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Chapter 10

Assessing The Binding Interaction Of Polystyrene Sulfonate With Amitriptyline In Healthy Volunteers: A Cross-Over Design The BIND-study

Submitted

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Abstract

Background

Polystyrene sulfonate is used for binding potassium in patients with chronic kidney disease (CKD). Because of its binding properties, it can potentially bind other medications before absorption and thereby decrease their bioavailability and efficacy. Amitriptyline, which may be used by CKD patients for neuropathic pain, shows significant binding to polystyrene sulfonate *in vitro. In vivo* information about this interaction is needed to assess its clinical relevance.

Objective

To determine the effect of polystyrene sulfonate on the exposure of amitriptyline when taken concomitantly in healthy volunteers.

Methods

We performed a prospective cross-over study in nine healthy volunteers. Participants were 18 years of age or older, did not use any medication and had no known allergy to amitriptyline or polystyrene sulfonate. Participants visited Deventer Teaching Hospital twice. Once they received a single dose of amitriptyline 50 milligrams and once they received a single dose of both polystyrene sulfonate 15 grams and amitriptyline 50 milligrams. After intake of the medication six blood samples were collected, at 2, 3, 4, 5, 6, and 8 hours. Blood samples were analysed to determine maximum concentration (Cmax) and area under the curve 0-8 hours after intake ($AUC_{0\text{-}8h}$). Difference in Cmax and $AUC_{0\text{-}8h}$ was analysed with a Wilcoxon signed rank test, a p-value <0.05 was considered statistically significant.

Results

Of the nine participants included, eight participants completed both visits to the hospital. Mean maximum concentration (Cmax) of amitriptyline was 35.61µg/l (±9.23µg/l) when taken alone, compared to 9.25µg/l (±3.19µg/l) when taken with polystyrene sulfonate ($p=0.012$). Mean $AUC_{0\text{-}8h}$ of amitriptyline was 168.20h*µg/l (±33.79h*µg/l) when taken alone and 45.78h*µg/l (±18.64h*µg/l) when taken with polystyrene sulfonate ($p=0.012$).

Conclusion

These results show a significant decrease in exposure of amitriptyline of approximately 75% when taken concomitantly with polystyrene sulfonate, thereby probably compromising therapy efficacy. Patients using both amitriptyline and polystyrene sulfonate should be informed to separate intake of these medications.

Introduction

Polystyrene sulfonate is a resin that is used to bind potassium for the treatment of hyperkalaemia. It is often used by patients with chronic kidney disease (CKD), who may also undergo haemodialysis, when dietary restrictions are not sufficient.[1,2] Polystyrene sulfonate is a non-absorbed cation exchange resin that lowers the plasma potassium concentration through exchange of potassium and sodium- or calcium-ions in the gastro-intestinal tract. The effect mainly occurs in the colon and partly in the small intestine.[3] Because of its binding properties, polystyrene sulfonate may potentially bind to other medications before absorption and thereby decrease their bioavailability and clinical efficacy.

Binding of polystyrene sulfonate to other medications has been investigated to a limited extent for a few medications in clinical studies or case reports.[4-6] An FDA Drug Safety Communication from 2017 discourages simultaneous use of polystyrene sulfonate with all other orally taken medication.[7] However, practically this is often difficult for patients with CKD and haemodialysis who have comorbidities and need several other medications.[8] Additionally, the prevalence of potential drug-drug interactions in this population is high, indicating that more drug binding interactions with polystyrene sulfonate may be of clinical relevance than already described in literature.[8,9-14] Therefore, it is necessary to gather more knowledge on drug binding interactions with polystyrene sulfonate.

A previous study of our research group identified several new potential binding interactions with polystyrene sulfonate, based on their chemical structure, one of which was the tricyclic antidepressant amitriptyline [unpublished]. Amitriptyline is usually used as an analgesic for neuropathic pain in patients with CKD and haemodialysis.[15,16]

We performed an *in vitro* screening of the binding capacity of polystyrene sulfonate to amitriptyline and found that amitriptyline is almost completely bound to polystyrene sulfonate [unpublished]. *In vitro* experiments in order to assess binding have a high sensitivity but specificity may be low.[17] In some studies *in vitro* binding of drug-resin combinations was also found *in vivo*, but in other studies *in vitro* binding could not be confirmed *in vivo.*[4,5,17-27]

Therefore, assessment of the clinical relevance of the *in vitro* binding between amitriptyline and polystyrene sulfonate *in vivo* is warranted. The aim of this study was to determine the effect of polystyrene sulfonate on the exposure of amitriptyline when taken simultaneously, in healthy volunteers.

