, lethargy, and flu-like symptoms. In the rofecoxib cases, serum lithium concentration increases ranged from 58% to 448% and reported adverse events included tremor, sedation, increased muscle tone, ataxia, confusion, asterixis, disorientation, nystagmus, right-sided weakness, renal insufficiency, and slurred speech. Among 17 cases that included outcomes, 15 patients recovered, 11 with discontinuation of the NSAID or reduction in lithium dosage, 2 with discontinuation of lithium, and 2 with unspecified treatment. The 2 remaining outcomes were ongoing ataxia and unspecified sequelae. See Tables 1 and 2 for more information on each case.

Literature Review

The published cases and studies show great variability in serum lithium concentration changes in different patients and with different NSAIDs. For example, serum lithium concentration changes ranged from an increase of 9% to a decrease of 59% in a study of 16 healthy male

Table 2. Rofecoxib/Lithium Interaction: Cases From the U.S. Food and Drug Administration's Adverse Event Reporting System

Demographics, Baseline Lithium Dose, Concentration, Duration	Rofecoxib Dose, Duration	Lithium Concentration, % Increase With Rofecoxib	Symptoms	Treatment and Outcome
Elderly female 900 mg/day Concentration unknown Duration "for years"	25 mg/d for about 3 mo to diagnosis of interaction, symptoms sooner	3 times normal 200% increase	Confusion, disorientation, ataxia CAT scan, sugar, renal function, electrolytes all normal	Hospitalize, dialyze, interrupt lithium, discontinue rofecoxib. Resume lithium at 900 mg/d. Recovered.
Female, 72 y 900 mg/d Concentration unknown Duration 20 y	25 mg/d for about 2.5 mo to diagnosis of interaction, symptoms sooner	3.32 mmol/L	Nystagmus, ataxia, asterixis SCr 1.2, BUN 20, Na 138	Hospitalize, dialyze, discontinue lithium and rofecoxib. Ataxia continued.
Female, 62 y 900 mg/d Concentration 0.6 to 0.8 (no units) On 600 to 900 mg/d for over 10 y	25 mg/d for about 2 wk	1.7 (no units) 112% increase	Confusion. Also diagnosed with urinary tract infection	Hospitalize, discontinue rofecoxib, reduce lithium to 600 mg/d. Final lithium concentration 0.7 (no units).
Male, 58 y 600 mg/d Concentration 0.5 mEq/L Duration unknown	Dose unknown Duration 9 d	2.74 mEq/L 448% increase	"Lithium neurotoxicity"	Hospitalize, specific treatment unknown. Recovered.
Female Dose unknown Concentration 1.7 (no units) Duration unknown	25 mg/d for less than 2 wk	3.6 (no units) 112% increase	Unknown	Hospitalize. Outcome unknown.
Female Dose unknown Concentration unknown Duration unknown	"Shortly"	"Toxic levels"	Unknown	Treatment unknown. Recovered.
Female, 67 y 600 mg/d Concentration unknown Duration 9 y	40 mg/d for about 2 wk	1.6 (no units)	Slurred speech, right-sided weakness, renal insufficiency, SCr 3.8, Ca++ 16.8, lactic acid 2.2	Hospitalize, discontinue rofecoxib, reduce lithium to 300 mg/d. Kidney cell tumor diagnosed, resected. Recovered.
Female, 69 y Alternating 1200 mg/d and 900 mg/d Duration unknown Concentration unknown	Dosage unknown Duration unknown	3.0 (no units)	Aphasia, unsteady gait, tremor, disorientation, SCr 1.4, BUN 22, Na+ 138	Hospitalize, administer intravenous normal saline, discontinue lithium. Recovered.
Female, 56 y Dose unknown Concentration unknown Duration unknown	Dosage unknown Duration unknown	"Increased"	Unknown	Discontinue rofecoxib. Lithium concentrations return to "normal."
Female, 91 y 450 mg/d Concentration 1.4 (no units) Duration unknown	Dosage unknown Duration less than 1 mo	3.0 (no units) 107% increase	Slurred speech, delirium, sedation	Hospitalize, discontinue lithium. Recovered.
Female, 57 y 600 mg/d Concentration "stable" Duration unknown	50 mg/d for 20 d	2.4 (no units)	Tremor, vomiting, double vision	Discontinue rofecoxib. Recovering.
Female, 71 y 600 mg/d Concentration 1.2 mmol/L Duration unknown	25 mg/d for 6 d	1.9 mmol/L 58% increase	Increased muscle tone, myoclonus, gait abnormality, mood changes, apathy	Intravenous fluids, discontinue rofecoxib. (Already hospitalized.) Recovered.
Female, 81 y 42 mg/d Concentration unknown Duration unknown	25 mg/d for 24 d	1.6 mmol/L	Rigidity, tremor, decreased consciousness, renal failure (SCr 265 micromol/L)	Hospitalize, discontinue rofecoxib and lithium. Recovered.

