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Intestinal Drug Absorption After Subarachnoid Hemorrhage and Elective Neurosurgery: Insights From Esomeprazole Pharmacokinetics

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OBJECTIVES: Subarachnoid hemorrhage (SAH) may critically impair cardiovascular, metabolic, and gastrointestinal function. Previous research has demonstrated compromised drug absorption in this group of patients. This study aimed to examine the impact of SAH on gastrointestinal function and its subsequent effect on the absorption of enterally administered drugs, using esomeprazole as a probe drug.

DESIGN: Prospective observational cohort study.

SETTING: Academic hospital in Germany.

PATIENTS: We included 17 patients with high-grade SAH and 17 controls, comparable in age, sex, body weight, and renal function, who underwent elective cranial surgery.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Both groups received esomeprazole per standard protocol to prevent acid-associated mucosal damage, either orally or through a nasogastric tube. On day 4, esomeprazole was administered IV to estimate oral bioavailability. Esomeprazole serum concentrations were measured on days 1, 3, and 4 in both groups and on day 7 in the SAH group. Patients with high-grade SAH exhibited severely impaired drug absorption. Most patients showed no improvement in intestinal drug absorption even a week after hemorrhage.

CONCLUSIONS: Following SAH, significantly reduced drug absorption may be attributed to decreased intestinal motility and compromised intestinal mucosal function. Clinicians should anticipate the reduced effectiveness of enterally administered medications for at least seven days after high-grade SAH.

KEYWORDS: critically ill patients; gastrointestinal dysfunction; intensive care medicine; subarachnoid hemorrhage

Effective drug therapy in critically ill patients can be administered parenterally or enterally. Research has shown that early enteral nutrition can lower mortality rates in the critically ill (1–4). Although early initiation of enteral feeding is common, medication is often administered parenterally due to impaired gastrointestinal drug absorption. This impairment is attributed to various factors related to the underlying disease and its treatments (5, 6). However, the extent and duration of impairment of intestinal absorption in critically ill patients and its effect on the bioavailability of drugs are yet to be fully understood.

Evidence suggests that severe brain injury impairs gastrointestinal function, depending on injury severity and intracranial pressure (7, 8). Recent research

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KEY POINTS

Question: To what extent is drug absorption compromised in patients with high-grade aneurysmal subarachnoid hemorrhage (SAH)? Furthermore, is the presumed intestinal impairment still there on days 3 and 7 after hemorrhage?

Findings: In patients with high-grade SAH, there is a five- to ten-fold reduction of intestinal drug absorption even 7 days after hemorrhage.

Meaning: Oral or nasogastric administration of vital drugs is inadequate for patients in the first week after high-grade aneurysmal SAH. More studies on pharmacokinetics in critically ill patients are required, and the interaction between the brain and gut in drug absorption may be an exciting future field of research.

hints at complex interactions within the brain-gut axis, including disturbances in intestinal integrity and changes in the microbiome (8). While aneurysmal subarachnoid hemorrhage (SAH) impacts multiple organs, its effect on gastrointestinal function and drug absorption is underexplored (9–11).

Previous studies (12, 13) highlight the challenges of enteral drug administration in high-grade SAH patients, showing very low oral bioavailability of nimodipine. However, nimodipine may not be an optimal probe drug for intestinal absorption due to its low and variable bioavailability, high cytochrome P450 3A (CYP3A)-mediated first-pass metabolism, and potential to alter intestinal motility. Thus, our study used esomeprazole as a probe drug to evaluate intestinal drug absorption. Proton pump inhibitors (PPIs) are widely used to prevent acid related gastrointestinal bleeding (14, 15) and knowingly reduce the risk of severe gastrointestinal bleeding in patients with SAH (16). Additionally, esomeprazole is approved for administration through nasogastric tubes, and its bioavailability with values between 60% and 90% is comparable whether administered orally or via feeding tubes (17). Esomeprazole blood concentrations are determined mainly by liver function, specifically by cytochrome P450 enzymes 2C19 and 3A4. Less than 1% is eliminated unchanged via the kidneys. Blood concentrations of 5′-OH-esomeprazole and 5-O-desmethylesomeprazole reflect hepatic CYP2C19 activity, whereas the esomeprazole metabolite omeprazole sulfone (OM-S) reflects cytochrome P450 3A4 (CYP3A4) activity (18). This study aimed to improve our understanding of enteral drug absorption in patients with SAH.

