# Sparing Effect of Sulindac on Lithium Levels

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Lithium is a monovalent cation useful in the treatment of manic-depressive disorders. It is readily absorbed from the gastrointestinal tract, is not metabolized, and is excreted almost entirely in the urine. Lithium is filtered by the glomeruli with 80% reabsorbed in the proximal renal tubules.[1] Lithium clearance has been shown to be markedly diminished by the administration of various nonsteroidal anti-inflammatory drugs (NSAIDs). Indomethacin has been shown to decrease lithium excretion by 23% with a subsequent 40% to 59% rise in steady-state plasma lithium levels.[2,3] Similar effects have also been noted following ibuprofen, naproxen, ketoprofen, mefenamic acid, phenylbutazone, piroxicam, and diclofenac therapy.[4–12] The interaction has not yet been reported following the use of aspirin, fenoprofen, tolmetin, and carprofen.

The effect of sulindac on lithium therapy has been studied in only six patients ranging in age from 50 to 60 years.[13,14] In these cases sulindac failed to elevate lithium levels; in fact, in two patients lithium levels fell within the first week of sulindac therapy and returned to previous serum levels within 2 months.[14] To further monitor this interaction and to determine whether this fall in lithium levels following sulindac initiation could be replicated, lithium levels were studied in a 67-year-old woman treated with sulindac over a 2-month period.

## CASE REPORT

A 67-year-old woman with a history of schizoaffective disorder received 300 mg of lithium carbonate twice daily, 25 mg of thioridazine twice daily, and 0.5 mg of lorazepam twice daily while under the care of a psychiatrist. She began to experience mild arthritis in 1970, for which she first sought treatment at another institution in 1976. At that time ibuprofen was prescribed but did not provide relief. What effect, if any, ibuprofen had on her lithium levels is not known.

In June 1988 she sought treatment at the Baylor College of Medicine Family Medicine Clinic for her mild, nondisabling arthritis, which primarily affected her right shoulder. A trough steady-state lithium level was obtained at 0.5 mmol/L (mEq/L) (therapeutic range 0.6 to 1.2 mmol/L). Her hematocrit was 0.42 (normal 0.33 to 0.46) and her hemoglobin level was 145 g/L (14.5 g/dL) (normal 110 to 155 g/L). She had no proteinuria, and her serum creatinine level was 88 μmol/L (1 mg/dL) (normal 62 to 159 μmol/L, 0.7 to 1.8 mg/dL). Sulindac therapy was instituted 1 week later at 150 mg twice daily. One week later the lithium level was 0.7 mmol/L (mEq/L). After 3 weeks of compliance with the sulindac therapy, the lithium level remained +0.7 mmol/L (mEq/L). At the end of 2 months of treatment, the lithium level had decreased slightly to 0.6 mmol/L (mEq/L) (Figure 1). At this time her hematocrit was 0.40 and her hemoglobin was 138 g/L (13.8 g/dL). Her serum creatinine level was 80 μmol/L (0.9 mg/dL). Her psychiatric symptoms remained under control, but because of dizziness and lack of marked benefit, sulindac was discontinued. The patient was instructed that aspirin, but not ibuprofen, obtained over the counter may afford relief without affecting her lithium levels.

## DISCUSSION

NSAID therapy concurrent with lithium therapy has resulted in elevation of lithium levels and, in some cases, toxicity.[4–12] Reduced prostaglandin synthesis following NSAID therapy is associated with diminished renal blood flow with consequent decreased glomerular filtration. As this route of excretion for lithium is primary, accumulation to potentially toxic levels may occur. Inhibition of renal prostaglandins may also increase proximal sodium reabsorption with attendant enhanced lithium reabsorption.[8]

Sulindac is metabolized intrarenally to its inactive forms, sulindac sulfoxide and sulindac sulfone, which therefore should spare intrarenal cyclooxygenase. Whereas indomethacin reduces renal prostaglandin synthesis by more than 50%, sulindac has been shown to spare renal

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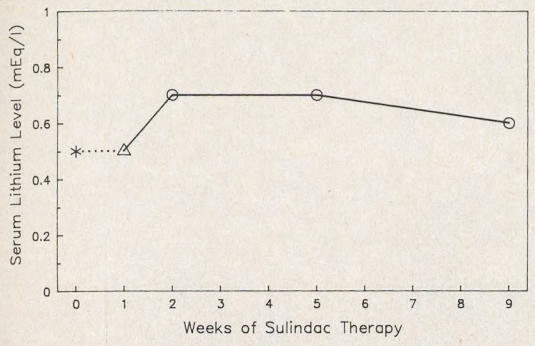


**Figure 1. Effect of sulindac therapy on lithium levels. (Asterisk refers to administration of lithium carbonate, 300 mg twice daily; triangle marks beginning of sulindac therapy, 150 mg twice daily.)**

prostaglandin synthesis.[15–17] Because of the renal-sparing effect of sulindac, it was presumed that sulindac would also not affect renal excretion of lithium.

Lithium levels have been reported in only six patients to date who received sulindac therapy concurrently. In four patients sulindac failed to affect lithium levels.[13] In two patients lithium levels fell during the first week following sulindac therapy but returned to baseline within 2 months.[14] Lithium levels dropped from 0.65 mmol/L (mEq/L) to 0.35 mmol/L (mEq/L) within 1 week of institution of sulindac and from 0.64 mmol/L (mEq/L) to 0.33 mmol/L (mEq/L) in another case following an increase in the sulindac dose.[14]

Over a 2-month period the patient reported herein (at the age of 67 years is the oldest patient studied thus far) experienced no statistically significant change in her lithium levels while receiving sulindac, 150 mg twice daily, concurring with the data presented by Ragheb and Powell,[13] in which minor changes in lithium levels following sulindac therapy did not achieve statistical significance. In fact, this patient experienced an increase from a baseline lithium level of 0.5 mmol/L (mEq/L) to 0.7 mmol/L (mEq/L) during the first week following institution of sulindac therapy. Based on the data presented, it is not possible to explain why these differences occurred. Additional study enrolling more patients will be required to further define this drug interaction. These studies will need to be undertaken in humans, as species-to-species variation exists in animal studies.[18]

Sulindac thus appears to offer a safe alternative to ibuprofen, naproxen, ketoprofen, mefenamic acid, phenylbutazone, piroxicam, and diclofenac for lithium-treated patients. As the population ages, this interaction will acquire increasing significance as more manic-depressive patients experience arthritic symptoms requiring treatment. Because lithium has a narrow therapeutic index, awareness of NSAID interactions with sulindac as a safe alternative will be essential as one strives to maintain lithium levels within the therapeutic range.

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