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ORIGINAL WORK

Incidence of Arterial Hypotension in Patients Receiving Peroral or Continuous Intra-arterial Nimodipine After Aneurysmal or Perimesencephalic Subarachnoid Hemorrhage

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Abstract

Background: Oral nimodipine is used for prophylaxis and treatment of delayed cerebral ischemia in patients with aneurysmal or perimesencephalic subarachnoid hemorrhage (SAH). In cases of serious refractory cerebral vasospasm, a continuous intra-arterial (IA) infusion of nimodipine (CIAN) may be required to avoid cerebral ischemia. Nimodipine can cause arterial hypotension requiring either a dosage reduction or its discontinuation. Aim of the present study was to examine the effect of different nimodipine formulations on arterial blood pressure in aneurysmal or perimesencephalic SAH patients and to measure the plasma levels after both, peroral administration as tablet or solution and IA infusion.

Methods: In a prospective setting, over a 1-year observation period, data on the course of arterial blood pressure and nimodipine dosage were collected for 38 patients undergoing treatment for aneurysmal or perimesencephalic SAH in an intensive care unit. In addition, plasma concentrations of nimodipine were measured by liquid chromatography–tandem mass spectrometry.

Results: The intended full dose of 60 mg of nimodipine given orally every 4 h could only be administered on 57.2% of the examined days. Ninety-seven episodes of relevant arterial hypotension probably caused by the administration of nimodipine were observed within the first 14 days of treatment. Drops in blood pressure occurred about three times as often after administration of nimodipine as oral solution than as tablet. However, there were no differences in nimodipine plasma levels between the two formulations. In patients suffering from higher-grade SAH, arterial hypotension and consequent dosage reduction or discontinuation of nimodipine were more frequent than in patients with lower-grade SAH. Plasma concentrations of nimodipine during CIAN did not exceed those achieved by oral administration.

Conclusions: Dosage reduction or discontinuation of oral nimodipine is often necessary in patients with higher-grade SAH. Oral nimodipine solutions cause drops in blood pressure more frequently than tablets. Intra-arterial infusion rates of less than 1 mg/h result in venous plasma concentrations of nimodipine similar to those observed after oral application of 60 mg every 4 h.

Keywords: Subarachnoid hemorrhage, Nimodipine, Plasma concentration, Arterial hypotension, Delayed cerebral ischemia

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Introduction

Delayed cerebral ischemia (DCI) is a main contributor to poor outcome in patients suffering from aneurysmal subarachnoid hemorrhage (SAH). DCI causes poor outcome or death in up to 30% of patients with SAH [1]. DCI is caused by multiple processes, including vasospasm in cerebral arteries, cortical spreading ischemia, microthromboembolism, loss of autoregulation, and capillary transit time heterogeneity [1–5].

Nimodipine, a dihydropyridine L-type calcium channel antagonist, has been shown to reduce the risk of DCI and poor outcome following SAH [6–9] and is commonly used for prophylaxis and treatment of DCI as recommended by international guidelines [10–12]. The oral administration of 60 mg nimodipine every 4 h for at least 14 days beginning immediately after the initial hemorrhage is still standard of care in neurointensive care units. Nimodipine for oral administration is available as oral solution or tablet. Higher doses of nimodipine seem to be more efficacious; however, peroral administration is often limited by arterial hypotension [13, 14], which exacerbates episodes of DCI due to reduced cerebral blood flow (CBF) and perfusion pressure [15].

Patients who experience serious and refractory cerebral vasospasm (CV) need measures beyond the peroral administration of nimodipine to avoid extensive cerebral ischemia. In these cases, endovascular treatment with intra-arterial (IA) infusion of calcium channel antagonists may improve the outcome [16–21]. Our in-house standard of treatment of refractory CV following aneurysmal or perimesencephalic SAH entails the longtime continuous IA infusion of nimodipine (CIAN) [22]. This approach, however, is also associated with hemodynamic side effects, and patients treated with CIAN need higher dosages of vasopressors compared to nimodipine given orally to maintain sufficient mean arterial pressure (MAP) [23].