MATERIALS AND METHODS

This study assesses esomeprazole pharmacokinetics in two groups: a target group consisting of critically ill patients with high-grade SAH and a control group of otherwise healthy patients undergoing elective cranial surgery.

Inclusion and Exclusion Criteria

The inclusion criteria for the SAH group included the diagnosis of acute aneurysmal SAH classified as Hunt & Hess 3, 4, or 5 (19), and the need for intubation or a feeding tube post-initial care due to a depressed level of consciousness. Patients were included into the study within 72 hours after the onset of SAH. The control group consisted of patients admitted for elective intracranial surgery. Both groups included only patients for whom PPI administration was clinically indicated. The exclusion criteria for all participants were younger than 18 years or older than 80 years and the requirement for clopidogrel. Clopidogrel is a pro-drug activated by the enzyme CYP2C19. Since esomeprazole is an inhibitor of CYP2C19 concurrent use may reduce the effectiveness of clopidogrel.

Ethical Considerations

Prior to any study-related action, informed consent was obtained from all eligible patients or their legal representatives if the patient was unable to provide consent. The study complied with the Helsinki Declaration of 1975 and was performed in accordance with the ethical committee of our institution. The study was approved by the local ethics review committee (application number: 10/01/19, approval date: May 13, 2019, study title: "Clinical cohort study evaluating gastrointestinal function in critically ill patients") and registered in the "German Register for Clinical Studies" (identification number DRKS00017624).

Drug Administration and Blood Sampling Protocol

All patients received 40mg of esomeprazole, administered orally or via a feeding tube, according to their level of consciousness. On the fourth day of the study, a single IV dose was administered to both groups. For oral dosing the multiunit pellet system (Nexium mups; Grünenthal, Aachen, Germany), suitable for both oral and nasogastric tube administration was used. The application through the nasogastric tube was performed according to the manufacturer's instructions. All patients in the SAH group received esomeprazole on all study days via the nasogastric tube (except for the IV dosing day) while the patients in the control group received esomeprazole orally. IV administration involved a 10-minute infusion of 40 mg Nexium prepared as per manufacturer's instructions. Blood samples were collected on days 1, 3, and 4 in both groups, with an additional sample collected on day 7 for the SAH group (**Fig. 1**). Sampling times were pre-drug administration (time 0) to evaluate the trough level in both cohorts and at 30, 60, 90, 120, 180, 240, 360, and 480 minutes post-administration, using potassium EDTA as an anticoagulant. The samples were centrifuged at room temperature within 2 hours for 10 minutes at 2000 g and stored at −20°C until further analysis.

