The effects of ziprasidone on steady-state lithium levels and renal clearance of lithium

G. Apseloff,¹ D. Mullet,¹ K. D. Wilner,² R. J. Anziano,² T. G. Tensfeldt,² S. M. Pelletier² & N. Gerber¹

¹Department of Pharmacology, Ohio State University, Columbus, OH, USA, and ²Department of Clinical Research, Pfizer Central Research, Groton, CT 06340, USA

Aims To assess the potential of ziprasidone to alter the renal clearance and steady-state serum levels of lithium.

Methods Healthy subjects who had stable serum lithium levels during the first 7 days of treatment with lithium 900 mg day⁻¹, given as two divided daily doses, were randomized to receive concomitant treatment with either ziprasidone, 40 mg day⁻¹, given as two divided daily doses, on days 9–11 followed by 80 mg day⁻¹, given as two divided daily doses on days 12–15 (*n* = 12), or placebo twice daily (*n* = 13). Ziprasidone or placebo was administered 2 h before each dose of lithium.

Results Ziprasidone administration was associated with a 0.07 mmol l⁻¹ (13%) mean increase in steady-state serum lithium levels compared with a mean increase of 0.06 mmol l⁻¹ (10%) with placebo. Mean renal clearance of lithium decreased by 0.09 l h⁻¹ (5%) in the ziprasidone group and by 0.14 l h⁻¹ (9%) in the placebo group. None of these differences between the two groups was statistically or clinically significant.

Conclusions Ziprasidone does not alter steady-state serum lithium concentrations or renal clearance of lithium.

Keywords: lithium, pharmacokinetics, renal clearance, ziprasidone

Introduction

Lithium salts were introduced into psychiatry for the treatment of mania nearly 50 years ago and are still widely used in the treatment of bipolar affective disorders [1, 2]. In recent years, lithium salts have been advocated for the treatment of depressive symptoms in individuals with schizophrenia or schizoaffective disorder [3]. A review of the literature has suggested that lithium and antipsychotics produce similar responses in patients with bipolar-type schizoaffective disorder and who are not highly agitated. Antipsychotics result in more favourable responses in highly agitated patients with bipolar-type schizoaffective disorder and patients with depressed-type schizoaffective disorder [4].

Antipsychotic agents have been used for the treatment of mood disorders in individuals with schizophrenia for several years. Recently, some of the newer antipsychotics have been shown to have efficacy in the treatment of mood disorders, both in patients with and without

schizoaffective disorder, and there is some suggestion that the newer antipsychotics may be more effective than neuroleptics in this respect [4–6]. It has also been suggested that combinations of lithium with antipsychotics may be more effective than either class of agent alone in the treatment of patients with bipolar-type schizoaffective disorder [7].

Lithium has a low therapeutic index that can complicate therapy. It is necessary to monitor serum concentrations of lithium regularly and to adjust the dose of the drug carefully to maintain serum concentrations within a narrow therapeutic range (0.4–1.5 mmol l⁻¹) [1, 8]. Steady-state serum lithium concentrations are usually attained within 5–6 days of the initiation of therapy and after discontinuation of treatment there is a rapid elimination phase, during which most of the drug is excreted in the urine, followed by a slower phase lasting 10–14 days [1, 8]. Lithium is known to interact with a variety of medications, including conventional and novel antipsychotics, nonsteroidal anti-inflammatory agents, antibiotics and thiazide diuretics [9–14]. The combination of lithium and tricyclic antidepressants and 5-HT reuptake inhibitors has been used for the treatment of some forms of refractory depression. This combination, however, has

Correspondence: Dr K. D. Wilner, Department of Clinical Pharmacology, Pfizer Central Research, Groton, CT 06340, USA.

been reported to cause adverse effects including mania and somnolence [15, 16]. Combination therapy with lithium and conventional antipsychotic agents, such as haloperidol, is generally well tolerated [1]. There are isolated case reports of neurotoxicity resulting from this combination [17] but these have not been substantiated by retrospective clinical studies or by general clinical experience [18].

