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Chapter 7

Subtherapeutic quetiapine serum concentrations after absorption inhibition by binding resins: a case report

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Abstract

We describe a patient with unexplainable low serum quetiapine concentrations. Our hypothesis was that this could be caused by a potential drug-drug interaction between quetiapine and the binding resins polysterene sulfonate and sevelamer. First, we performed an *In vitro* binding assay which showed pH-independent absorbance inhibition of quetiapine by polystyrene sulfonate and pH-dependent absorbance inhibition by sevelamer. Second, the time of ingestion of quetiapine, polysterene sulfonate and sevelamer was separated, where after serum quetiapine concentrations rose from <20 µg/L to 345 µg/L (therapeutic C_{min} range 100 - 500 µg/L). Our observations were complicated by the start of concurrent haemodialysis treatment. However this led to another observation: a substantial amount of quetiapine is probably extracted during haemodialysis. Psychiatrists and other clinical physicians should be aware of this potential drug-drug interaction as this could lead to treatment failure with quetiapine.

Introduction

Quetiapine is a second generation antipsychotic drug that is being used in the first-line treatment of several mental disorders such as psychosis, bipolar disorder and depression.[1,2] Low serum quetiapine concentrations can lead to therapy failure.

Sodium polystyrene sulfonate (Resonium A®) is a potassium-binding resin used for the treatment of hyperkalemia in a dosage of 15 grams qd-qid.[3] Polystyrene sulfonate is not absorbed from the gastro-intestinal tract and is completely excreted in the faeces.[4] Binding drug interactions with sodium polystyrene sulfonate which may result in lower plasma levels of the bound drugs are known following simultaneous oral use of either lithium or thyroxine.[4] Sevelamer carbonate (Renvela®) is a potent phosphate binder which is most effective if taken with meal to bind dietary phosphate in the treatment of hyperphosphatemia. Sevelamer is not absorbed from the gastrointestinal tract.[11] Bio-availability of ciprofloxacin is significantly reduced when co-ingested with sevelamer.[5] There are also reports of reduced serum concentrations of several immunosuppressive drugs during concurrent use with sevelamer.[6,7] This case report describes a patient with unexplained low serum quetiapine serum concentrations, possibly due to co-treatment with polystyrene sulfonate and sevelamer.

Case description

A 45-year-old female with bipolar disorder and diabetic nephropathy was treated with quetiapine, polystyrene sulfonate, sevelamer, furosemide, insulin, atorvastatin, ipratropium, irbesartan and sodium hydrogen carbonate. In January 2014 she was admitted to our hospital for diabetic disregulation. A serum quetiapine concentration was determined because of a suspicion of adverse effects. The serum quetiapine concentration revealed to be < 20 µg/L (therapeutic range through levels between 100 - 500 µg/L). The dose quetiapine was Seroquel XR 800 mg qd. This low concentration could be caused by non compliance, however, after 7 days of hospitalisation and administration of quetiapine by a nurse the serum quetiapine concentration was 40 µg /L, still subtherapeutic.

Another explanation could be enhanced metabolism of quetiapine by CYP3A5*1 polymorphism.[8] However the patient was genotyped as being wild type homozygous CYP3A5*3, so the low serum concentration could not be explained by this pharmacogenetic marker. Evaluation of the co-medication did not reveal any known drug-drug interactions, but she used polystyrene sulfonate and sevelamer for which binding interactions are known.[4-7] The polystyrene sulfonate 15 g qd was co-ingested with quetiapine at 8 AM. Sevelamer was dosed as 2,4 g at 8 AM, 12 PM, and 10 PM, and 4,8 g at 5 PM. We suspected these drugs to bind quetiapine analogous to other drugs, causing absorption inhibition of quetiapine resulting in low serum concentrations.