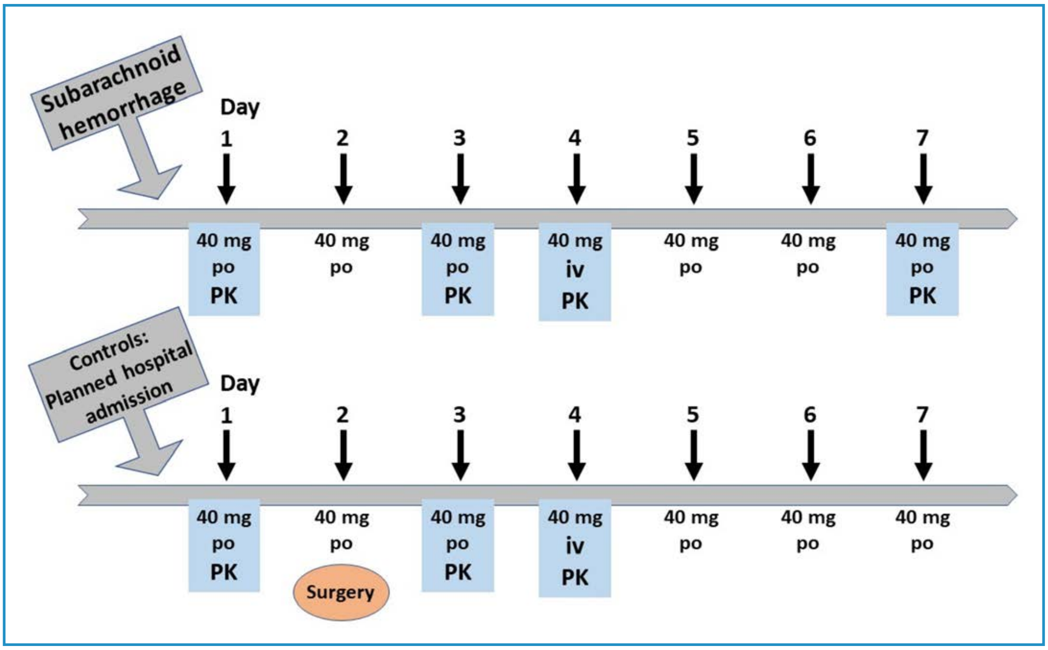

Figure 1. Design of the study on enteral absorption after subarachnoid hemorrhage (SAH). Study day 1 refers to day 1 or 2 after ictus in all patients. Each dose corresponds to esomeprazole administered once daily. In all patients with SAH who could not swallow, application (per os [po]) was performed via a nasogastric tube according to the manufacturer's instructions. On day 1, control patients were in a stable state without major cardiovascular, gastrointestinal, or neuropsychiatric disabilities and could swallow the po dose. As studied earlier, the oral bioavailability of esomeprazole is almost identical if administered via a nasogastric tube or swallowed orally (17). PK = pharmacokinetic analysis.

Analytical Method

Serum concentrations of esomeprazole and its metabolites (5′-hydroxy esomeprazole [OH-OM], 5-O-desmethyl esomeprazole (DM-OM), and OM-S were quantified using high-pressure liquid chromatography (Brownlee SPP RP-Amide column; PerkinElmer, Waltham, MA) combined with tandem mass spectrometry (API 4000TM LC-MS/MS system; Sciex, Framingham, MA). Deuterated omeprazole (D3; Cayman Chemical, Ann Arbor, MI) was used as internal standard for omeprazole, esomeprazole was from Sigma-Aldrich (Taufkirchen, Germany) and reference substance of the three metabolites was from Toronto Research chemicals (Toronto, ON, Canada). The lower limit of quantification for esomeprazole was 1 ng/mL and the inter-assay coefficient of variation remained below 5% across the control samples at concentrations of 30, 300, and 3000 ng/mL. For the metabolites, the lower limit was 3 ng/mL, with inter-assay coefficients of less than 10%.

Pharmacokinetic Analysis

Noncompartmental pharmacokinetic analysis was performed using WinNonlin version 6.4 (Certara, Princeton, NJ). Predefined parameter of primary interest was time to maximum plasma concentration (Tmax) as the time of maximum blood concentration (Cmax). Both, Tmax and Cmax were as measured, that is, without interpolation. The absorption delay time (lag time) was the time between oral dosing and the first increase in blood concentration. The area under the concentration time curve (AUC) of esomeprazole and its metabolites was calculated from zero (before dosing) to last measurement (8 hr after dosing) by the linear trapezoidal rule. Bioavailability was calculated as F= (AUC [per os]/(AUC [IV]).

Sample Size

The sample size was estimated using G*Power software (Version 3.1.7; University of Kiel, Germany/Düsseldorf, Germany) based on an expected mean Tmax of 2.1 hours with a SD of 0.9 hours. Anticipating a two-fold difference between the two groups, a total of at least 22 participants (11 per group) were required to achieve a significance level of p value of equal to 0.05 with a statistical power of 0.8.

Statistical Analysis

The analysis was carried out using IBM SPSS Statistics (Version 27.0; IBM Corp., Armonk, NY). Categorical data were presented as counts and percentages. Metric data were presented primarily as median and range. The Shapiro-Wilk test was used to assess the normality of the data distribution.

For within-group comparisons, the Wilcoxon signed-rank test was used, and for between-group comparisons, the Mann-Whitney U test was applied as appropriate. The primary parameter for analysis was Tmax, with a p value of less than 0.05 considered statistically significant. It should be noted that the significance values provided for other parameters were not adjusted for multiple testing.

