Pharmacokinetics and dose recommendations of Niaspan® in chronic kidney disease and dialysis patients

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Abstract
Background. Niaspan® is an extended-release formulation of nicotinic acid with improved tolerability compared with the immediate-release and sustained-release formulations. It is used to treat hypertriglyceridaemia with low high-density lipoprotein levels. This type of dyslipidaemia frequently appears in patients with chronic kidney disease (CKD). Dose recommendations for these patients are not available because pharmacokinetic data are missing. The present study was performed to analyse the pharmacokinetics of prolonged-release nicotinic acid in CKD and in dialysis patients to derive dose recommendations.

Methods. Ten dialysis patients and eight patients with CKD were enrolled in a prospective, three-period, open-label pharmacokinetic study. They received in the first week 500 mg Niaspan® per day, in the second week 1000 mg/day and in the third week 1500 mg/day. On the fourth day of every treatment unit, 11 plasma samples were collected for 24 h post-dose and analysed for nicotinic acid (NA) and its metabolites nicotinamide and nicotinuric acid (NUA).

Results. Median plasma NA concentrations in subjects with CKD were obviously higher than in dialysis patients, but not higher than reported in patients without renal impairment. tmax of NA were on average 0.75 h in dialysis patients and 3.0 h in CKD patients and, therefore, especially in dialysis patients, clearly shorter than expected for extended-release formulations. It is particularly noticeable that the AUC, Cmax and t1/2 of the metabolite NUA are significantly higher in dialysis patients in comparison to CKD patients. This may indicate that the dialysis was not effective in removing this metabolite. However, there was no correlation between the incidence of flush and the concentration of NUA. Another possibility could be a drug–drug interaction with omeprazole via CYP450 enzymes.

Conclusions. These data suggest that no dose adjustment of Niaspan® is necessary in patients with renal impairment. Despite an extended-release formulation of NA, we could not detect a delay in tmax especially in dialysis patients. We found no correlation between the incidence of flush and the NUA concentration. Furthermore, there were hints of an interaction with omeprazole.

Keywords: dialysis patients; dose recommendation; extended-release nicotinic acid; patients with CKD; pharmacokinetics

Introduction
Nicotinic acid (niacin) is a naturally occurring water-soluble vitamin of the B complex (vitamin B3) and has been used for decades to treat dyslipidaemia. It lowers plasma triglyceride
levels as well as low-density lipoprotein (LDL) and very-low-density lipoprotein cholesterol. Furthermore, its high-density lipoprotein (HDL) cholesterol-elevating effect has stimulated a new interest in its pharmacological potential [1]. However, the side effects of flushing and hepatotoxicity considerably restrict the use of niacin. With the development of a new extended-release (ER) formulation of niacin, the risk of hepatotoxicity was appreciably reduced. Nicotinic acid is currently available in three formulations, including immediate release (IR), sustained release (SR) and ER. The ER niacin formulation has a delivery system intermediate to that of IR and SR niacin allowing drug absorption over 8–12 h, which should also reduce the incidence of flushing [2].

Newer studies showed a dose-dependent effect of the ER formulation on lipid parameters. LDL cholesterol, triglycerides and lipoprotein(a) were reduced by 5–25, 27–38 and 14–30%, respectively, whereas HDL cholesterol increased by 23–29% [3–6]. Furthermore, Taylor et al. [7] demonstrated that the use of ER niacin in combination with a statin causes a significant regression of carotid intima–media thickness and that niacin is superior to ezetimibe in this aspect.

Niacin is rapidly absorbed after oral administration and undergoes extensive, saturable first-pass metabolism via two major metabolic pathways [2,8]; variant one involves a number of oxidation–reduction reactions leading first to nicotinamide (NAM), which is then further metabolized to, among others, nicotinamide adenine dinucleotide; these are then renally excreted. At intermediate and high pharmacological doses (1–3 g), an increasing fraction of nicotinic acid is conjugated with glycine to form nicotinuric acid (NUA) and excreted by the kidney [1]. NUA has been reported to be linked to the flushing effect, whereas the metabolites of the non-conjugative pathway are likely to be involved in the hepatotoxicity [9,10].

Until now, there are few published pharmacokinetic data on niacin, and no pharmacokinetic data are available in patients with renal impairment. Therefore, the present study was performed to analyse the pharmacokinetics of extended-release nicotinic acid in patients with chronic kidney disease (CKD) and patients with chronic renal failure requiring dialysis to derive dose recommendations. Furthermore, the incidence of essential adverse effects of the study should be examined.

