Tenidap sodium decreases renal clearance and increases steady-state concentrations of lithium in healthy volunteers

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- 1 An open-label, randomised placebo-controlled study was conducted to determine the effects of tenidap sodium, a novel, cytokine-modulating anti-rheumatic drug, on the steady-state concentrations and renal clearance of lithium carbonate.
- 2 Eighteen healthy male volunteers received 450 mg lithium carbonate twice daily for 15 days and once on day 16. On days 9–16 subjects also received either placebo or 120 mg day⁻¹ tenidap 2 h prior to the morning dose of lithium.
- 3 Following a single dose of tenidap, the renal clearance of lithium decreased significantly by 0.36 l h⁻¹ (–23%) compared with the clearance in the placebo group, which increased by 0.18 l h⁻¹ (+14%). Steady-state serum lithium levels increased after a single dose of tenidap by 0.069 mEq l⁻¹ (+13%), and in the placebo group levels increased by 0.003 mEq l⁻¹ (+0.5%); this difference was not significant.
- 4 After 7 days' continuous administration of tenidap, the renal clearance of lithium had decreased by 0.38 l h⁻¹ (–25%), compared with the placebo group in which clearance had increased by 0.16 l h⁻¹ (+12%). The steady-state serum concentration of lithium increased by 0.208 mEq l⁻¹ (+39%) in the tenidap group and by 0.063 mEq l⁻¹ (+10%) in the placebo group. Both of these differences were significant.
- 5 Two subjects who received lithium plus tenidap experienced gastrointestinal side effects, compared with none of those who were administered lithium plus placebo.
- 6 It is recommended that serum lithium levels be monitored when tenidap and lithium are administered concomitantly.

Keywords tenidap sodium lithium carbonate renal clearance antirheumatic drug

Introduction

Lithium, the third element of the periodic chart, can substitute for other alkaline earth metals at various sites in the body. Consequently, it can cause changes in neuroendocrine and renal function, and interacts with many other drugs, including non-steroidal anti-inflammatory drugs (NSAIDs) [1], antibiotics [2], neuroleptics [3] and thiazide diuretics [4].

In the United Kingdom lithium is currently approved for the prophylaxis and treatment of bipolar disorder, as well as the treatment of self-mutilating behaviour. The drug has also been studied in many other illnesses including cluster headaches [5], aggression in the mentally retarded [6], skoptic syndrome (an obsessional gender dysphoria) [7] and unipolar

depressive illness [8, 9]. Lithium has a low therapeutic index; therefore, factors which may influence its disposition merit consideration.

Ninety-five percent of lithium is excreted by the kidneys [10]. Prostaglandins have been shown to mediate electrolyte excretion by the kidneys, and inhibition of prostaglandins may influence the renal elimination of lithium ions [10–12]. This may explain the increase in the serum concentrations and the decrease in the clearance of lithium reported after administration of NSAIDs [10, 12].

Tenidap sodium is a novel anti-rheumatic agent developed for the treatment of rheumatoid arthritis and osteoarthritis [13, 14]. Recently it has been shown

to reduce levels of interleukin-1, interleukin-6 and tumour necrosis factor *in vitro* [15], as well as cyclo-oxygenase [16].

The aim of the present study was to explore the possibility of a pharmacokinetic interaction between lithium carbonate and tenidap in healthy volunteers, by evaluating the steady-state serum concentration and renal clearance of lithium.

Methods

Subjects

After providing written informed consent, healthy male volunteers were enrolled in an open-label, randomised, placebo-controlled study. Subjects were excluded from the study if they had evidence or history of haematological, allergic, renal, pulmonary, endocrine, gastrointestinal, hepatic, cardiovascular or neurological disease, or had known drug or alcohol dependence, drug allergies, or any condition which might affect drug absorption. Neither concomitant drug therapy nor donation of blood or blood components was permitted during the study, and subjects were not permitted to receive any medications (including over-the-counter) for at least 2 weeks before the study began. Approval of the investigation was granted by the Human Subjects Biomedical Sciences Review Committee at the Ohio State University.

Protocol

Subjects received 450 mg lithium carbonate (3×150 mg tablets) orally twice daily for 15 days and a further single, oral dose of 450 mg on day 16. From days 9 to 16 inclusive each subject was randomised to receive either 120 mg tenidap sodium (Pfizer Central Research, Groton, CT, USA) or matching placebo as a single, oral dose 2 h before administration of the morning dose of lithium.

