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Short communication

Lithium pharmacokinetics during cisplatin-based chemotherapy: a case report

J. H. Beijnen[1,2*], E. M. Bais[2], W. W. ten Bokkel Huinink[2]

[1] Department of Pharmacy, Slotervaart Hospital/Netherlands Cancer Institute, Louwesweg 6, 1066 EC Amsterdam, The Netherlands
[2] Department of Medical Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

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Abstract. A 33-year-old patient, treated for several years with lithium carbonate for a manic depressive disorder, received four courses of combination chemotherapy (bleomycin, etoposide, cisplatin) after the diagnosis of disseminated testicular cancer. Lithium therapy was continued throughout all the courses. Serum and urine lithium concentrations were determined during and between all chemotherapy courses. During the first course a transient 64% decrease in serum lithium concentrations was found. This effect became less pronounced during the consecutive courses. The changes in serum lithium concentrations were without perceptible clinical significance. However, careful monitoring of serum lithium concentrations is mandatory in patients treated with cisplatin-based chemotherapy, as this is accompanied by profound disturbances of lithium pharmacokinetics.

Introduction

Lithium is the cornerstone of the current treatment of bipolar (manic-depressive) psychosis [4]. The mechanism of action of this psychotropic drug has been the subject of many investigations but remains to be elucidated. Lithium is given orally, in most cases as the carbonate salt; the absorption is rapid (Tmax, 1–2 h) and complete (bioavailability, 80%–100%). After absorption it is unevenly distributed among several tissue compartments including the brain, but mainly in body water. Lithium ions are not bound to plasma proteins and are excreted solely by the kidneys. The serum half-life ranges from 12 to 48 h. After glomerular filtration, about 60%–80% is reabsorbed in the proximal tubule and the ascending limb of the loop of Henle in the nephron. To some extent lithium behaves like sodium ions in the nephron but in contrast to sodium, it is not absorbed from the distal tubule.

Lithium has a narrow therapeutic range, and careful monitoring of the serum concentration is warranted to guard against toxicity and to ensure clinical efficacy. The therapeutic range is 0.3–1.3 mmol/l [1, 6]. Many factors can influence serum lithium pharmacokinetics, mainly by influencing the excretion of the drug. The sodium balance is an important determinant. A negative sodium balance following treatment with natriuretic diuretics or sodium-poor diets will lead to a reduced lithium excretion and, consequently, to an increase in serum concentrations. Fluid loading and the use of a potentially nephrotoxic drug such as cisplatin can theoretically also intervene in lithium pharmacokinetics.

Thus far, two cases have been reported of patients receiving both lithium and cisplatin-based chemotherapy [2, 5]. In one case a transient decrease in serum lithium levels was observed and in the other, no change occurred during cisplatin containing chemotherapy. Due to multiple differences (e.g., clinical status, fluid load, concomitant medication), a comparison between these two cases is not relevant. Whether cisplatin, fluid or sodium loading, or a combination of these factors alters the disposition of lithium during cisplatin-based chemotherapy remains unclear. As far as we know, no other data are available on this potential drug interaction. Herein we report on a patient who used lithium for several years and was treated in our hospital with the combination of cisplatin, etoposide, and bleomycin for testicular cancer. Serum and urine lithium concentrations were determined daily during the 5-day chemotherapy regimen and at all four courses.

Case report

A 33-year-old white man was referred to our hospital for chemotherapeutic treatment of metastatic testicular cancer. The patient had a history of bipolar (manic-depressive) affective disorders and lived under the supervision of a psychiatry hospital. He was treated successfully for several

Correspondence to: J.H. Beijnen

Table 1. Lithium values and serum creatinine concentrations measured before, during, and between the chemotherapy courses

Day	[Li+] (mmol/l)	24-h Li+excretion (mmol)	Renal Li+ clearance[a] (ml/min)	Serum creatinine (μmol/l)	Fluid balance (ml)
Course 1:					
−1	0.62	23.5	26.3	105	ND
1	0.61	16.2	18.4	100	− 170
2	0.22	19.7	62.2	96	+ 295
3	0.38	34.5	63.0	102	+ 75
4	0.43	24.2	39.1	97	− 250
5	0.55	28.5	36.0	97	+ 475
8	0.62	ND	ND	95	ND
Course 2:					
−1	0.89	ND	ND	103	ND
1	0.81	ND	ND	ND	+ 35
2	0.42	38.8	64.2	ND	−1070
3	0.43	38.1	61.5	ND	− 320
4	0.61	31.7	36.1	93	+ 200
5	0.47	24.6	36.3	106	ND
8	0.92	47.5	35.9	97	ND
Course 3:					
−1	0.73	ND	ND	97	ND
1	0.73	ND	ND	ND	+2050
2	0.46	19.3	29.1	ND	+ 125
3	0.49	59.7	84.6	ND	− 550
4	0.48	16.9	24.5	ND	−3900
5	0.38	34.4	62.9	ND	ND
6	0.60	ND	ND	ND	ND
Course 4:					
−2	0.82	ND	ND	105	ND
1	0.90	ND	ND	ND	+ 425
2	0.61	25.1	28.6	ND	− 250
3	0.60	34.2	39.6	ND	− 650
4	0.51	26.6	36.2	ND	− 170
5	0.47	47.0	69.4	ND	+ 975
6	0.42	ND	ND	ND	ND