Methods

We performed a prospective cross-over trial in healthy volunteers. Eligible participants were aged 18 years or older. Participants were excluded from the trial if they met one

of the following criteria: known allergy to amitriptyline or polystyrene sulfonate, known renal or hepatic impairment, pregnancy, breast feeding, use of other medication within 24 hours of the study period (oral contraceptives within 12 hours of the study period), contra-indication for one of the investigated substances (such as recent myocardial infarction, cardiac arrhythmias, hypokalaemia and obstructive bowl disease) or history of a gastro-intestinal condition that may interfere with the absorption of amitriptyline. All participants gave written informed consent before study entry.

Participants visited the Deventer Teaching Hospital on two separate days. On day one they received a single dose of amitriptyline 50 milligrams and on day two a single dose of amitriptyline 50 milligrams in combination with a single dose of sodium polystyrene sulfonate 15 grams. Participants were given the same snack on both occasions before intake of the medication, as polystyrene sulfonate is usually taken with meals. After intake of the medication, six blood samples were collected, at 2, 3, 4, 5, 6, and 8 hours. Side effects of amitriptyline and polystyrene sulfonate were registered. There was a wash out period between the first and second visit of at least one week, to ensure all amitriptyline was removed from the body before the second visit, based on the half-life of amitriptyline of 25 hours.[28]

The primary objective was to determine whether polystyrene sulfonate has a significant effect on exposure of amitriptyline, when taken simultaneously, compared to amitriptyline taken alone. This was expressed as Cmax and area under the curve 0-8 hours after intake ($AUC_{0\text{-}8h}$). The assay used to quantify amitriptyline serum concentrations was developed and validated in our laboratory.

The number of participants needed was based on the mean maximum concentration (Cmax) after a single dose of amitriptyline 50 milligrams (30.95µg/l) and an expected reduction of 50% in Cmax of amitriptyline when taken concomitantly with polystyrene sulfonate.[28] The expected reduction was based on results of our previous *in vitro* study [unpublished]. The probability is 93% that we detect a difference in Cmax at a one-sided 0.025 significance level, if the true difference between treatments is 16µg/l (50%), based on the assumption that the standard deviation of the difference in Cmax is 9µg/l.[28] As a result, to compensate for possible loss-of-follow-up, nine persons were included in the trial in order to be able to evaluate six participants.

Amitriptyline concentrations were quantified using a LC/MSMS method (Shimadzu LCMS-8050). A kinetex 1.7 um 30x2.1mm UPLC column was used combined with a binary gradient from 80% ammonium formate 10mM in 0.1% formic acid to 80% 0.1% formic acid in acetonitrile. The oven temperature was set at 40°C, the flow at 0.6 ml/min and the injection volume was 3 µl. Amitriptyline-D3-HCl was used as internal standard. Amitriptyline was detected with MRM 278.20 → 233.35 and amitriptyline-D3-HCl with MRM 281.2 → 233.1, measured in positive mode. Linearity was demonstrated from

1-100 µg/l. The between run accuracy ranged from 88.5-107.0%. The variation coefficient of the between run precision ranged from 5.7-7.4%. The method was validated in line with the European Medicines Agency guideline on bioanalytical validation.[29] This assay is routinely used for Therapeutic Drug Monitoring in clinical practice. Data is reported quantitatively for all time points.

Cmax was determined as the highest concentration measured and $AUC_{0\text{-}8h}$ was calculated by using the trapezoidal rule. Difference in Cmax and $AUC_{0\text{-}8h}$ was analysed with a Wilcoxon signed rank test, a p-value <0.05 was considered statistically significant. Participant demographics; age, length, weight, gender and race, were collected at inclusion.