Methods

Subjects

Thirty-four, nonsmoking, healthy men aged 18–45 years, who weighed between 61 and 91 kg and who were within 10% of the ideal weight range for age, height and frame, were enrolled in the study. None had received prescription drug therapy or over-the-counter preparations or recreational drugs for at least 2 weeks before entering the study, and none had received investigational drug treatment for at least 4 weeks. No concomitant medications were allowed during the study.

The study protocol was approved by the Ohio State University Institutional Review Board Committee, USA, and all subjects provided written informed consent.

Study design

The study was of a randomized, open-label, parallel-group design. An 8 day period of treatment with lithium monotherapy (days 1–8) was followed by 7 days of treatment with lithium in combination with either ziprasidone or placebo (days 9–15).

Lithium (lithium carbonate, Eskalith[®] tablets, Smith-Kline Beecham) 450 mg was administered every 12 h with 120 ml water. Subjects received their first daily dose of lithium 2 h after eating a standard breakfast, which was consumed within a period of 20 min, and their second daily dose of lithium 2 h after eating an evening meal.

Subjects who had stable serum lithium levels (see below for definition) after 7 days of lithium monotherapy remained in the clinical research centre under continuous medical or paramedical supervision from the evening of day 7 until the morning of day 16 (i.e. 24 h after the last dose of lithium). They were then randomized to receive either ziprasidone or placebo (40 mg day^{-1} , in two divided daily doses, on days 9–11 and 80 mg day^{-1} , in two divided daily doses, on days 12–15). Ziprasidone and placebo were administered with 50 ml of water immediately after breakfast and the evening meal (i.e. 12 h apart and 2 h before lithium).

Subjects could continue in the study if their serum lithium levels on days 6, 7 and 8 were no greater than 1.0 mEq l^{-1} , and if their serum lithium levels varied by no more than 0.1 mEq l^{-1} (15%) between days 6 and 7,

and 7 and 8. Subsequently, the subjects could continue in the study if their serum lithium levels on days 9–15 were no greater than 1.5 mEq l^{-1} .

Pharmacokinetic sampling

Venous blood samples sufficient to provide 5 ml serum were collected for lithium analyses immediately before and up to 12 h after morning lithium dosing on days 8 and 15. These samples were collected in tubes that were free of preservative, anticoagulant or serum separator and were kept at room temperature until clotting had occurred. Serum was separated from the whole blood in a refrigerated centrifuge within 1 h of collection and stored at -20°C until analysis.

Urine samples were also collected for lithium analysis. These samples were collected over 12 h periods on days 8 and 15, commencing immediately before the morning dose of lithium. The total volume of each 12 h collection was recorded before being frozen at -20°C until analysis.

Additional venous blood samples were collected for ziprasidone analysis immediately before morning ziprasidone dosing on days 9 and 15 and stored as described for lithium.

Sample analysis

Serum and urinary concentrations of lithium were determined by atomic absorption spectrometry. Samples and standards were diluted in deionized water and aspirated into an air-acetylene oxidizing flame. Absorption of light emitted by a lithium cathode lamp was measured at spectral line 670.8 nm [19].

Serum ziprasidone levels were assayed using a validated high-performance liquid chromatography (h.p.l.c.) method involving solid phase extraction with u.v. detection. The assay had a lower limit of quantification of 1 ng ml^{-1} and an upper limit of 250 ng ml^{-1} [20].

Pharmacokinetic assessments

Steady-state serum lithium concentrations were observed directly from the experimental data. The area under the serum concentration *vs* time curve from time 0–12 h after dosing ($\text{AUC}(0,12 \text{ h})$) was calculated using linear trapezoidal approximation. Renal clearance of lithium was calculated as the amount of lithium excreted within 12 h divided by the $\text{AUC}(0,12 \text{ h})$.