Recently, we showed that niacin lowers asymmetric dimethylarginine (ADMA), a methylated amino acid that causes endothelial dysfunction by competitive inhibition of the NO synthase in 26 patients from a lipid clinic with low HDL cholesterol [11]. As it is now widely accepted that CKD is a risk factor for cardiovascular disease, ADMA might represent a novel risk factor in this context. CKD is associated with increased oxidative stress, with correlations between ADMA and markers such as erythrocyte superoxide dismutase and oxidized LDL [12]. Oxidative stress is associated with reduced dimethylarginine dimethylaminohydrolase (DDAH) activity, the enzyme that metabolizes ADMA to yield citrulline and dimethylamine, and ADMA accumulation. Therefore, the effect of niacin on ADMA plasma levels in CKD and dialysis patients should be examined.

**Materials and methods**

**Study design**

The study was performed as a prospective, three-period, open-label trial. Each patient received in the first week 500 mg Niaspan® per day, in the second week 1000 mg/day and in the third week 1500 mg/day, whereas the tablets were taken orally at 8:00 a.m. every day. On the fourth day of every treatment unit, venous blood samples (7.5 mL) were taken immediately before the application of Niaspan® and 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after administration. After coagulation, blood cells were separated by centrifugation at 2440× g for 15 min. The resulting blood serum was stored at −20°C until analysis.

**Subjects**

Ten dialysis patients (mean age 50.8±2.8 years) and eight patients with CKD (mean age 63.7±2.0 years) participated in the study. The demographic data and co-medication for all 18 study patients are shown in Table 1. The glomerular filtration rates (GFR) of all patients were estimated by the Modification of Diet in Renal Disease formula. All dialysis patients (GFR 7.2±2.1 mL/min) underwent intermittent haemodialysis every third or fourth day. The median time of dialysis sessions was 12.5 h (9.0–16.5 h). The sessions started at different times of the day (in the morning, in the midday and sometimes also in the evening). Blood flow was between 280 and 300 mL/min. Dialysates used were D 263 (Gambro, Hannover, Germany; composition: 4.0 mmol/L potassium, 1.25 mmol/L calcium, 110.5 mmol/L magnesium, 0.5 mmol/L calcium, 110.5 mmol/L magnesium, 1.0 g/L glucose, 138.0 mmol/L sodium, 32.0 mmol/L bicarbonate and 3.0 mmol/L acetate) or D 283 (Gambro; composition: 3.0 mmol/L potassium, 1.25 mmol/L calcium, 109.5 mmol/L chloride, 0.5 mmol/L magnesium, 1.0 g/L glucose, 138.0 mmol/L sodium, 32.0 mmol/L bicarbonate and 3.0 mmol/L acetate) or D 283 (Gambro; composition: 138.0 mmol/L sodium, 32.0 mmol/L bicarbonate and 3.0 mmol/L acetate) or D 283 (Gambro; composition: 138.0 mmol/L sodium, 32.0 mmol/L bicarbonate and 3.0 mmol/L acetate). Interdialytic fluid over the night was between 250 and 300 mL. The inclusion criteria were dialysis treatment for at least 4 weeks and absence of any acute clinical event (e.g. myocardial infarction, stroke) or inflammation at the time of recruitment. Niacin was applied on a non-dialysis day (short interval). The patients with CKD had an estimated GFR of 31.0±16.7 mL/min. All patients gave their written informed consent to the study. The study protocol was approved by the ethics committee of the University of Magdeburg and was conducted in accordance with the declaration of Helsinki and German federal guidelines.

**Pharmacokinetic analyses**

Plasma concentrations of nicotinic acid (NA) and its main metabolites NAM and NUA were determined by liquid chromatography–mass spec-
The lipid parameters are shown for all 18 patients in Table 2. Treatment with 1500 mg niacin increased HDL cholesterol by 24% in dialysis patients and by 11% in patients with CKD (P=0.008 and P=0.036, respectively). Triglycerides were significantly reduced by 27% (P=0.012) only in patients with CKD. There was a slight decrease in LDL cholesterol by 9.8% (P=0.036) in dialysis patients. Neither patient group showed any significant disturbance in safety parameters.