In the present prospective study, we examined the frequency of clinically relevant arterial hypotension episodes following the administration of different formulations of oral nimodipine in patients after aneurysmal or perimesencephalic SAH and the necessity to reduce the nimodipine dose. In addition, we measured venous nimodipine plasma levels in patients receiving oral nimodipine either as tablet or oral solution as well as in patients treated with CIAN.

Methods

The study was approved and conducted according to the ethical care committee of the University of Regensburg (Approval Number 16-101-0231). Included were all patients older than 18 years suffering from acute aneurysmal or perimesencephalic SAH who had been admitted to the neurointensive care unit of the University Hospital Regensburg between November 2016 and October 2017.

According to the in-house standard protocol for acute aneurysmal or perimesencephalic SAH, patients were to receive an oral dose of 60 mg of nimodipine every 4 h beginning on the day of admission to the intensive care unit (ICU) for at least 14 days. The attending nurse decided whether to give nimodipine as tablet (Nimodipin Hexal® 30 mg, Hexal, Holzkirchen, Germany) or oral solution (Nimotop® 30 mg/0.75 mL, Bayer, Leverkusen, Germany). When drops in arterial pressure occurred after the administration of nimodipine, the dose of nimodipine was either reduced or its administration paused according to the estimation of the attending ICU physician. Norepinephrine was used as first-line vasopressor when hemodynamic support was required.

In cases of increasing mean flow velocity on transcranial Doppler sonography in a middle cerebral artery to values higher than 160 cm/s or an increase of more than 50% within 24 h or if a deterioration of the neurological status in alert patients occurred despite ensuring normovolemic hypertension, severe CV was suspected, and patients were subsequently treated according to a standard operating procedure (SOP, Fig. 1). When values of multimodal cerebral monitoring indicated persistent cerebral ischemic conditions and severe CV was confirmed in digital subtraction angiography, CIAN therapy was initiated as described by Bele et al. [22]. CIAN was started at a rate of 0.5 mg/h (Nimodipine 10 mg i.v. Carino®, Carinopharm, Elze, Germany) via microcatheter and adapted individually to maintain target values for multimodal neuromonitoring (brain tissue oxygen, $PbtO_2 \geq 15$ mmHg, cerebral blood flow ≥ 20 ml/100 g/min). Once patients were in stable condition, nimodipine infusion was gradually reduced and finally stopped. Oral nimodipine was paused during CIAN therapy and started again thereafter.

Blood specimens for blood gas analysis were drawn via arterial cannula or central venous catheter without any specifications for the time of blood draw. As long as the patients received nimodipine, the residual samples were collected and immediately centrifuged (10 min, 756 g). The supernatant was then frozen at − 18 °C until analysis. In order to be able to draw reasonable quantitative conclusions on nimodipine plasma levels, we only considered blood specimens which appeared to be drawn within 15 min after nimodipine administration for further analysis. All other samples were discarded. Measurement of nimodipine plasma level was