Statistical analysis

Mean differences between the ziprasidone and placebo groups in changes in renal clearance and steady-state concentrations of lithium, between days 8 and 15, were

examined using 95% confidence intervals. The treatment differences were analysed using two-tailed, Student's *t*-tests. Values of $P < 0.05$ were considered statistically significant.

Results

Subjects

Thirty-four healthy men aged 19–45 years entered the trial. Nine were withdrawn during lithium monotherapy: two because of adverse events (severe rash and viral syndrome); six because they failed to achieve stable serum levels of lithium, and one for personal reasons. The remaining 25 subjects were randomized to receive

Table 1 Baseline demographic characteristics.

	Lithium + ziprasidone (<i>n</i> = 12)	Lithium + placebo (<i>n</i> = 13)
<i>Age (years)</i>		
Mean	26.6	25.3
Range	20–45	19–32
<i>Weight (kg)</i>		
Mean	81.5	77.1
Range	68–93	67–89
<i>Race</i>		
Asian	0	0
Black	4	3
Hispanic	0	1
White	8	9

Figure 1 Plasma concentration–time curves for serum lithium at the end of monotherapy (day 8, ----) and at the end of combination therapy (day 15, —) with ziprasidone 40–80 mg day^{−1} (a) or placebo (b).

ziprasidone (*n* = 12) or placebo (*n* = 13). No subject withdrew from the trial after randomization. Demographic characteristics of the randomized subjects are shown in Table 1.

Pharmacokinetics

Serum concentration–time curves at the end of lithium monotherapy (day 8) and after 7 days of treatment with ziprasidone or placebo (day 15) are shown in Figure 1.

The mean steady-state serum concentration of lithium was not significantly altered by concomitant administration of ziprasidone. On day 8, the mean steady-state serum concentrations of lithium were 0.49 mEq l^{−1} in the ziprasidone group and 0.55 mEq l^{−1} in the placebo group. On day 15, these had both increased slightly to 0.56 mEq l^{−1} and 0.61 mEq l^{−1}, respectively. Thus, the mean increase in steady-state serum lithium concentration was 0.07 mEq l^{−1} (14%) in the ziprasidone group and 0.06 mEq l^{−1} (11%) in the placebo group. The difference between the mean change in the two treatment groups (0.01 mEq l^{−1}) was not statistically significant (95% CI: −0.05; 0.07; $P = 0.79$) (Table 2).

Table 2 Lithium steady-state serum concentration and renal clearance.

	Mean value		Difference between means (95% CI)	P value
	Ziprasidone	Placebo		
<i>Lithium steady-state concentration (mEq l^{−1})</i>				
Day 8	0.49	0.55	−0.06 (−0.14,0.03)	0.19
Day 15	0.56	0.61	−0.05 (−0.15,0.05)	0.32
Day 15 − Day 8	0.07	0.06	0.01 (−0.05,0.07)	0.79
<i>Lithium clearance (l h^{−1})</i>				
Day 8	1.69	1.56	0.13 (−0.19,0.45)	0.42
Day 15	1.60	1.42	0.18 (−0.05,0.41)	0.12
Day 15 − Day 8	−0.09	−0.14	0.05 (−0.185,0.29)	0.65

Similarly, the mean lithium clearance was not significantly altered by concomitant administration of ziprasidone. On day 8, the mean lithium clearance was 1.69 l h^{-1} in the ziprasidone group and 1.56 l h^{-1} in the placebo group. On day 15, these had both decreased slightly to 1.60 l h^{-1} and 1.42 l h^{-1} , respectively. Thus, the mean decrease in lithium clearance was 0.09 l h^{-1} (5%) in the ziprasidone group and 0.14 l h^{-1} (9%) in the placebo group. The difference between the mean change in the two treatment groups (0.05 l h^{-1}) was not statistically significant (95% CI: -0.19 ; 0.29 ; $P=0.65$) (Table 2).