In-vitro binding assay

In order to investigate possible binding of polystyrene sulfonate or sevelamer to quetiapine, a binding assay was performed in twofold. Therefore 800 mg quetiapine fumarate was dissolved in 600 ml water alone and together with either 15 g polysterene sulfonate and 2,4 g sevelamer. The intraluminal pH of the gastro-intestinal tract fluctuates from pH < 3 in the stomach to 7.4 in the terminal ileum and drops to 5.7 in the caecum.[9] In order to simulate the different pH environments of the gastro-intestinal tract, which may affect binding, the assays were executed at pH 1.5, 5.0 and 7.4, adjusted with either sodium hydroxide or hydrochloric acid. Twenty-five ml of the assay solution was incubated at 37°C for 1 hour under gently shaking conditions after which it was centrifuged and the quetiapine concentration of the supernatant was analysed by HPLC-DAD. The results of the binding assays are depicted in figure 1. Nearly all quetiapine was bound to polystyrene sulfonate (99,1%) independent of the tested pH. Quetiapine was partly bound to sevelamer (62% and 70% at respectively pH 5.0 and 7.4). Under very acidic conditions (pH 1.5) no binding to sevelamer was observed. In the control samples binding percentages of quetiapine were found of about 10% independent of pH, which is probably explained by recovery loss of the assay. These results support the hypothesis that quetiapine could be bound by polystyrene sulphonate and dependent on the pH partly by sevelamer.

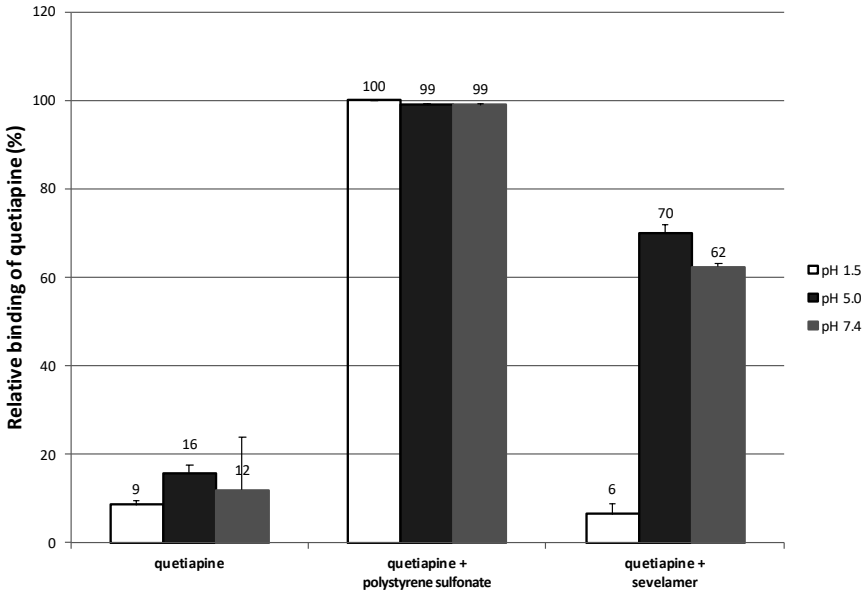

Figure 1 Relative binding of quetiapine fumarate in vitro experiment with polystyrene sulfonate or sevelamer at different pH.

Error bars represent standard deviation of two independent measurements

Separating administration of quetiapine and the resins

In order to further investigate the results from the *in-vitro* experiment in our patient, we changed the time of the quetiapine dose to 10 PM, the polystyrene sulfonate dose to 8 AM and the sevelamer doses to 8 AM, 12 PM and 5 PM. Meanwhile haemodialysis was started in this patient because of further decline of her kidney function. Renal insufficiency should not affect serum quetiapine concentrations but the effect of haemodialysis on serum quetiapine concentrations is unknown.[12,13] Therefore the serum quetiapine concentration was determined before dialysis and after dialysis (duration of the dialysis was 4 hours). The results were 345 µg/L and 145 µg/L respectively.

Discussion

Both polysterene sulfonate and sevelamer are important medicines in the binding of potassium and phosphate respectively. However, little is known about the drug-drug interactions between these resins and quetiapine.