ND, Not determined [a] Calculated as the excretion rate divided by the serum lithium concentration

years with lithium carbonate given at a daily dose of 1000 mg (27 mmol) in divided doses of 400 mg in the morning and 600 mg in the evening. Serum lithium levels were controlled once per month. Concomitant oral medication included 2 mg biperidene, 50 mg promethazine, 2×200 mg carbamazepine, 20 mg temazepam, 2×5 mg haloperidol, and 500 mg disulfiram. Previous treatment, before referral to our hospital, was a right-sided orchidectomy. Histological research of the pathological tissue confirmed the diagnosis of a nonseminomatous germ-cell tumor of the testis. After surgery an enlarged retroperitoneal lymph node, interpreted as a metastasis, remained as verified by a computerized tomographic (CT) scan. No other sign of metastasis was found. The serum alpha-fetoprotein level was 940 μg/l (normal, < 15 μg/l) at that time.

The patient was then referred to our hospital and was treated with four courses of chemotherapy consisting of bleomycin, etoposide, and cisplatin (BEP regimen) repeated at 3-week intervals. The chemotherapy comprised 120 mg/m^2 etoposide infused i.v. in 1 l 0.9% sodium chloride over 1 h on days 1–3, 30 mg bleomycin given i.v. in 100 ml 0.9% sodium chloride over 10 min on day 2, and 20 mg/m^2 cisplatin infused i.v. in 1 l 0.9% sodium chloride over 4 h on days 1–5. The hydration regimen consisted of 4.5 l 0.9% sodium chloride per day divided equally over 24 h, supplemented with magnesium, potassium, and calcium. This was given every day during each 5-day chemotherapy course. Antiemetic therapy consisted of 8 mg ondansetron given i.v. 3 times per day during chemotherapy. The patient experienced no emesis or bowel disturbance.

Serum sodium and potassium levels were measured daily during admission, and blood urea nitrogen (BUN) levels were determined on a regular basis. The fluid balance and body weight of the patient were registered daily. Lithium therapy was continued throughout all chemotherapy courses. Blood samples for lithium analysis were drawn before and on each day during all chemotherapy courses. The samples were taken in the morning, about 12 h after the evening dose but before the morning dose. The sample obtained on day 1 was taken just before the start of chemotherapy. Serum and urinary lithium concentrations were determined with atomic absorption flame photometry (Perkin Elmer Atomic Absorption Spectrometer 3100, Perkin Elmer Corporation, Norwalk, Conn., USA).