RESULTS

A total of 34 patients were included in the study, with 17 participants in each group. Indications for the neurosurgical procedure included glioma (6/17), cerebral metastasis (6/17), meningioma (3/17), chondrosarcoma (1/17), and lymphoma (1/17). Open surgery with an osteoplastic craniotomy was performed in 13 patients; two patients underwent a stereotactic biopsy, and in two patients, a decompression of the orbit was performed. Within the SAH group, 59% of the patients (10/17) underwent microsurgical clipping, and 41% (7/17) were treated with endovascular coiling. Overall, five fatalities occurred during the study period in the SAH group. Data from these patients and those who dropped out due to other reasons were included in the analysis for the duration of their participation. Basic medical characteristics did not differ significantly between the two groups (**Table 1**). All patients received disease-stage-adapted, guideline-based enteral nutrition therapy and had normal liver and kidney function

TABLE 1.
Demographic Data of Study Participants

Variable	Control Cohort	Subarachnoid Hemorrhage Cohort
Age (yr)	62 (23–70)	62 (33–80)
Sex, male	9 (53%)	6 (35%)
Height (cm)	171 (157–182)	168 (160–190)
Body weight (kg)	76.5 (47–113)	80 (53–100)
Serum creatinine day 1	0.80 (0.55–2.14)	0.86 (0.58–1.35)
Serum creatinine day 3	0.79 (0.48–1.37)	0.69 (0.49–1.04)
Total serum bilirubin	0.50 (0.30–1.3)	0.45 (0.30–1.20)
Surgical time (min)	155 (50–360)	NA
Hunt and Hess score	NA	4.5 (3–5)
IV fluids day 1 (L)	NA	3.61 (1.32–7.22)
IV fluids day 3 (L)	NA	4.26 (1.69–8.90)
IV fluids day 4 (L)	NA	4.11 (2.32–5.70)
IV fluids day 7 (L)	NA	3.45 (1.59–4.62)

NA = not applicable.
None of the parameters showed any significant difference between the subarachnoid hemorrhage and the control group (elective surgery). Data were presented as median (range) or n (%).