subjects when meloxicam was discontinued after stabilizing subjects on both meloxicam and lithium.[3] Similarly, increases in serum lithium concentrations of 26%[4] to 280%[5] have been reported with concomitant piroxicam use. One study looked at change in peak serum lithium concentration after lornoxicam discontinuation in 12 healthy volunteers stabilized on both lornoxicam and lithium.[6] The group mean serum lithium concentration decreased 17%, but in one patient who exhibited peak lornoxicam concentrations, 3 times that of the group mean, serum lithium concentration decreased 38%.[6]

Changes in serum lithium concentration following addition or discontinuation of concomitant NSAID use in 36 English-language literature reports are summarized in Table 3. Table 3 presents the range of lithium concentration changes in individuals rather than change in group mean, when possible, to illustrate the interindividual differences in response to concomitant lithium and NSAID use. Reported toxicities are consistent with the known toxic effects of lithium. One study published in abstract form was omitted because single-dose lithium was used and the results may not be comparable to those found with steady-state lithium.[29]

Reports for most NSAIDS indicate an increase in serum lithium concentration with addition of an NSAID or a decrease in serum lithium concentration with NSAID discontinuation. However, the reported effects of aspirin and sulindac on serum lithium concentrations are inconsistent in the literature. Studies exploring an aspirin/lithium interaction in 11 healthy female volunteers aged 22 to 46 years[30,31] and 1 female and 6 male psychiatric inpatients aged 56 to 62 years[32] found no significant changes in serum lithium concentration when aspirin was added to lithium therapy. However, a pilot study in one patient, a 43-year-old healthy man, found a 32% increase in serum lithium concentration with aspirin addition.[33] Similarly, the literature contains conflicting evidence regarding a sulindac/lithium interaction. Three cases, one each in a 50-year-old man,[34] a 60-year-old woman,[34] and a 67-year-old woman,[35] and one study in 6 male psychiatric inpatients aged 53 to 62 years[36] found no significant changes in serum lithium concentrations when sulindac was added to lithium therapy. In fact, in the 50-year-old man and 60-year-old woman, serum lithium concentrations initially decreased with sulindac addition.[34] In contrast, in 2 cases, one each in a 23-year-old man and a 27-year-old woman, serum lithium concentrations increased 100% and 89%, respectively, with sulindac addition to stable lithium therapy.[37]

Reports of lithium interactions with the COX-2 inhibitors are beginning to appear in the literature. One published case reports a 130% increase in serum lithium concentration in a 64-year-old woman after celecoxib addition.[38] Another case reports a 67% increase in serum lithium concentration when rofecoxib was prescribed to a 73-year-old man.[39] Both of these patients exhibited lithium toxicity in the form of confusion, tremor, and gait disturbances. A study in 10 patients on lithium therapy found that rofecoxib addition increased serum lithium concentration in 9 patients and that the increase was highly statistically correlated with baseline lithium concentration[40]; that is, patients with higher baseline concentrations had greater increases. Serum lithium concentrations were not reported.