### Pharmacokinetic parameters

Median pharmacokinetic parameters for patients with CKD are given in Table 3 and for dialysis patients in Table 4. The plasma concentrations of NA and NAM tended to be higher in CKD patients than in dialysis patients, whereas maximum plasma concentrations (C\(_{\text{max}}\)) were achieved very early in both groups. t\(_{\text{max}}\) values of NA were on average 0.75 h in dialysis patients and 3.0 h in patients with CKD, and significantly different (P=0.008) from each other. This is, particularly for dialysis patients, clearly shorter than expected for extended-release niacin.

### Results

Side effects and blood samples

Adverse effects, including flushing and pruritus, were registered. Furthermore, all lipids (triglycerides, total cholesterol, HDL and LDL cholesterol) and safety parameters (ALT, AST, γ-GT) were determined by commercial enzymatic methods in a random-access analyzer (Modular, Roche Diagnostics) on the fourth day of every treatment. All reagents and calibrators were also from Roche Diagnostics.

For the determination of plasma asymmetric dimethylarginine levels, we used the high performance liquid chromatography–tandem mass spectrometry method published recently by our group [14]. The intra-day precision was 4.6% and the inter-day precision was 3.3%.

### Statistical analyses

Results were expressed as the mean±SD values and as the median±interquartile ranges, respectively. Since the data showed no normal distribution, the Mann–Whitney U-test was applied and differences were considered significant at P<0.05 (SPSS 15.0).

<table>
<thead>
<tr>
<th>Nicotinic acid</th>
<th>Baseline</th>
<th>After therapy with 1500 mg</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (μg/mL)</td>
<td>0.06 (0.3)</td>
<td>2.42 (3.8)</td>
<td>4.22 (2.0)</td>
</tr>
<tr>
<td>t(_{\text{max}}) (h)</td>
<td>3.0 (1.5)</td>
<td>3.0 (1.0)</td>
<td></td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>1.77 (1.46)</td>
<td>0.63 (2.38)</td>
<td></td>
</tr>
<tr>
<td>AUC (μg h/mL)</td>
<td>1.44 (0.06)</td>
<td>6.66 (7.05)</td>
<td>12.41 (11.16)</td>
</tr>
</tbody>
</table>

### Table 3. Median pharmacokinetic parameters (interquartile ranges) in patients with CKD

<table>
<thead>
<tr>
<th>Nicotinuric acid</th>
<th>Baseline</th>
<th>After therapy with 1500 mg</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (μg/mL)</td>
<td>0.08 (0.05)</td>
<td>0.09 (0.05)</td>
<td>0.55 (0.49)</td>
</tr>
<tr>
<td>t(_{\text{max}}) (h)</td>
<td>8.0 (4.0)</td>
<td>8.0 (4.0)</td>
<td>3.5 (4.0)</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>25.84 (21.99)</td>
<td>25.84 (21.99)</td>
<td>8.65 (14.46)</td>
</tr>
<tr>
<td>AUC (μg h/mL)</td>
<td>1.55 (1.11)</td>
<td>4.25 (4.05)</td>
<td>6.27 (6.25)</td>
</tr>
</tbody>
</table>

### Table 4. Median pharmacokinetic parameters (interquartile ranges) in dialysis patients

<table>
<thead>
<tr>
<th>Nicotinic acid</th>
<th>Baseline</th>
<th>After therapy with 1500 mg</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (μg/mL)</td>
<td>0.82 (2.14)</td>
<td>0.82 (2.14)</td>
<td>6.09 (15.42)</td>
</tr>
<tr>
<td>t(_{\text{max}}) (h)</td>
<td>2.0 (7.0)</td>
<td>2.0 (7.0)</td>
<td>2.0 (4.5)</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>43.96 (75.05)</td>
<td>43.96 (75.05)</td>
<td>22.53 (6.25)</td>
</tr>
<tr>
<td>AUC (μg h/mL)</td>
<td>12.98 (50.33)</td>
<td>12.98 (50.33)</td>
<td>88.61 (349.45)</td>
</tr>
</tbody>
</table>
release formulations. In the second (1000 mg/day) and the third (1500 mg/day) week of Niaspan® treatment, an approximately 2-fold higher AUC was observed in CKD patients compared with dialysis patients.

The plasma elimination half-life of the metabolite NAM was in dialysis patients significantly longer than in the other group (P=0.001). Furthermore, it is particularly noticeable that the AUC, $C_{\text{max}}$, and $t_{1/2}$ of the metabolite NUA were significantly higher in dialysis patients in comparison to patients with CKD.