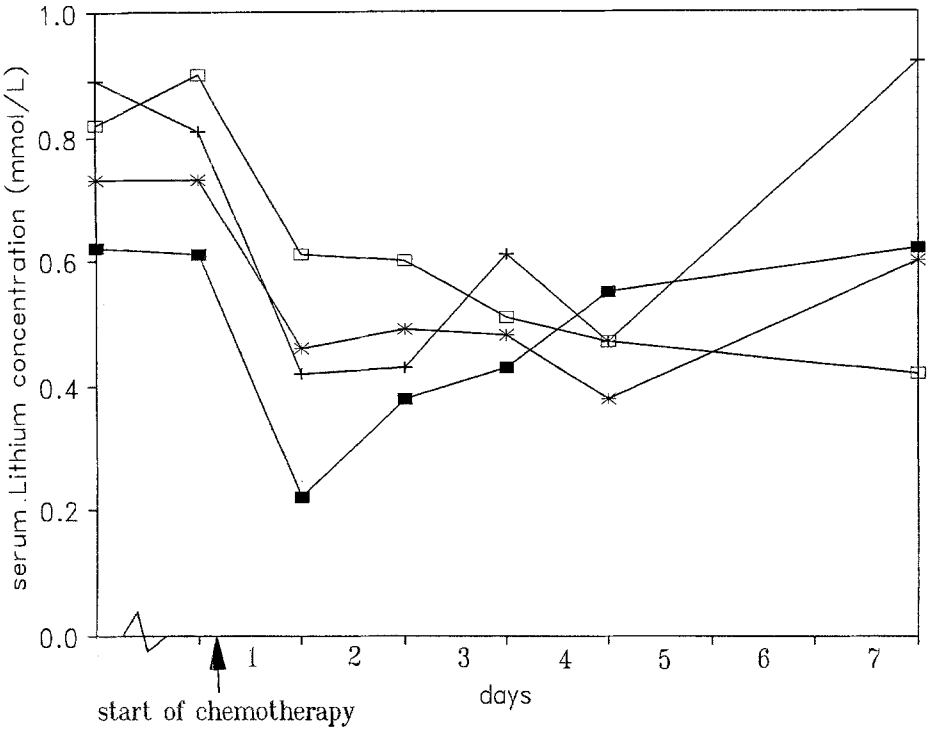

Fig. 1. Serum lithium concentrations measured before, during, and between four courses of BEP chemotherapy. ■, First course; +, second course; *, third course; □, fourth course

After the four courses of chemotherapy the alpha-fetoprotein level was normalized (<2.8 µg/l) but on the CT scan, residual suspected tissue in the retroperitoneal lymph node remained visible. This was removed surgically and was investigated histologically, with no sign of any active tumor cell being found. The patient has been in complete remission for two years now.

Results and discussion

The results of the daily serum lithium determinations are listed in Table 1 and are depicted graphically in Fig. 1. Baseline lithium concentrations varied between 0.6 and 0.9 mmol/l. Within 24 h after the start of the first chemotherapy course the serum lithium level dropped from 0.61 to 0.22 mmol/l, corresponding to a 64% decrease. During the three subsequent courses, this initial decrease was 48%, 37%, and 32%, respectively. This effect seemed to diminish during subsequent courses. With the exception of the fourth course, the nadir of the serum lithium concentration was reached in the morning of the 2nd day of each course. After the nadir value had been reached, the serum concentration increased to the baseline level at day 8 during the first course. During the other courses, lithium levels altered erratically but showed an overall rise, except for the fourth course. The average (±SD) value measured for 24-h lithium excretion was 31±11 mmol, which is in reasonable agreement with a daily intake of 27 mmol lithium. No significant change in the serum creatinine level was measured during or between the four chemotherapy courses. The measured BUN levels were also within normal ranges. The fluid balance of the patient remained within acceptable limits during therapy except at the third course, where the fluid balance was +2050 ml on day 1 and −3900 ml on day 4. The patient's body weight, determined daily, did not change throughout the study period.

The main observation in this study was that during the first administration of the BEP regimen, the serum lithium concentration showed a rapid fall, which was compensated to some extent during the following days; this effect was less clear during subsequent courses. In principle, three factors could have influenced lithium pharmacokinetics: the fluid loading, the sodium loading, and the treatment with the potentially nephrotoxic agent cisplatin. There is no indication of nephrotoxic effect of bleomycin or etoposide. Cisplatin can impair renal function in association with a reduction in glomerular filtration as indicated by an increase in serum creatinine levels [3]. Furthermore, renal dysfunction during cisplatin therapy can be caused by the drug's effect on sulphydryl groups containing proteins involved in active reabsorptive transport processes in the nephron, which can lead to a distortion of the electrolyte balance. Both effects are unlikely to account for the observed transient decrease in serum lithium concentrations. No change in the serum creatinine level or in the BUN or electrolyte concentration was found that could be related to renal dysfunction. Besides, the most striking effect (64% decrease) was seen as early as during the first course, whereas the nephrotoxic effects of cisplatin are not likely to be maximal at 24 h after the start of the first administration of 20 mg/m^2. Interestingly, Pietruszka et al. [5] have found a 70% decrease from 1.0 to 0.3 mmol/l during the first hospitalization and a 38% decrease from 0.8 to 0.5 mmol/l during the second course, comparable with our findings.

A vigorous hydration regimen is required for the safe application of cisplatin chemotherapy. Our patient received between 6 and 8 l fluid per day. Although the intake and

excretion of fluid was well balanced, the hydration at the start of each course may have accounted for the initial and transient decrease in serum lithium concentrations. A temporarily positive fluid balance at the start of the hydration may cause an initial dilution effect by which the lithium level decreases shortly after the start of chemotherapy. The rapid recovery of the serum concentrations may indicate that the putative temporarily positive fluid balance is rapidly corrected, resulting in a return to homeostatis. The body water compartment is then in balance and the serum lithium concentration returns to its initial value.

It must be noted, however, that all measured serum lithium concentrations remained within the therapeutic window of 0.3–1.3 mmol/l, except for the value obtained on day 2 of the first course, which was without any clinical relevance. Nevertheless, this study demonstrates that the BEP regimen including hydration can have a distinct influence on the serum concentration of lithium, a drug with a narrow therapeutic index, and it is therefore imperative that lithium levels be monitored closely to prevent the concentrations from reaching values outside the therapeutic window.

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