Only subjects who had attained steady-state serum concentrations of lithium by day 6 remained in the study. Each subject was required to have a serum trough lithium level of less than 0.75 mEq l^{-1} on day 9, with a change no greater than 0.1 mEq l^{-1} or 15% between days 6 and 7 and between days 7 and 8. In addition, any subject with serum trough levels greater than 1.0 mEq l^{-1} on days 9–16 was discharged from the study.

Subjects were required to return to the clinic for the morning and evening doses of lithium on days 1–7 and were confined to the Clinical Pharmacology Unit for at least 10 h prior to receiving tenidap or placebo on day 8 and until at least 24 h after the last dose of tenidap or placebo on day 16.

Pharmacokinetic assessments

On days 6–16 blood samples sufficient to provide at least 5 ml serum were collected in non-heparinised tubes immediately before the morning dose of lithium (12 h after the previous dose) to measure the serum

lithium concentration. On days 8, 9 and 16 blood samples were also collected at 2, 4, 6, 8, 10 and 12 h after the morning dose of lithium. All blood samples were kept at room temperature for 1 h to clot; serum was then separated by centrifugation and stored at -20°C until being assayed for lithium.

The concentration of lithium in urine was determined from 10 ml samples collected on day 1 before the morning dose, and also from samples collected continuously from 0 to 12 h after the morning dose of lithium on days 8, 9 and 16. Two 10 ml samples from each 12 h collection period were frozen at -20°C pending analysis.

Serum and urine lithium concentrations were determined by atomic absorption spectrometry on a Varian AA6 Techtron Flame Spectrophotometer with a lithium-argon lamp as previously described [17]. Absorbance was monitored at 670.8 nm, and standard calibration curves were prepared daily at 2.5, 5.0, 7.5, 10, 20 and 30 mEq l^{-1} in urine and at one tenth of these concentrations in serum.

On days 8, 9 and 16 a 6 h blood sample sufficient to provide 2 ml serum was collected in non-heparinised tubes for determination of serum creatinine at the midpoint of the post-dose (0–12 h) urine collection period. The concentration of creatinine in urine was determined from samples collected on day 1 before the morning dose, and also from 0 to 12 h after the morning lithium dose on days 8, 9 and 16. Samples from each collection period were frozen at -20°C until assay.

For determination of plasma tenidap concentration, blood samples sufficient to provide 3 ml plasma were collected in heparinised tubes before the first dose of either tenidap or placebo on day 9 and before dosing on day 16. Samples were centrifuged to separate plasma and stored at -15°C until assayed by h.p.l.c. with ultraviolet detection at 365 nm [18].

Tenidap concentration was measured by h.p.l.c. (Waters 481) using a $200 \times 4.6 \text{ mm}$ Novopak C-18 column packed with $5\text{-}\mu\text{m}$ particles, preceded by a $50 \times 3.9 \text{ mm}$ guard column. The mobile phase consisted of 0.025 M Tris-phosphate buffer (pH 6.5) and methanol in a ratio of 55:45. The flow rate was 1 ml min^{-1} , and ultraviolet absorbance was monitored at 365 nm.

Standard curves, constructed over a concentration range of $0.5\text{--}25.0 \mu\text{g ml}^{-1}$, were run after every 30 samples. Acetonitrile (0.1 ml) containing CP-66,993 as an internal standard was added to $50 \mu\text{l}$ plasma. The samples were vortexed and centrifuged at 4°C , and $50 \mu\text{l}$ of the supernatant was added to vials containing $50 \mu\text{l}$ Tris-phosphate buffer (pH 7.4). A volume of $20 \mu\text{l}$ was analysed by h.p.l.c.

Statistical evaluation

The renal clearance of lithium was calculated as the ratio of the urinary excretion of lithium (0–12 h) to the area under the serum lithium concentration-time curve in the 12 h following the morning dose. The area under the concentration-time curve during the 12 h after lithium administration ($\text{AUC}[0,12\text{h}]$) was calculated by the linear trapezoidal rule.

The effect of a single dose of tenidap on the serum concentration and clearance of lithium was calculated by computing the difference between the mean values on days 9 and 8 and comparing these differences in the tenidap and placebo groups using the two-sample *t*-test. The effect of eight consecutive doses of tenidap was calculated in the same manner but using the lithium concentrations on days 8 and 16.

Results

Eighteen subjects had attained steady-state concentrations of lithium by day 6 and were entered into the study. The baseline demographic characteristics of these subjects were comparable between treatment groups (Table 1).

None of the 18 subjects randomised to receive tenidap or placebo was discontinued because of high serum trough levels of lithium; however, two of the nine subjects who received tenidap plus lithium reported adverse events (both gastrointestinal), and one was withdrawn from the study. Therefore, 17 subjects were included in the pharmacodynamic analysis. No adverse events were reported among the nine subjects who received lithium plus placebo.