The mean plasma concentration curves of NA, NAM and NUA are shown in Figures 1, 2 and 3. Mean NA
and NAM plasma concentrations were not significantly different between the two groups, but tend to be higher in patients without dialysis. However, particularly noticeable were the significantly higher NUA plasma concentrations in dialysis patients. This indicates that the dialysis was not effective in removing this metabolite.

Correlation of pharmacokinetic parameters and adverse effects

The metabolite NUA is supposed to be responsible for the flushing effect of niacin. Although there are significantly higher levels of NUA in dialysis patients than in patients with CKD (Figure 3), we could not find any correlation between the incidence of flush and the concentration of NUA.

Most subjects experienced cutaneous flushing and pruritus during the study. Of the 18 subjects receiving Niaspan®, only five subjects showed no flushing (one with acetylsalicylic acid). Moderate flushing and pruritus occurred in 6 out of 10 dialysis patients and seven out of eight patients with CKD, whereas two patients were taking acetylsalicylic acid. Overall, the number of flushing episodes appeared to increase as the dose increased. Only four subjects showed flushing during the first week of treatment (500 mg Niaspan®), whereas eight subjects reported flushing and pruritus in the second week (1000 mg Niaspan®). The delay from ingestion of study treatment to the onset of flushing and itching tended to increase with time, from a median duration of 30 min at Week 1 (500 mg Niaspan®) to 60 min at Week 3 (1500 mg Niaspan®). Women tended to flush for a longer period than men, with median duration of flushing of 60 and 35 min, respectively.

No other adverse effects were observed.

Observed drug interaction

There might be evidence to suggest an interaction between omeprazole and Niaspan® in dialysis patients. We found a decreased plasma NA concentration in dialysis patients under omeprazole therapy (Figure 4). Additionally, the metabolism of NUA or excretion was decelerated (Figure 5).

Effect on ADMA plasma concentration

The effect of the different dosages of Niaspan® on ADMA plasma concentrations is shown in Figure 6. A repeated measures ANOVA revealed a main effect of dosage that was due to smaller ADMA levels after the highest dose of Niaspan® in the dialysis patients, probably indicating a reduced oxidative stress (F=3.57, P=0.031). On the other hand, this effect was not found in the CKD patients.

Fig. 4. Mean plasma concentration courses of nicotinic acid over 24 h on Day 4 after intake of an oral dose of 1000 mg/day niacin (black circle) and 1000 mg/day niacin under omeprazole therapy (grey square) in dialysis patients.

Fig. 5. Mean plasma concentration courses of the metabolite nicotinuric acid over 24 h on Day 4 after intake of an oral dose of 1000 mg/day niacin (black circle) and 1000 mg/day niacin under omeprazole therapy (grey square) in dialysis patients.

Fig. 6. Effect of niacin treatment with 500, 1000 and 1500 mg and placebo for 1 week on ADMA concentrations versus baseline. A repeated measures ANOVA revealed a main effect of dosage that was due to a reduction of ADMA concentrations at the highest dose of Niaspan® in dialysis patients probably indicating a reduced oxidative stress.
Discussion

Niacin has been known for decades to reduce blood lipids, but no pharmacokinetic data on niacin and its metabolites are available in patients with renal impairment. Menon et al. [15] reported in healthy male volunteers that niacin is extensively metabolized following oral administration, whereas plasma levels of the parent niacin were higher than its metabolites. In our dialysis patients (on a non-dialysis day), the AUC levels of the metabolites especially of NUA were considerably higher than the parent niacin level. Also, in patients with renal insufficiency, plasma levels of NUA were clearly higher than plasma levels of niacin.

These data indicate that niacin is extensively metabolized in patients with renal impairment and is dialysable. Niacin has a protein binding <20% and a molecular weight of 121 g/mol [16]. However, the metabolites, particularly NUA, accumulated in patients with renal impairment and is dialysable. NUA were clearly higher than plasma levels of niacin. Of NUA were considerably higher than the parent niacin level. In our dialysis patients (on a non-dialysis day), the AUC levels of the metabolites especially than its metabolites. In our dialysis patients (on a non-
dialysis day), the AUC levels of the metabolites especially of NUA were considerably higher than the parent niacin level. Also, in patients with renal insufficiency, plasma levels of NUA were clearly higher than plasma levels of niacin.