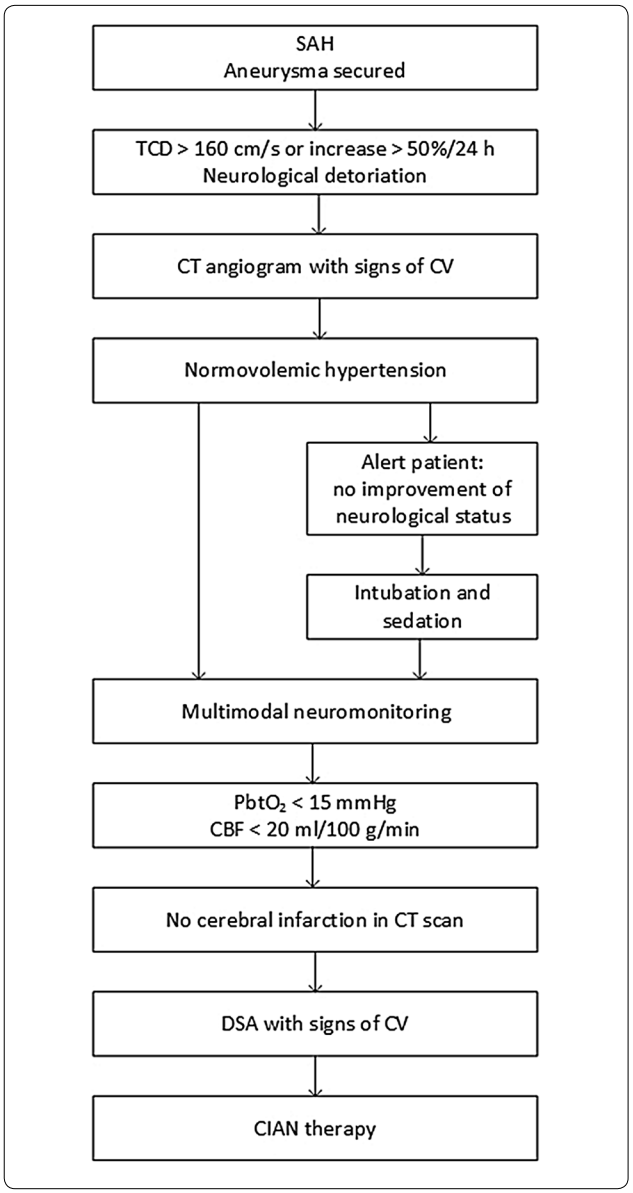

Fig. 1 Diagnostic and therapeutic algorithm in cases of cerebral vasospasm (CV): Cerebral aneurysms which are detected to be the bleeding source are secured either by endovascular or by surgical technique as soon as possible. All patients are examined daily with transcranial Doppler sonography. In cases of increasing mean flow velocity in a middle cerebral artery in patients receiving sedative medication to values > 160 cm/s or an increase > 50% within 24 h or if a deterioration of the neurological status in alert patients occurres, serious CV is assumed. First step then is computed tomography angiography (CTA). All patients with corresponding signs of severe CV in the CTA (arterial narrowing of more than 50% of the vessel diameter or irregularities in vessel diameter) are immediately treated according to normovolemic hypertension strategy. In alert patients, the efficiency of this is monitored by frequent clinical examination of the neurological status. Sedated patients receive multimodal neuromonitoring (MMM) by additional bilateral measurement of brain tissue oxygen ($PbtO_2$), and monitoring of cerebral blood flow (CBF) in the area supposed to be mostly affected. In cases of persisting deteriorated neurological status, patients who did not require sedation in the course of intensive care unit treatment so far are also intubated and sedated and receive MMM. When $PbtO_2$ remains < 15 mmHg and CBF < 20 ml/100 g/min, digital subtraction angiography (DSA) is conducted. When severe CV is confirmed in DSA (arterial narrowing of more than 50% of the vessel diameter or irregularities in vessel diameter), continuous intra-arterial nimodipine infusion (CIAN) is started. Patients with signs of cerebral infarctions in prior CT scans are generally excluded from CIAN therapy due to suspected high risk of cerebral bleeding into the infarct areas with the onset of therapeutic anticoagulation necessary for CIAN

performed by high-performance liquid chromatography–tandem mass spectrometry (LC–MS/MS). The description of nimodipine plasma level quantification is given in supplementary data (Suppl. 1).

We examined the course of ICU treatment in all patients and recorded all modifications of nimodipine dosage and relevant episodes of arterial hypotension within the first 14 full days of ICU treatment or, if patients had been dismissed from ICU earlier, until the last full day in the ICU. Hemodynamic parameters, points of nimodipine administration, and drawing of blood samples were recorded in 15-min intervals. Relevant arterial hypotension was assumed when systolic blood pressure dropped below 100 mm Hg or the dose of intravenous (IV) norepinephrine had to be increased above 0.3 mg/h in alert and 1.0 mg/h in sedated patients, respectively, and if it was necessary to increase the dose of norepinephrine for at least 0.3 mg/h within the past 60 min. For all detected episodes of relevant arterial hypotension, two experienced neurointensive care specialists estimated the probability for this event to have been caused by a preceded administration of oral nimodipine as being "highly probable", "possible", or "improbable" retrospectively. For the classification "highly probable," it was required that the patient had experienced hypotension within 60 min of oral administration of nimodipine and both neurointensive care specialists agreed with this classification. Episodes of hypotension occurring more than 4 h after the last administration of nimodipine were considered "improbable" to have been caused by nimodipine. Other reasons for arterial hypotension, such as volume deficit, anaphylaxis, septic shock, and coincident administration of other drugs known to potentially lower blood pressure or inhibit cytochrome P450 3A3 (CYP3A4, nimodipine is metabolized via CYP3A4), respectively, were also assessed by screening available records in the patient data management system (PDMS, MetaVision Suite™, iMDsoft, Tel Aviv, Israel). Episodes under CIAN therapy were examined separately.