The manufacturer explored the effect of celecoxib on serum lithium concentrations in a pharmacokinetic study that was submitted to the FDA during regulatory review of celecoxib. The random crossover, 3-arm study in 24 healthy volunteers included 7 days in each of 3 treatments: lithium, 450 mg twice a day, with celecoxib, 200 mg twice a day; lithium, 450 mg twice a day; and celecoxib, 200 mg twice a day. Group mean serum lithium concentration was increased by 15.9% (p value $< .05$, 90% confidence interval = 8.6% to 23.6%) during concomitant celecoxib use. Although the study data are proprietary information, not releasable outside the FDA, the review of this study is available on the approved drug products page of the FDA Web site (www.FDA.gov).[41]

DISCUSSION

Reports of interactions between the new COX-2–selective NSAIDs and lithium are beginning to appear in the medical literature and in FDA's postmarketing AERS database. Serum lithium concentrations in the cases reported to the FDA increased up to 99% and 448% with the addition of celecoxib and rofecoxib, respectively, to stable lithium therapy. Because of the popularity of these new NSAIDs and the narrow therapeutic window of lithium, it is important that prescribers and patients be aware of this interaction.

Although 1 unpublished pharmacokinetic study of the interaction between celecoxib and lithium in 24 subjects showed the group mean serum lithium concentration to increase by only 15.9%,[41] some patients, of course, may experience changes in serum lithium concentration greater than the mean value observed in this trial. Indeed, the AERS cases show interindividual differences in the magnitude of serum lithium concentration changes with concomitant celecoxib use. Serum lithium concentration changes ranged from 56% to 99% in the 3 AERS cases that include baseline concentrations, and one published case reported an increase of 133% in serum lithium concentration with celecoxib use.[38] This interindividual variability in the magnitude of increase in serum lithium concentration with concomitant NSAID use is also seen in the AERS data for rofecoxib and literature data for other NSAIDs.

The exact mechanism for the interaction between NSAIDs and lithium is not known. Over 95% of lithium is

Table 3. Published Reports of Lithium Concentration Changes With Changes in Nonsteroidal Anti-Inflammatory Drug (NSAID) Therapy[a]