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee, the 1964 Helsinki Declaration and its later amendments, and Good Clinical Practice. The trial protocol was approved by an independent ethics committee and institutional review boards.

Results

Eight of the nine participants enrolled in the study completed both visits to the hospital. Demographic information is presented in table 1.

One participant did not complete the study, because sample withdrawal was experienced as unpleasant.

Table 1 Demographics of the participants

Subject characteristics	N=8
Age, years (median, Q1-Q3)	27.5 (24.25-28.75)
Length, cm (median, Q1-Q3)	179 (166-188)
Weight, kg (median, Q1-Q3)	72 (66-80)
Gender n (%)	
Male	4 (50)
Female	4 (50)
Race n (%)	
Caucasian	8 (100)

Figure 1 shows the serum concentration time curves of amitriptyline of the eight participants, when taken alone and when taken concomitantly with polystyrene sulfonate.

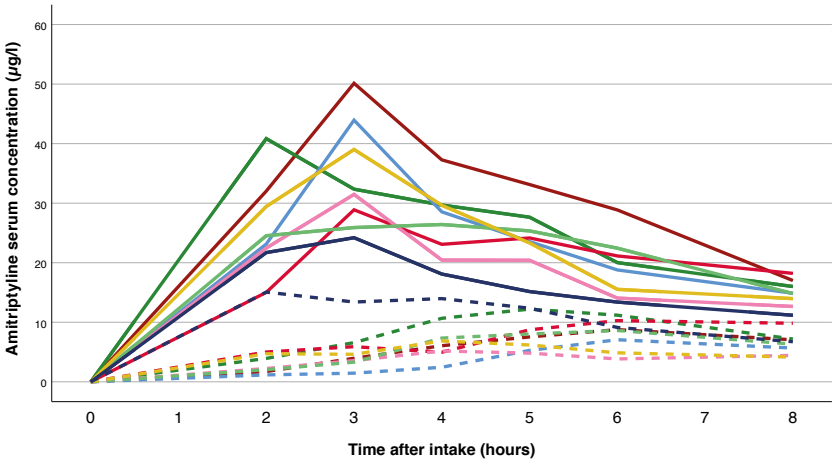

Figure 1 Amitriptyline serum concentration over time (µg/l) of each participant after intake of amitriptyline alone (continuous line) and concomitantly with polystyrene sulfonate (dotted line)

The Cmax of amitriptyline when taken alone amounted 35.61 µg/l ± 9.23 µg/l, compared to a Cmax of 9.25 µg/l ± 3.19 µg/l when amitriptyline was taken with polystyrene sulfonate. This difference was statistically significant (p=0.012) and these results are depicted in figure 2. Cmax was reached at a later time point, in all but one participant, when amitriptyline was taken with polystyrene sulfonate, compared to amitriptyline alone, i.e. 4-6 hours versus 2-4 hours (figure 1).

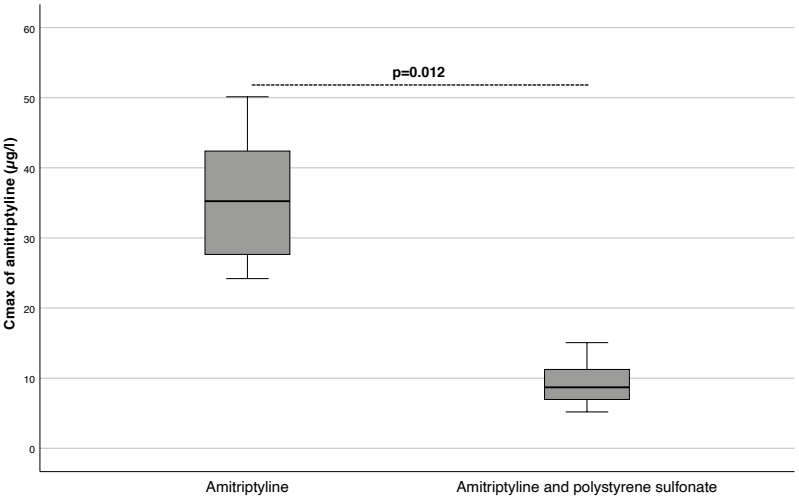

Figure 2 Comparison of Cmax of amitriptyline after intake of amitriptyline alone and concomitantly with polystyrene sulfonate