We demonstrated with the *in-vitro* test that quetiapine binds to polystyrene sulfonate and sevelamer. Separating the administration of quetiapine, polystyrene sulphonate and sevelamer resulted in significantly higher serum quetiapine concentrations, from subtherapeutic to therapeutic concentrations. The interpretation of the serum concentrations was however complicated by the start of haemodialysis treatment. In order to examine the influence of haemodialysis serum quetiapine concentrations were measured before and after 4 hours of dialysis. The concentration dropped from 345 µg/L to 145 µg/L indicating that a substantial amount of quetiapine is extracted. Based on these observations we therefore conclude that the absorption of quetiapine improved by separating the co-ingestion of quetiapine with either polystyrene sulfonate and sevelamer. However, our case report has several shortcomings as our *in-vivo* data is limited to one patient. We separated the ingestion times of quetiapine, polystyrene sulfonate and sevelamer but quetiapine was administered as an extended-release formulation which gradually releases the active substance over a period of 20 hours.[10] How long polysterene sulfonate is present in the intestinal tract in unknown. For sevelamer the manufacturer recommends to ingest co-medication 1 hour before or 3 hours after sevelamer intake to avoid possible interactions.[11] Because of the extended-release formulation of quetiapine it is possible that separating the ingestion times not entirely led to elimination of binding of quetiapine to sevelamer or polystyrene sulfonate. Quetiapine immediate release tablets are maybe a better alternative.

During the observation period, our patient started with haemodialysis, which complicated the interpretation of the results, however renal insufficiency should not influence quetiapine serum concentrations. Nevertheless, we think that the *in-vitro* and *in-vivo*

results give a strong indication of a possible quetiapine absorbance inhibition by polysterene sulfonate and sevelamer which needs further investigation. Also, this is the first report that shows that quetiapine is being extracted during haemodialysis which also justifies further research.

Psychiatrists, clinical physicians and pharmacists should be aware of this potential drug-drug interaction as this could lead to treatment failure with quetiapine. We recommend to separate the ingestion times, use quetiapine immediate release tablets and monitor clinical response and serum quetiapine concentrations when patients are treated with quetiapine together with either two of these resins.

References

1. Asmal L, Flegar SJ, Wang J, Rummel-Kluge C, Komossa K, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia (Review). *Cochrane Database Syst Re*v 2013;11:CD006625
2. Adityanjee, Schulz SC. Clinical use of quetiapine in disease states other than schizophrenia. *J Clin Psychiatry* 2002;63 Suppl 13:32-38
3. Chaaban A, Abouchacra S, Gebran N, Abayechi F, Hussain Q, Al Nuaimi N, Hassan ME. Potassium Binders in Hemodialysis Patients: A Friend or Foe? *Ren Fail* 2013;35(2):185-188
4. Summary of product characteristics, Resonium A, Dutch Medicines Evaluation Board, 2 may 1990
5. Kays MB, Overholser BR, Mueller BA, Moe SM, Sowinski KM. Effects of Sevelamer Hydrochloride and Calcium Acetate on the Oral Bioavailability of Ciprofloxacin. *Am J Kidney Dis* 2003;42(6):1253-1259
6. Pieper AK, Buhle F, Bauer S, Mai I, Budde K, Haffner D, Neumayer HH, Querfeld U. The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. *Nephrol Dial Transplant* 2004;19(10):2630-2633
7. Merkle M, Wornle M, Rupprecht HD. The effect of sevelamer on tacrolimus target levels. *Transplantation* 2005;80(5):707
8. Kim KA, Joo HJ, Lee HM, Park JY. Influence of ABCB1 and CYP3A5 genetic polymorphisms on the pharmacokinetics of quetiapine in healthy volunteers. *Pharmacogenet Genomics* 2014;24(1):35-42
9. Fallingborg J. Intraluminal pH of the human gastrointestinal tract. *Dan Med Bull* 1999;46(3):183-196
10. Bui K, Earley W, Nyberg S. Pharmacokinetic profile of the extended-release formulation of quetiapine fumarate (quetiapine XR): clinical implications. *Curr Med Res Opin* 2013;29(7):813-825
11. Summary of product characteristics, Renvela, European Medicines Agency, 10 June 2009
12. Summary of product characteristics, Seroquel, European Medicines Agency, August 2013
13. The Renal Drug Handbook (Third Edition), edited by Ashley C & Currie A, 2009, monograph Quetiapine, p.626