NSAID	References	N	Change in Blood Lithium Concentration in mEq/L With Addition or Discontinuation, if Specified, of NSAID[b]	Reported Symptoms
Aspirin	Four studies[30,31,32,33]	19	Group means changed insignificantly (N = 18)[30,31,32]; increased 32% (0.41 to 0.54; N = 1)[33]	Weight loss possibly due to sodium restriction[30]
Celecoxib	One case[38]	1	Increased 133% (0.6 to 1.39; N = 1)[38]	Tremor, confusion, gait disturbance, nystagmus, serum creatinine increased[38]
Diclofenac	One study[8] One case[9]	6	Group mean increased 24.9% ± 3.6% (0.6 to 0.8; N = 5)[8]; increased 86% (0.7 to 1.3; N = 1)[9]	Weight loss possibly due to sodium restriction,[8] tremor,[9] disturbed consciousness,[9] EEG abnormalities,[9] myclonus[9]
Flurbiprofen	One study[10]	11	Group mean increased 18.6% (0.43 to 0.51; N = 11)[10]	None
Ibuprofen	Two studies[11,12] Three cases[13,14,15]	23	Unquantified increase (N = 1)[13]; increased 4.2%–27.3% (0.71 to 0.74 and 0.73 to 0.93; N = 11)[11]; increased 187% (0.99 to 2.84; N = 1)[14]; increased 12%–66.5% (values not available; N = 9)[12]; decreased 43% when discontinue NSAID (0.7 to 0.4; N = 1)[15]	Anorexia,[14] ataxia,[13] blood urea nitrogen (BUN) increased,[12] confusion,[13] drowsiness,[11,12] fatigue,[11] light-headedness,[11] serum creatinine increased,[12,13] hyperreflexia,[14] nausea,[14] stupor,[13] tremor,[12,14,15] unsteadiness[15]
Indomethacin	Three studies[16,17,30] One case[18]	20	Group mean increased 59% in manic patients (values not available; N = 3) and 30% in healthy volunteers (values not available; N = 4)[16]; increased 150% (1.4 to 3.5; N = 1)[18]; group mean increased 40% (0.60 to 0.84; N = 5)[30]; group mean increased 20% (0.132 to 0.158) during high Na+ diet, increased 26% (0.144 to 0.182) during low Na+ diet (N = 7)[17]	BUN increased,[18] confusion,[18] serum creatinine increased,[18] dysarthria,[18] restlessness,[18] sweating,[18] tremor,[18] weight loss possibly due to sodium restriction[17,30]
Ketorolac	One study[19] Two cases[20,21]	7	Group mean increased 29% (0.76 to 0.98; N = 5)[19]; increased 50% (0.6 to 0.9; N = 1)[20]; increased 57% (0.5 to 0.7; N = 1)[21]	Serum creatinine increased,[21] dysarthria,[20] facial masking,[20] nausea,[21] tremor,[20] vomiting[21]
Lornoxicam	One study[6]	12	Group mean decreased 17% (0.66 ± 0.18 to 0.55 ± 0.10) when discontinue NSAID (N = 12)[6]; decreased 38% (1.11 to 0.69) in patient with high NSAID concentration (N = 1)[6]	None reported
Mefenamic acid	Two cases[22,23]	2	Increased 300% (0.4 to 1.7; N = 1)[22]; unquantified increase (N = 1)[23]	Ataxia,[23] serum creatinine increased,[22] disorientation,[23] dysarthria[23]
Meloxicam	One study[3]	16	Change ranged from increase 9% to decrease 59% when discontinue NSAID (values not available; N = 16)[3]	Not specified
Naproxen	Two studies[24,36]	16	Increased 0%–50% (0.2 to 0.3; N = 9)[24]; increased 0%–41.9% (values not available; N = 7)[30]	Depression,[30] polydipsia,[30] polyuria,[30] staggering,[30] tremor[30]
Phenylbutazone	One study[25]	5	Increased 0%–15.35% (values not available; N = 5)[25]	Confusion,[25] disorientation,[25] drowsiness,[25] paranoid delusions[25]
Piroxicam	Five cases[4,5,15,26,27]	5	Increased 26% (0.7 to 1.18; N = 1)[4]; increased 280% (0.75 to 2.85; N = 1)[5, c]; increased 100% (1.2 to 2.4; N = 1)[27, d]; increased 50% (1.0 to 1.5; N = 1)[26]; increased 92% (0.6 to 1.15; N = 1)[15]	Agitation, ataxia,[4,27] BUN increased,[27] confusion,[4,26,27] incoordination,[27] serum creatinine increased,[27] slurred speech,[27] trembling,[26] tremor,[4] unsteadiness[26]
Rofecoxib	One study[40] One case[39]	11	Increased (values not available; N = 9)[40]; no significant change (values not available; N = 1)[40]; increased 67% (0.9 to 1.5)[39]	Tremor,[39] confusion,[39] somnolence,[39] gait disturbance,[39] serum creatinine increased[39]
Sulindac	One study[36] Five cases[37,34,35]	11	Group mean changed insignificantly (N = 6)[36]; increased 89% and 100% (0.9 to 1.7 and 1.0 to 2.0; N = 2)[37]; temporary decreases of 39% (0.65 to 0.39) and 51% (0.53 to 0.26) with return to baseline level with continued NSAID use (N = 2)[34, e]; increased 40% (0.5 to 0.7) dropping to 20% (0.6) with continued NSAID use (N = 1)[35]	Depression,[36] drowsiness,[36] polyuria,[36] restlessness,[37] tremors[36, 37]
Tiaprofenic acid	One case[28]	1	Increased 80% (0.36 to 0.65; N = 1)[28]	Serum creatinine increased[28]