Table 1 Patient characteristics, including demographic data, localization and therapy of aneurysm, and outcome

Sex	
Female	21 (55.3%)
Male	17 (44.7%)
Mean age (years)	55 (33–80)
Mean body weight (kg)	79 (55–130)
WFNS	
1	19 (50.0%)
2	3 (7.9%)
3	3 (7.9%)
4	2 (5.3%)
5	11 (28.9%)
Localization of ruptured aneurysm	
No aneurysm	14 (36.8%)
ACI	4 (10.5%)
ACoA	8 (21.1%)
MCA	5 (13.2%)
PICA	3 (7.9%)
A. pericallosa	2 (5.3%)
A. calloso marginalis	1 (2.6%)
BA	1 (2.6%)
Intervention	
None	14 (36.8%)
Clipping	5 (13.2%)
Coiling	18 (47.4%)
WEB device	1 (2.6%)
GOS (end of ICU)	
1	1 (2.6%)
2	3 (7.9%)
3	11 (28.9%)
4	7 (18.5%)
5	16 (42.1%)
Mean length of stay in ICU (days)	19 (4–46)

ACI internal carotid artery; *ACoA* anterior communicating artery; *BA* basilar artery; *GOS* Glasgow Outcome Scale; *ICU* Intensive care unit; *MCA* middle cerebral artery; *PICA* posterior inferior cerebellar artery; *WEB device* Woven EndoBridge device; *WFNS* World Federation of Neurosurgical Societies grade

Statistical analysis was performed using IBM SPSS Statistics™ 25 (IBM, Armonk, USA). Categorical data were displayed according to their distribution frequency. Statistical significance was calculated using the Chi-square test of independence. Metric data were displayed as median (IQR) or were graphically represented using boxplot diagrams. Metric data were analyzed using Mann–Whitney *U* test. Significance was supposed when P was < 0.05.

Results

Between November 2016 and October 2017, a total of 38 patients with acute aneurysmal or perimesencephalic SAH were admitted to the ICU and included in the present study regardless of the presence of an aneurysm. Table 1 shows demographic data for the patients, including localization of the aneurysm, the Glasgow Outcome Scale score at the time of ICU discharge, and mean length of stay in the ICU.

We were able to analyze a total of 374 patient days of intended oral administration of 60 mg of nimodipine every 4 h. The full dose of nimodipine was only given on 214 days (57.2%). On 47 days (12.6%), nimodipine could be administered every 4 h, but single doses had to be reduced sometimes (26 days, 7.0%) or always (21 days, 5.6%). Nimodipine had to be paused once per day on 33 days (8.8%) and more than once per day on 46 days (12.3%), respectively. Complete discontinuation of nimodipine was necessary on 34 days (9.1%).

Fourteen patients experienced no relevant arterial hypotension within the first 14 days of ICU treatment. The remaining 24 patients suffered 126 events of arterial hypotension according to our definition. Fifty-nine and 38 events, respectively, were estimated to have been caused with high probability or possibly by the administration of oral nimodipine.

Overall, 1835 oral doses of nimodipine were administered over the 374 days, either as tablet ($n = 1161$) or oral solution ($n = 674$). Of the 97 events classified as "highly probably" or "possibly" associated with the application of nimodipine, 35 and 62 had occurred after the respective administration of nimodipine as tablet or oral solution. This means that the rate of relevant drops in blood pressure was significantly ($P < 0.001$) higher after the administration of an oral solution of nimodipine compared to tablet application. Twenty-two patients suffered from lower-grade SAH with World Federation of Neurosurgical Societies (WFNS) grade 1 or 2, while 16 had a higher-grade SAH with WFNS grades 3 to 5. Administration of the intended full dose of nimodipine was more often possible in patients with lower than higher-grade SAH: 80.0% (60.5%, 86.5%), vs. 39.5% (0.0%, 62.3%) of the examined days, $P = 0.009$. In addition, drops in blood pressure classified to be "highly probably" or "possibly" associated with the administration of oral nimodipine occurred more often in patients with higher-grade SAH: 0.00 (0.00, 0.13) in patients with WFNS 1–2, 0.20 (0.10, 0.55) events/day in patients with WFNS 3–5, $P = 0.002$).

