

## Lithium intoxication associated with simultaneous use of trimethoprim

### Introduction

Lithium carbonate, has been approved for the Dutch market for *the treatment of manic episodes of a bipolar disorder, as prevention for both manic and depressive episodes of a bipolar disorder as well as for the prevention of repeated unipolar depressive episodes*[1].

The drug is excreted in the urine for approximately 95%. The elimination half-life averages 20 to 24 hours. Lithium has a low therapeutic index, so concentrations in plasma or serum must be monitored to facilitate the safe use of the drug[2].

It is known that various concomitantly used drugs may interact on the drug-serum concentration. Examples of interacting drugs are diuretics, antipsychotic drugs and Non-Steroidal Anti-inflammatory drugs, which may increase the drug level of lithium. Also some antibiotics like tetracyclins and metronidazole may interact with lithium[3].

The Netherlands Pharmacovigilance Centre Lareb received two case-reports concerning a possible drug-drug interaction due to the simultaneous use of trimethoprim and lithium. One case report was published in the 'Nederlands Tijdschrift voor Geneeskunde'[4]. A second report has been received, confirming the findings described in the previous report.

This possible drug-drug interaction is not mentioned in the Dutch Summary of Product Characteristics of either trimethoprim or lithium[1].

### Reports

Patient A is a 40-year-old woman with a schizo-affective disorder has been treated with lithium carbonate 1200 mg daily. Concomitant medication consisted of olanzapine 100 mg three times daily, diazepam 10 mg od, and oxazepam 10 mg if needed. During simultaneous treatment with trimethoprim because of a urinary tract infection, she experienced complaints of nausea, malaise, concentration problems, uncertain gait, and muscle spasms. She had no fever. The lithium carbonate level appeared to be elevated (2.1 mmol/l, reference values 0.6-1.5 mmol/l). Her fluid intake was not diminished. Additional laboratory examination revealed: Na<sup>+</sup> 135 mmol/l, K<sup>+</sup> 5,0 mmol/l, creatinin 197 mmol/l. Following clinical rehydration, she made a good recovery. She has never had an increase in the plasma-levels of lithium before[4].

Patient B is an 87-year-old woman, which had been treated with lithium carbonate 400 mg od for one year. Concomitant medication consisted of clomipramine 75 mg od, carbasalate calcium 38 mg od, lactulose twice daily, and temazepam 20 mg od. Because of a urinary tract infection, she was treated with trimethoprim 300 mg once daily for five days. Six days after the start of trimethoprim, she complained of a tremor and nervousness. Because a drug-drug interaction between trimethoprim and lithium was suspected, the drug levels of lithium were measured again (1.31 mmol/l). The next days, drugs levels of lithium gradually decreased. The time course of the drug level of lithium carbonate during and after the use of trimethoprim is plotted in Figure 1.

The case histories of these two patients point at a possible interaction between lithium carbonate and trimethoprim. Although plasma levels of lithium carbonate of patient B were still within the normal range, there was a significant increase with respect to her 'base-line levels'.

### Other sources of information

#### Literature

Information on a possible interaction between lithium carbonate and trimethoprim is sparse. Only the case history of patient A was published previously in literature. Desville and Sevestre describe two patients on lithium carbonate, who showed signs of intoxication within a few days of being given co-trimoxazole. However, their lithium levels were found *to have fallen* from 0.75 mmol/l to 0.3-0.4 mmol/l[5].

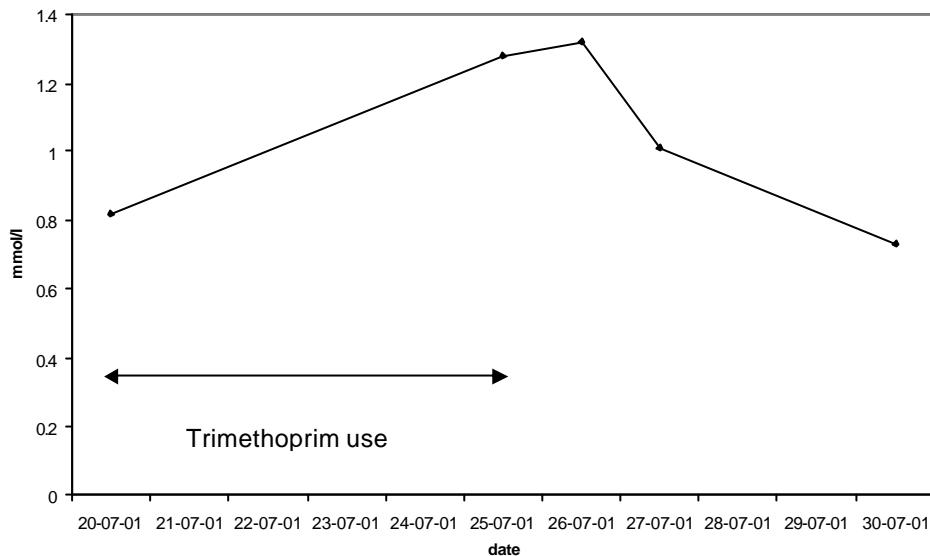


Figure 1. Time course of the plasma levels of lithium carbonate during and after the concomitant use of trimethoprim in patient B.

### Databases

In the database of the Netherlands Pharmacovigilance Centre 94 reports on lithium (carbonate) and 205 reports on trimethoprim are filed until December 2001. Only in two reports (Patient A and B) both lithium and trimethoprim were used simultaneously.

The WHO database currently contains 10.285 possible ADRs during the use of lithium or lithium carbonate. An increase in the drug level of lithium carbonate was mentioned in 643 reports. Since it was not possible to gain insight into the concomitantly used medication, responsible for this increase, this data set is not suitable to analyse drug-drug interactions.

### Mechanism

Trimethoprim was found to reduce renal potassium excretion in the distal nephron, in a manner identical to the potassium-sparing diuretic amiloride.[6] Therefore it may have the same effect as amiloride, a potassium-sparing diuretic, for which it is known that its combined use with lithium can result in increase of the lithium level although this is less well established[7]. Also in patient A, the level of  $K^+$  was slightly elevated, although still within the normal range. Both patients however used trimethoprim because of a urinary tract infection. It cannot be ruled out that a slight degree of dehydration may have influenced the plasma levels of lithium.

### Conclusion

Two cases in the Lareb database point to a possible drug interaction between trimethoprim and lithium carbonate. This association has a pharmacological plausibility.

### References

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