[a]NSAID dosages were within the recommended therapeutic ranges contained in product labeling or in Drug Facts and Comparisons[7] unless otherwise noted.
[b]Range is given when available to demonstrate interindividual variation range.
[c]62-year-old female began treatment for urinary tract infection the day after serum lithium concentration measurement.
[d]Patient received 40 mg/day of piroxicam (20 mg/day recommended).
[e]One patient received 200 mg/day of sulindac (300 to 400 mg/day recommended).

excreted through the kidneys by glomerular filtration and about 80% is reabsorbed in the proximal tubules.[42] Thus, any factor that influences either glomerular filtration or tubular reabsorption might affect serum lithium concentrations. NSAIDs can affect both of these processes, presumably through inhibition of renal prostaglandin synthesis, as demonstrated by NSAID-mediated decreased renal blood flow and increased sodium reabsorption.[43] However, differences in inhibition of these processes by different NSAIDs do not correlate with differences in renal prostaglandin synthesis inhibition or in lithium retention effects. For example, aspirin inhibits renal prostaglandin synthesis comparably to other NSAIDs,[30] yet shows variable effects on serum lithium concentrations.[30,33] A study comparing the effects of 3-hour intravenous infusions of aspirin (acetylsalicylic acid) and of sodium salicylate on renal prostaglandin E_2 synthesis and on lithium clearance found sodium salicylate to inhibit lithium clearance but not renal prostaglandin E_2 synthesis; and, conversely, aspirin inhibited renal prostaglandin E_2 synthesis but not lithium clearance.[31] Similarly, a 2-week, 3-arm study of rofecoxib's renal effects compared to indomethacin and placebo in a total of 36 healthy elderly adults on sodium-controlled diets found an early transient increase in sodium retention and no depression of glomerular filtration rate (GFR) with rofecoxib.[44] In spite of rofecoxib's lack of effect on the pertinent renal processes in this small study, rofecoxib is associated with substantial increases in serum lithium concentrations in the AERS cases. Also, a recent review article states that effects of sulindac, an NSAID that may be renal-sparing due to its metabolic characteristics, on renal blood flow and renal prostaglandin synthesis are the same as those of comparator NSAIDs in some studies and negligible in other studies.[43]

Thus, all data do not support the hypothesis that NSAIDs reduce lithium clearance by renal prostaglandin synthesis inhibition, which in turn leads to decreased renal blood flow and increased tubular reabsorption. The differing results in various studies of NSAID renal effects and the wide range in serum lithium concentration changes with NSAID use in individual patients suggest as yet unidentified patient differences in renal effects of NSAIDs or in lithium disposition. The variety of reports included in this review represents different patient populations, different concomitant disease states and drugs, different lithium and NSAID dosages, different dietary compositions, and different compliance levels; that is, the variety of reports represents real-world drug use conditions. Therefore, until greater understanding is reached, it must be assumed for patient safety, based on the available evidence, that any NSAID has the potential to increase serum lithium concentration in any particular patient.

The narrow therapeutic window and potentially serious outcomes from lithium toxicity argue for care in lithium dosing and careful monitoring during the initiation or discontinuation of regular NSAID use. Accordingly, we recommend that clinicians consider NSAID use in the differential diagnosis of lithium toxicity; monitor patients, including their serum lithium concentrations, during the initiation or discontinuation of NSAID therapy; and be aware that the selective COX-2 inhibitors, like other NSAIDs, can increase serum lithium concentrations, which may lead to toxicity.

Drug names: celecoxib (Celebrex), diclofenac (Cataflam and others), flurbiprofen (Ansaid and others), ibuprofen (Motrin, Ibu, and others), indomethacin (Indocin and others), ketorolac (Toradol, Acular, and others), lithium (Eskalith, Lithobid, and others), mefenamic acid (Ponstel), meloxicam (Mobic), naproxen (Naprosyn), piroxicam (Feldene and others), rofecoxib (Vioxx), sulindac (Clinoril and others).

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