CIAN therapy was required in six of the 38 included patients (15.8%). Table 2 shows key data regarding CIAN therapy for each case.

For each patient, a mean daily number of 4.4 blood specimens were collected for the determination of venous nimodipine plasma levels. As stated above, for measurement of nimodipine plasma levels, only blood specimens drawn within 15 min after nimodipine administration

Table 2 Key data of CIAN therapy

Patient	Onset of CIAN therapy	Duration of CIAN therapy	Mean daily infusion rate of IA nimodipine (mg/h)	Mean daily dose of norepinephrine (mg/h)	Mean SBP during CIAN therapy (mm Hg)
1	Day 9	16 days	0.7	2.3	180
5	Day 10	6 days	0.5	0.6	167
15	Day 10	14 days	0.8	1.4	194
16	Day 6	12 days	0.6	1.6	185
33	Day 4	4 days	0.3	1.1	178
36	Day 6	9 days	0.6	1.0	170

CIAN continous intra-arterial infusion of nimodipine; *IA* intra-arterial; *SBP* systolic blood pressure

Table 3 Mean plasma levels of nimodipine within 15 min after oral administration

Application	Dose (mg)	Mean plasma concentration (ng/mL)	SD (ng/mL)	n
Tablet	30	2.5	1.8	7
	60	11.6	17.5	68
Solution	15	8.1	9.0	4
	30	8.4	9.3	18
	60	11.2	13.5	20

were considered, and all other samples were discarded. The remaining counts of measurements after tablet, solution, or CIAN administration were 75, 42, and 87, respectively. The mean plasma levels after oral administration are summarized in Table 3. Regardless of the formulation, the mean venous plasma levels of nimodipine showed no difference after 60 mg administration (about 11 ng/mL). With a reduced dose (15 or 30 mg), a reduction in the mean plasma levels seems to occur, but due to the low case numbers ($n=7$ or $n=4$), a statistical comparison was not feasible. The quantification of plasma levels during CIAN therapy included infusion rates between 0.02 and 1.5 mg/h ($1 \leq n \leq 14$ per rate). Figure 2 shows the corresponding venous nimodipine plasma concentrations. Venous plasma levels of IA administered nimodipine mainly did not exceed those of orally given 60-mg nimodipine doses (about 11.4 ng/mL), when the infusion rates were kept below 1 mg/h.