The plasma concentration of tenidap on day 16 in the subjects who received tenidap ranged from 3.0 to 22 $\mu\text{g ml}^{-1}$. In the group which received tenidap the decrease in the renal clearance of lithium (-0.36 l h^{-1} [-23%]) after a single dose of tenidap (day 9) was significantly greater than the change in renal clearance ($+0.18 \text{ l h}^{-1}$ [$+14\%$]) after placebo ($P = 0.0003$) (Table 2). However, the increase in trough steady-state serum lithium concentration after a single dose of tenidap (0.069 mEq l^{-1} [$+13\%$]) was not significantly greater than that in the placebo group (0.003 mEq l^{-1} [$+0.5\%$]). On day 16, after 7 days' successive administration of tenidap, the renal clearance of lithium had decreased in the tenidap group (-0.38 l h^{-1} [-25%]) compared with a smaller increase among placebo recipients ($+0.16 \text{ l h}^{-1}$ [$+12\%$]) ($P = 0.0015$). Con-

Table 1 Demographic characteristics of subjects randomised to receive 450 mg lithium carbonate plus either 120 mg tenidap sodium or matching placebo

	<i>Lithium + tenidap</i>	<i>Lithium + placebo</i>
Number of subjects	9	9
Age (years)		
Range	25–44	20–42
Mean	33.8	29.7
Weight (kg)		
Range	62.3–85.9	66.8–88.6
Mean	74.3	77.3
Ethnic origin		
White	7	6
Black	2	1
Asian	0	1
Hispanic	0	1

currently, there was an increase in steady-state lithium of 0.208 mEq l^{-1} ($+39\%$) in the tenidap group compared with a small increase in the placebo group (0.063 mEq l^{-1} [$+10\%$]) ($P = 0.01$).

Discussion

The pharmacokinetic data concerning lithium in this study are consistent with those of other multiple-dose studies of lithium in healthy volunteers [12, 17, 19]. The results of the present investigation indicate that there is a pharmacokinetic interaction between lithium and tenidap in healthy male volunteers, with decreased renal clearance of the lithium resulting in increased serum concentration. However toxic concentrations of lithium were not observed and there were no lithium-induced side-effects.

This interaction between lithium and tenidap is important because lithium has a narrow therapeutic range ($0.8\text{--}1.4 \text{ mEq l}^{-1}$) [12]. Lithium is widely used in the long-term treatment of patients with bipolar disorder; among geriatric patients this disorder may

Table 2 Comparison of tenidap vs placebo on the mean steady-state serum concentration of lithium (immediately before the morning dose of lithium) and on the mean renal clearance of lithium in healthy subjects

	<i>Lithium + tenidap</i> (n = 8)			<i>Lithium + placebo</i> (n = 9)		
Study day	8	9	16	8	9	16
Number of days receiving tenidap or placebo	0	1	7	0	1	7
<i>Serum concentration of lithium (mEq l⁻¹)</i>						
Mean	0.533	0.601	0.740*	0.602	0.606	0.666
s.d.	0.073	0.126	0.130	0.061	0.106	0.117
<i>Renal clearance of lithium (l h⁻¹)</i>						
Mean	1.54	1.18**	1.17***	1.32	1.50	1.48
s.d.	0.27	0.34	0.26	0.25	0.18	0.11

*Day 16–day 8 value differs significantly from placebo group ($P = 0.01$).

**Day 9–day 8 value differs significantly from placebo group ($P = 0.0003$).

***Day 16–day 8 value differs significantly from placebo group ($P = 0.0015$).

co-exist with arthritis, perhaps necessitating concomitant administration of both lithium and tenidap. The theoretical potential for an interaction between tenidap and lithium might be increased in the elderly or patients with renal impairment.

Other investigators have shown that NSAIDs, including indomethacin, ibuprofen, diclofenac and naproxen decrease renal clearance of lithium and increase serum concentrations [10, 12]. For example, in healthy volunteers Reimann *et al.* [12] showed that plasma concentrations of lithium increased from 0.68 to 0.84 mEq l⁻¹ (+23.5%) and renal clearance of lithium decreased from 25.3 to 19.4 ml min⁻¹ (-23.3%) when concomitant indomethacin was administered. Results from the present study suggest that tenidap may have a similar effect.