Exposure to amitriptyline in both situations is shown in figure 3. The $AUC_{0\text{-}8h}$ of amitriptyline was 168.20 h*µg/l ± 33.79 h*µg/l when taken alone compared to 45.78 h*µg/l ± 18.64 h*µg/l when taken simultaneously with polystyrene sulfonate (p=0.012).
The Cmax and $AUC_{0\text{-}8h}$ of amitriptyline decreased with 74% and 73%, respectively, when intake was concomitant with polystyrene sulfonate.
Most common adverse effects of amitriptyline taken alone were drowsiness/sleepiness in eight subjects (100%), and nausea and dry mouth, both in one subject (12.5%). When amitriptyline and polystyrene sulfonate were taken concomitantly four subjects reported drowsiness/sleepiness (50%), one subject reported dizziness (12.5%) and one subject had a tingling sensation in the fingers (12.5%).

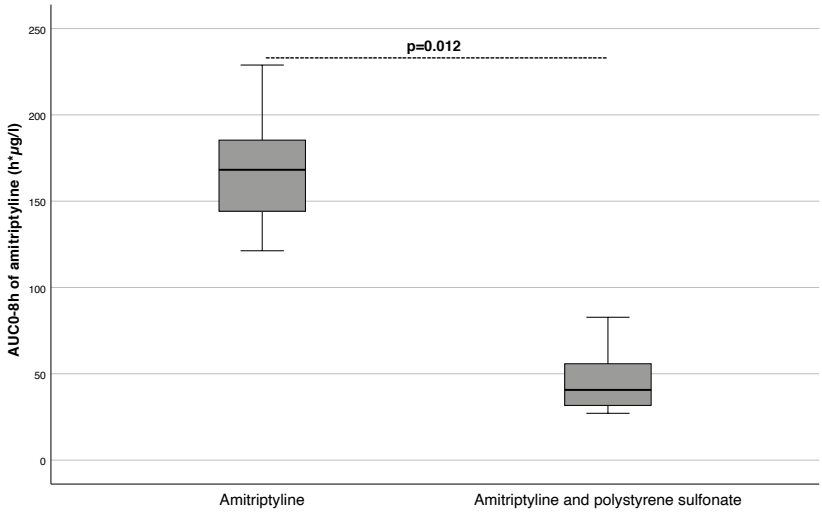

Figure 3 Comparison of $AUC_{0\text{-}8h}$ of amitriptyline after intake of amitriptyline alone and concomitantly with polystyrene sulfonate

Discussion

In this prospective cross-over trial in healthy volunteers we have shown that Cmax and $AUC_{0\text{-}8h}$ of amitriptyline is significantly decreased when it is taken simultaneously with polystyrene sulfonate. This result confirms that the binding interaction between amitriptyline and polystyrene sulfonate that was found *in vitro* is also present *in vivo*.
Some medications have already been identified that bind to polystyrene sulfonate. Hoge et al. described a case where quetiapine blood concentrations were undetectable with simultaneous use of polystyrene sulfonate in a haemodialysis patient. A binding

interaction was detected *in vitro* after which intake of medication was separated by eight hours and therapeutic blood levels of quetiapine were achieved.[4] Another case has been described where therapy with levothyroxine failed after initiation of concomitant polystyrene sulfonate therapy and was restored after staggered intake of the medication. This binding interaction was also confirmed *in vitro*.[6] Moreover, a study in healthy volunteers showed a reduction in AUC and peak concentration of lithium when taken simultaneously with polystyrene sulfonate.[5] The results of our study add to the already known binding interactions with polystyrene sulfonate. Our own previous *in vitro* study indicates that there may be more relevant binding interactions that are still unknown which should be investigated *in vivo* to be able to give tailored advice. This would be preferred to the current general advice by the FDA which is staggered intake of polystyrene sulfonate with all other orally taken medication. This is very difficult to achieve in daily practice considering frequent polypharmacy and associated complex dosing schedules in this population.[3,7] Moreover, currently, medication surveillance on oral co-medication with polystyrene sulfonate in general is not performed in clinical practice. Our study highlights the need for specific drug-drug interaction monitoring for patients taking polystyrene sulfonate, instead of a general advice that is not feasible in clinical practice.