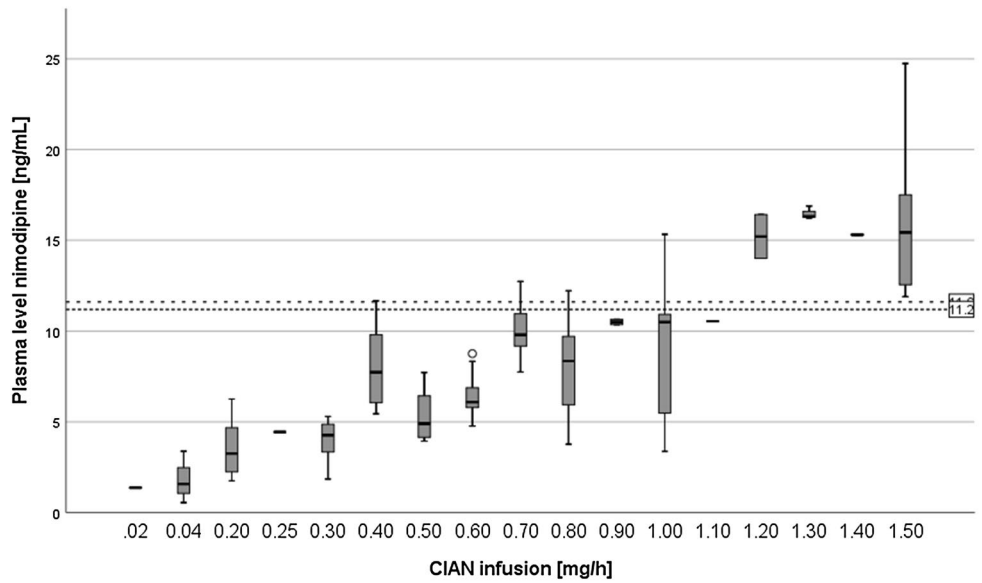

Fig. 2 Relationship between nimodipine infusion rates and plasma concentrations. Dotted lines: mean concentrations after 60 mg oral administration. Medians, 25 and 75% percentiles

Discussion

Aggressive management of DCI seeking normovolemic hypertension can contribute to improved functional outcomes [10, 24, 25]. Episodes of arterial hypotension following the administration of oral nimodipine counteract this strategy and can worsen DCI [15, 26] and, consequently, require an escalation of the dosage of vasopressors and a reduction in the dosage of nimodipine [14]. In an older study, the dose of nimodipine had to be adjusted due to arterial hypotension in 30% of patients receiving IV nimodipine versus 6% given nimodipine orally [13]. Choi et al. found an average decrease of 1.33 mm Hg in MAP upon administration of oral nimodipine in patients suffering from poor-grade SAH [27].

In a recently published study, the frequency and clinical significance of dose modifications of oral nimodipine within the first 14 days after aneurysmal SAH were evaluated retrospectively [28]. It was also intended to administer 60 mg nimodipine orally every 4 h. The full dose was possible in 43.6% of the patients. A dose reduction due to arterial hypotension was necessary in 28.6% and a discontinuation in 27.7%, respectively. Most patients in the nimodipine discontinuation group did not receive any nimodipine during the time period at highest risk for vasospam. Dose reduction or discontinuation was more often necessary in patients in a poor clinical condition. In contrast, successful administration of the full nimodipine dose was associated with a decreased risk of unfavorable outcome. Concordant with our findings, arterial hypotension following the administration of nimodipine occurred more often in patients with high-grade SAH. Accordingly, the cumulative dosage of nimodipine was lower in patients with higher-grade SAH. Compared to low-grade SAH patients, patients with high-grade SAH require more often prolonged sedation, mechanical ventilation, and vasopressor support irrespective of the occurrence of CV. This constellation could imply a higher vulnerability regarding the impact of nimodipine on blood pressure. Strategies to maintain a continuous application of nimodipine especially in patients with high-grade SAH are needed. The intraventricular or intracisternal application of a sustained-release microparticle formulation of nimodipine (EG-1962) has been considered, a promising strategy to avoid arterial hypotension associated with the oral administration of nimodipine. However, a phase 3 trial comparing EG-1962 to oral nimodipine was stopped recently due to ineffectiveness in an interim analysis [29–32].

A distinct result of the present study is the obvious differential effect on blood pressure between nimodipine given as tablet or oral solution. The latter exerts a significantly stronger effect on blood pressure. In our ICU, the liquid formulation is preferred when nimodipine has to be given via a feeding tube. Interestingly, the nimodipine plasma levels did not differ between the two drug formulations. The lack of perception of a pharmacokinetic difference between the two formulations is probably due to the study design. One also has to consider that we chose only those samples for measurement of nimodipine plasma levels that had been drawn within 15 min after an oral nimodipine administration. Peak levels of nimodipine, however, can be expected at about 1 h from administration (e.g., professional information on Nimodipin Hexal® 30 mg, Hexal, Holzkirchen, Germany). Based on our findings, use of nimodipine oral solution may be associated with more frequent occurrence of arterial hypotension compared to nimodipine tablets, warranting frequent monitoring of blood pressure.