It is believed that the reduction in renal lithium clearance that occurs on concomitant administration of NSAIDs may be mediated by an effect on renal prostaglandins [10–12]. A similar mechanism may explain why tenidap also reduces renal lithium clearance because tenidap, in common with the NSAIDs, also inhibits cyclo-oxygenase [16]. However, tenidap can be differentiated from NSAIDs by its ability to modulate cytokines [20] and acute phase proteins [14].

In conclusion, the results of the present study indicate that co-administration of 450 mg lithium carbonate twice daily and 120 mg day⁻¹ tenidap sodium decreases the renal clearance of lithium in healthy males. When these drugs are administered concurrently, the serum concentration of lithium should be monitored.

References

- 1 Ragheb M, Ban TA, Buchanan D, Frolich JC. Interaction of indomethacin and ibuprofen with lithium in manic patients under a steady-state lithium level. *J clin Psychiatry* 1980; **41**: 397–398.
- 2 McGennis AJ. Lithium carbonate and tetracycline interaction. *Br med J* 1978; **1**: 1183.
- 3 Amdisen A. Lithium and drug interactions. *Drugs* 1982; **24**: 133–139.
- 4 Jefferson JW, Greist JH. Lithium and the kidney. In *Psychopharmacology update: new and neglected areas*, eds Davis JM, Greenblatt D. New York, Grune & Stratton, 1979; 81–104.
- 5 Bussone G, Leone M, Peccarisi C, *et al.* Double blind comparison of lithium carbonate and verapamil in cluster headache prophylaxis. *Headache* 1990; **30**: 411–417.
- 6 Spreat S, Behar D, Reneski B, Miazzi P. Lithium carbonate for aggression in mentally retarded persons. *Compar Psychiatry* 1989; **30**: 505–511.
- 7 Coleman E, Cesnik J. Skoptic syndrome: the treatment of an obsessional gender dysphoria with lithium carbonate and psychotherapy. *Am J Psychother* 1990; **44**: 204–217.
- 8 Kim HR, Delva NJ, Lawson JS. Prophylactic medication for unipolar depressive illness: the place of lithium carbonate in combination with antidepressant medication. *Can J Psychiat* 1990; **35**: 107–114.
- 9 Austin LS, Arana GW, Ballenger JC. Rapid response of patients simultaneously treated with lithium and nortriptyline. *J clin Psychiatry* 1990; **51**: 124–125.
- 10 Ragheb M. Ibuprofen can increase serum lithium level in lithium-treated patients. *J clin Psychiatry* 1987; **48**: 161–163.
- 11 Ragheb M. The clinical significance of lithium-non-steroidal anti-inflammatory drug interactions. *J clin Psychopharmac* 1990; **10**: 350–354.
- 12 Reimann IW, Diener U, Frolich JC. Indomethacin but not aspirin increases plasma lithium ion levels. *Arch gen Psychiatry* 1983; **40**: 283–286.
- 13 Loose LD, Littman BH, Sipe JD. Modulation of acute phase proteins by tenidap, a new antiinflammatory, anti-rheumatic drug. *Clin Res* 1990; **38**: 579A.
- 14 Loose LD, Sipe JD, Bartle L. Modulation of acute phase proteins by tenidap. *Br J Rheumatol* 1992; **31** (suppl 2): 175.
- 15 Sipe JD, Bartle LM, Loose LD. Modification of proinflammatory cytokine production by the anti-rheumatic agents tenidap and naproxen. A possible correlate with clinical acute phase response. *J Immunol* 1992; **148**: 480–484.
- 16 Carty TJ, Showell HJ, Loose LD, Kadin SB. Inhibition of both 5-lipoxygenase (5-LO) and cyclooxygenase (CO) pathways of arachidonic acid metabolism by CP-66,248, a novel antiinflammatory compound. *Arthritis Rheum* 1988; **31** (suppl 4): S89.
- 17 Apseloff G, Wilner KD, von Deutsch DA, *et al.* Sertraline does not alter steady-state concentrations or renal clearance of lithium in healthy volunteers. *J clin Pharmac* 1992; **32**: 643–646.
- 18 Wilner KD, Gardner MJ. Tenidap sodium does not alter the clearance or plasma protein binding of tolbutamide in healthy male volunteers. *Br J clin Pharmac* 1995; **39**: 39S–42S.
- 19 Hunter R. Steady-state pharmacokinetics of lithium carbonate in healthy subjects. *Br J clin Pharmac* 1988; **25**: 375–380.
- 20 Katz P, Borger AP, Loose LD. Evaluation of CP-66,248 [5-chloro-2,3-dihydro-3-(hydroxy-2-thienylmethylene)-2-oxo-1 indole-1-carboxamide] in rheumatoid arthritis (RA). *Arthritis Rheum* 1988; **31**: S52.