Discussion

Findings from this study indicate that concomitant administration of ziprasidone does not alter steady-state pharmacokinetics of lithium in healthy subjects. The pharmacokinetics of lithium in the present study were consistent with those previously reported [8] and there was no clinically or statistically significant difference between the lithium+ziprasidone group and the lithium+placebo group in either the mean steady-state serum lithium concentration or the 12 h urinary clearance of lithium. This lack of interaction between ziprasidone and lithium is clinically relevant because lithium has a narrow therapeutic range (0.14 – 1.5 mmol l^{-1}) [8] and in clinical practice, is likely to be prescribed in combination with ziprasidone.

In summary, the results reported here suggest that ziprasidone administered in combination with standard doses of lithium does not alter the steady-state concentration or clearance of lithium.

References

- Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In *The Pharmacological Basis of Therapeutics*, Ninth Edition. eds, Gilman AG, Molinoff PB, Ruddon RW, Hardman JG, Limbird LE. New York: McGraw-Hill, 1995; 431–459.
- Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 1995; **29**: 172–191.
- Siris SG. Pharmacological treatment of depression in schizophrenia. In *Depression in Schizophrenia*, ed. Delisi LE, Washington, DC: American Psychiatric Press, 1990; 141–162.
- Keck PE Jr, McElroy SL, Strakowski SM, et al. Pharmacologic treatment of schizoaffective disorder. *Psychopharmacol Berl* 1994; **114**: 529–538.
- Kimmel S, Calabrese JR, Woysville MJ, et al. Clozapine in treatment-refractory mood disorders. *J Clin Psychiatry* 1994; **55**(Suppl B): 91–93.
- Madhusoodanan S, Brenner R, Araujo L, et al. Efficacy of risperidone for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. *J Clin Psychiatry* 1994; **56**: 514–518.
- Azarin JM. Long-term treatment of mood disorders in schizophrenia. *Acta Psychiatr Scand* 1995; **388**(Suppl): 20–23.
- Marcus WL. Lithium: a review of its pharmacokinetics, health effects and toxicology. *J Environ Pathol Toxicol Oncol* 1994; **13**: 73–79.
- 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.
- McGennis AJ. Lithium carbonate and tetracycline interaction. *Br Med J* 1978; **1**: 1183.
- Amdisen A. Lithium and drug interactions. *Drugs* 1982; **24**: 133–139.
- Jefferson JW, Greist JH. Lithium and the kidney. In *Psychopharmacology Update: New and Neglected Areas*, eds, Davis JM, Greenblatt D. New York: Grune and Stratton, 1979; 81–104.
- Meyer MC, Baldessarini RJ, Goff DC, Centorrino F. Clinical significant interactions of psychotropic agents with antipsychotic drugs. *Drug Safety* 1996; **15**: 333–346.
- Harvey NS, Merriman S. Review of clinically important drug interactions with lithium. *Drug Safety* 1994; **10**: 455–463.
- Hadley A, Cason MP. Mania resulting from lithium-fluoxetine combination. *Am J Psychiatry* 1989; **145**: 1637–1638.
- Evans M, Marwick P. Fluvoxamine and lithium: an unusual interaction. *Br J Psychiatry* 1990; **156**: 286.
- Loudon JB, Waring H. Toxic reactions to lithium and haloperidol. *Lancet* 1976; **ii**: 1088.
- Baastrup PC, Hollnagel P, Sorensen R, Schon H. Adverse reactions in treatment with lithium carbonate and haloperidol. *JAMA* 1976; **236**: 2645–2646.
- Hansen JL. The measurement of serum and lithium by atomic absorption spectrometry. *Am J Med Tech* 1968; **34**: 1–9.
- Janiszewski JS, Fouda HG, Cole RO. Development and validation of a high-sensitivity assay for an antipsychotic agent, CP-88,059, with solid-phase extraction and narrow-bore high-performance liquid chromatography. *J Chromatogr* 1995; **668**: 133–139.