Determination of nimodipine concentration in human plasma has been accomplished by different methods [33, 34]. Here, we used high-performance liquid chromatography–tandem mass spectrometry as described in detail in Supplement 1. Expected plasma levels of nimodipine after IV or oral administration in unselected individuals are known and can be derived from the information provided by the pharmaceutical companies (e.g., professional information on Nimodipin Hexal® 30 mg, Hexal, Holzkirchen, Germany for nimodipine tablets, professional information on Nimodipin 10 mg i.v. Carino®, Carinopharm, Elze, Germany for IV therapy). Vinge et al. measured peak levels ranging from 7.0 to 96.0 ng/mL in patients with aneurysmal SAH (aSAH) treated with 45 mg of oral nimodipine every 4 h. During continuous IV infusion of 2 mg/h nimodipine in patients with Asah, the mean plasma concentration was 26.6 ± 1.8 ng/mL [35]. In a recently published study, Albanna et al. found a median nimodipine serum concentration of 17.3 ng/mL in aSAH patients treated with oral, IV, and IA nimodipine, respectively. The modality of application was not associated with differences in serum concentration [36]. Abboud et al. reported on a lower bioavailability of enteral nimodipine administration after SAH compared to IV application [37]. In the present study, we measured plasma concentrations ranging from 0.58 to 128.5 ng/mL ($n = 117$) within a 15-min time window after oral application of 15–60 mg nimodipine. CIAN therapy led to concentrations (during infusion) between 0.54 and 24.7 ng/mL ($n = 87$), and extreme values seen after oral administration could be avoided (128.5 vs. 24.7 ng/mL). As we did not draw blood at fixed times after administration of nimodipine, we cannot infer a possible association between drops in blood pressure after administration of nimodipine and higher nimodipine plasma levels. Vinge et al. found arterial hypotension to occur at plasma concentrations above 30 ng/mL [35].

The main strength of the present study is its prospective design. However, there are certain limitations. First, there might be a certain bias regarding the adjustment of the nimodipine dosage, as we did not use a protocol for how to react to arterial hypotension possibly induced by the oral administration of nimodipine. In fact, the attending ICU physician decided on an individual basis what had to be seen to be a relevant drop in arterial pressure, when a dose reduction or pausing of oral nimodipine was necessary and when the re-administration of nimodipine was possible again. Furthermore, as we limited the prospective observation period to 1 year, we could only include 38 patients in our study. In addition, more than 33% of the patients had no identified aneurysm and most of the patients suffered from low-grade SAH. The results of our study may have been different, if there had been a higher percentage of patients with high-grade aneurysmal SAH. We could not gather any information regarding IV nimodipine as we only used oral nimodipine for prophylaxis and oral or IA nimodipine for treatment of DCI. Finally, as the present study was not designed as a pharmacokinetic/pharmacodynamic study, we had not specified times at which to draw blood after the administration of nimodipine. Here, we considered only those samples that had been drawn within 15 min after an oral nimodipine administration. This way we could calculate mean plasma concentrations. However, the number of suitable samples was too low to correlate clinically suspected effects of nimodipine on blood pressure with particular plasma levels.

Conclusion

Dose reduction or discontinuation of oral nimodipine due to episodes of relevant arterial hypotension is frequently required, especially in patients with higher-grade SAH. Drops in blood pressure were observed more frequently after administration of oral nimodipine solution compared to application in tablet form, even though the measured plasma concentrations did not differ. During CIAN therapy in cases of serious refractory CV, plasma concentrations of nimodipine did not exceed the average concentrations after oral administration when administered at less than 1 mg/h.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s12028-019-00676-w) contains supplementary material, which is available to authorized users.

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Authors' Contributions

MK contributed to study concept and design, data collection, data analysis, and manuscript drafting; MG contributed to study concept and design, laboratory work, data analysis, and manuscript drafting; IK carried out study concept and design, data collection, and data analysis; KD performed laboratory work and manuscript revisions; PJO carried out manuscript revisions; SB performed data collection and manuscript revisions; CW collected the data; ST carried out the laboratory work; BG performed manuscript revisions; CE contributed to study concept and design, data collection, data analysis, and critical review of manuscript.

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Compliance with Ethical Standards

Conflicts of interest

All authors declare that they have no conflict of interest.

Ethical approval and Informed consent

The study was approved and conducted according to the ethical care committee of the University of Regensburg (approval number 16-101-0231). Written informed consent was obtained from all patients.

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