The most frequent side effect was flushing, as expected. The incidence of flushing (72%) was similar to that observed previously with this agent in controlled trials, where an incidence of flushing of 58–83% has been reported at daily nicotinic acid doses of 1000–2000 mg [20,21]. It was assumed that NUA is likely to be involved in the flushing effect, whereas NAM appears to be linked to hepatotoxicity [9,10]. However, Stern [17] reviewed that NA and not NUA is responsible for the flushing effect and that the suggestion that NAM causes hepatotoxicity could not be supported by any data. The results of our study supported the hypothesis that NUA is not responsible for the flushing effect. First, we could not find any correlation between the incidence of flush and the concentration of NUA. Secondly, more patients with CKD and consequently higher plasma concentrations of NA showed flushing than dialysis patients with lower NA plasma concentrations. The reported C\text{max} value of 4.9 μg/mL for oral 1500 mg Niaspan® in patients without renal impairment [15] is similar to that found in our patients with CKD. However, dialysis patients achieved lower C\text{max} levels. We wonder about the difference in C\text{max} of NA between dialysis patients and patients with CKD. This indicates an extensive hepatic metabolism. We checked the co-medication and found that 7 of the 10 dialysis patients received omeprazole. Omeprazole is metabolized in the liver via cytochrome P450 enzyme system (CYP450, CYP3A4 and CYP2C19). Nothing is known about the interaction between niacin and CYP450 in vivo.

Recently, an in vitro inhibition study revealed that, at their therapeutic concentrations, both NA and NAM inhibit CYP2D6 [18]. Nothing is known concerning induction, and CYP2C19 was not tested. However, one could speculate that omeprazole induces faster metabolism of NA and is therefore responsible for the reduced C\text{max} of niacin in the dialysis patients and for the higher concentration of NUA. The underlying mechanism is unclear from our data and should be the focus in further in vivo studies. Additionally, a further interaction between niacin and phenprocoumon (extensively metabolized via CYP450), and simvastatin and atorvastatin, respectively, could not be completely excluded. However, all three patients without omeprazole received phenprocoumon, simvastatin or both and still had higher plasma levels of niacin. Moreover, four of the seven patients who underwent omeprazole therapy had neither phenprocoumon nor a statin, but exhibited reduced C\text{max}. Therefore, an interaction between niacin and omeprazole is probable.

Niacin is known to improve lipid metabolism and exert antioxidant/anti-inflammatory actions. In a recent study, it was shown in rats with chronic renal failure that long-term niacin supplementation resulted in partial amelioration of proteinuria, glomerulosclerosis and tubulointerstitial injury, which is also probably mediated by a reduction of oxidative factors [19]. We could demonstrate here that, in dialysis patients but not in patients with CKD, the highest dose of niacin reduced the cardiovascular risk factor ADMA. The majority of ADMA is metabolized by the enzyme DDAH, and this enzyme can be reduced by various oxidative stresses resulting in an increased ADMA concentration. Obviously, niacin could have reduced oxidative stress and therefore decreased the ADMA concentration. We have no explanation at the moment for the fact that this effect was only found in dialysis patients and not in CKD patients.

In conclusion, these data suggest that no dose adjustment of Niaspan® is necessary in patients with renal impairment. Furthermore, there is obviously no advantage of the extended-release preparation of niacin especially in dialysis patients. However, physicians should be aware of the possibility of adverse effects, particularly at high doses of niacin.

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Conflict of interest statement. None declared.

References

Low-GDP peritoneal dialysis fluid (‘balance’) has less impact in vitro and ex vivo on epithelial-to-mesenchymal transition (EMT) of mesothelial cells than a standard fluid

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Abstract

Background. Peritoneal membrane deterioration during peritoneal dialysis (PD) is associated with epithelial-to-mesenchymal transition (EMT) of mesothelial cells (MC), which is believed to be mainly due to glucose degradation products (GDPs) present in PD solutions. Here we investigate the impact of GDPs in PD solutions on the EMT of MC in vitro and ex vivo.

Methods. For in vitro studies, omentum-derived MC were incubated with standard PD fluid or low-GDP solution diluted 1:1 with culture medium. For ex vivo studies, 33 patients, who were distributed at random to either the ‘standard’ or the ‘low GDP’ groups, were followed over 24 months. Effluents were collected every 6 months to determine EMT markers in effluent MC.

Results. Exposure of MC to standard fluid in vitro resulted in morphological change into a non-epitheloid shape, down-regulation of E-cadherin, indicative of EMT, and in a strong induction of vascular endothelial growth factor (VEGF) expression. In contrast, in vitro exposure of MC to low-GDP solution did not lead to these phenotype changes. This could be confirmed ex vivo, as the prevalence of non-epitheloid...