A strength of this study is the cross-over design, which eliminates variation between subjects when comparing Cmax and $AUC_{0\text{-}8h}$ in both situations. In addition, subjects where healthy adults that did not use any other medication that might influence the amount of binding of polystyrene sulfonate to amitriptyline. Because of this, we were able to properly investigate the effect of polystyrene sulfonate on the exposure of amitriptyline. Also, amount and composition of the food consumption before intake of the medication was standardized, in accordance with daily practice, in which polystyrene sulfonate is taken with food. By consuming the same snack at both visits, we minimalised variation in the effect of food on absorption of amitriptyline and on the binding capacity of polystyrene sulfonate. However, in daily practice polystyrene sulfonate is taken with larger meals to increase the degree of binding to potassium, which is obtained with a patient's diet. The snack given to the participants in this study might not have completely simulated the effect of a meal, so the binding capacity of polystyrene sulfonate to amitriptyline may be smaller when taken with a full meal, instead of a snack, with less effect on exposure of amitriptyline than seen in this study.

A limitation of this study concerns the inclusion of healthy volunteers, whereby the effect of CKD itself and associated comorbidities on exposure of amitriptyline is not accounted for. It is known that CKD patients may experience gastroparesis, which may affect the extend and rate of drug absorption.[30,31] The amount of binding by polystyrene sulfonate to amitriptyline seen in this study might, therefore, be different in patients with CKD and haemodialysis.

Based on the results of this study, where we see a decrease in Cmax of amitriptyline of 74% and a decrease in $AUC_{0\text{-}8h}$ of 73% because of simultaneous intake with polystyrene sulfonate, staggered intake of these medications is needed in daily practice. We also advice to include this binding interaction in the electronic medication surveillance system of pharmacists and physicians.

The optimal time interval between intake of polystyrene sulfonate and comedication has not been assessed yet. In clinical practice, a time interval of three hours is recommended between intake of polystyrene sulfonate and other orally taken medications, which is based on time needed for gastric emptying in healthy individuals.[3] However, a substantial part of CKD patients experience gastroparesis in which a high variability in gastric emptying is seen, which can be accompanied by dysmotility-like dyspepsia. This makes it hard to evaluate whether gastroparesis is present in the individual user of polystyrene sulfonate.[30,31] Gastroparesis may prolong the time to reach maximum drug concentrations, but this delay generally does not affect the extent of absorption.[33] This raises the question whether the standard time interval for staggered dosing can be used or that a longer time interval between intake of polystyrene sulfonate and amitriptyline is needed in CKD patients. This has to be further investigated.

The adverse effects, sleepiness, nausea, dry mouth and dizziness, reported by subjects are all known adverse effects of amitriptyline.[28] Nausea is also reported in users of polystyrene sulfonate, but is usually seen when calcium polystyrene sulfonate is used and not the sodium salt that was used in this study.[3,33] Sleepiness/drowsiness seems to be reported less by participants when amitriptyline is combined with polystyrene sulfonate, which is in line with our results of decreased exposure.

Our findings are clinically relevant because reduced bioavailability of amitriptyline due to concomitant intake with polystyrene sulfonate can lead to reduced efficacy and treatment failure of amitriptyline in CKD and haemodialysis patients. This is particularly not wanted in these patients for which polypharmacy is common, the risk of drug-drug interactions is high and appropriate alternative treatment is difficult to find.

Conclusion

Polystyrene sulfonate significantly decreases exposure to amitriptyline with approximately 75% when taken concomitantly and intake should therefore be staggered. Further research in patients with CKD and haemodialysis is needed to establish the optimal time interval needed between intake for safe and effective use of amitriptyline in combination with polystyrene sulfonate.

Ethics approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee, the 1964 Helsinki Declaration and its later amendments. The trial protocol was approved by the independent ethics committee of Isala (Zwolle, Netherlands).

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