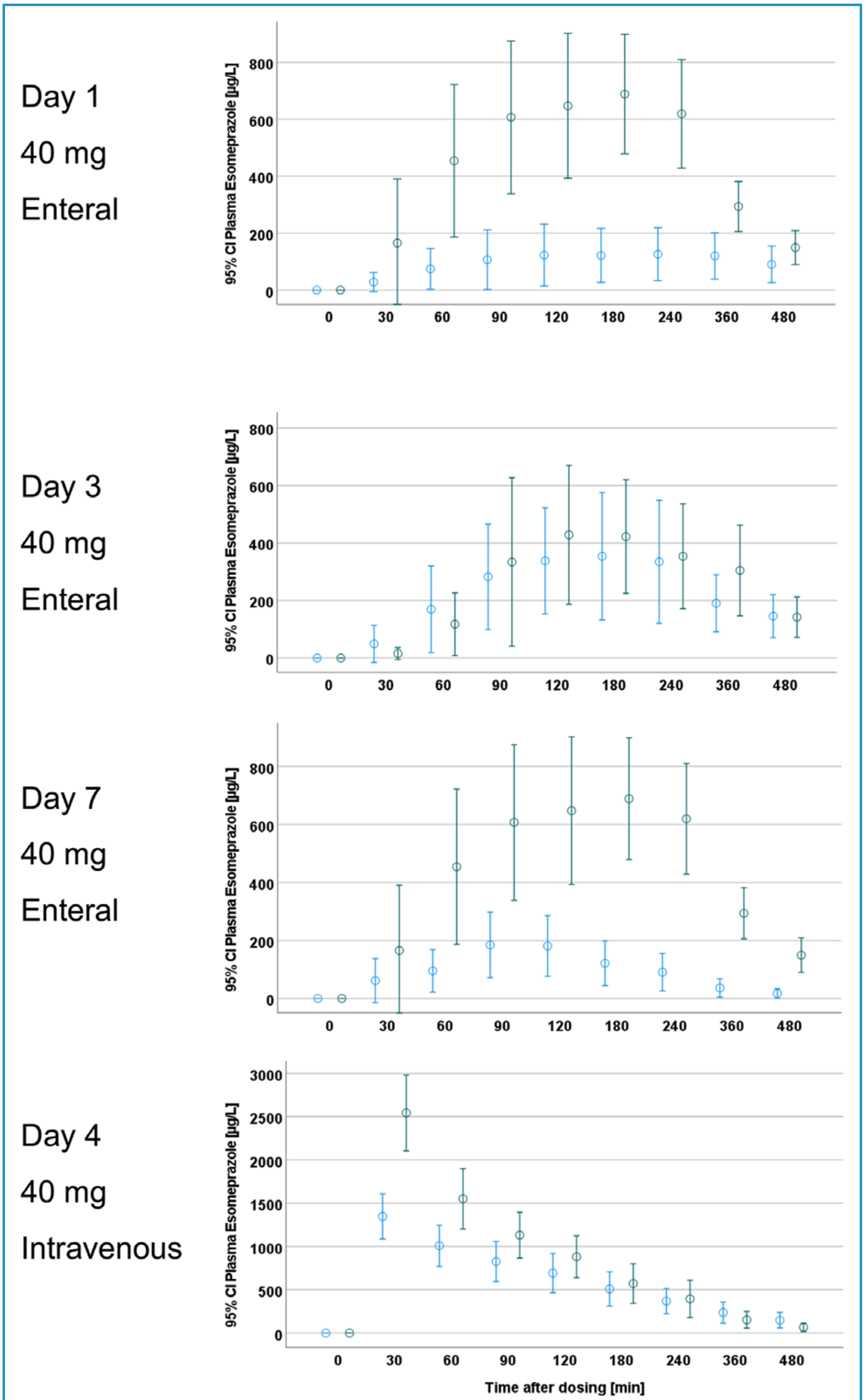

Figure 2. Means and 95% CIs of esomeprazole plasma concentrations in patients with high-grade subarachnoid hemorrhage (SAH) (*blue*) compared with patients admitted to the hospital for elective neurosurgery (*green*). On day 7, pharmacokinetic analysis was not performed in the control group. Instead, the control patients' data from day 1 are compared here. At day 1, the control patients, being comparable concerning age and gender with the SAH patients, had normal intestinal and cardiovascular function, and the comparison of esomeprazole blood concentrations of the SAH patients at day 7 illustrates how severe their intestinal absorption impairment still was.

except for one patient in the SAH group with moderate renal impairment. There was also no significant difference in serum creatinine, serum bilirubin, or international normalized ratio (INR) as indicator of liver function between the SAH and control patients.

Pharmacokinetics

The esomeprazole concentrations differed substantially between the two groups. In the SAH group, esomeprazole plasma concentrations were very low and remained low on the third study day (**Fig. 2**). However, on the third study day a moderate increase in blood concentrations was observed due to a significant increase in five patients. As illustrated in Figure 2 and **Table 2**, even 7 to 10 days after the acute SAH event, intestinal absorption of esomeprazole was poor with a median AUC being eight times lower compared with day 1 in the control group ($p < 0.001$; Table 2). After IV administration on day 4, both groups exhibited less variability in peak concentrations; however, these values were significantly higher in the control group (Fig. 2).

After enteral administration on day 1, the median Cmax in the SAH group was approximately ten times lower compared with the control group ($p < 0.001$; Table 2), and even on day 3, the median Cmax in the SAH group was nominally four times lower (**eFig. 1**, http://links.lww.com/CCM/H615). Nonetheless, there was a significant increase in Cmax in the

TABLE 2.
Esomeprazole Pharmacokinetics in the Subarachnoid Hemorrhage Cohort and Control Cohort

Group	Day 1 (p.o.), $n = 34$	Day 3 (p.o.), $n = 32$	Day 7 (p.o.), $n = 12$	Day 4 (IV), $n = 27$
Maximum plasma concentration of esomeprazole (µg/L)				
SAH cohort	96.3 (2.7–772)	190 (24.1–1555)	180 (8.8–574)	1461 (494–2032)
Control cohort	1140 (343–1797)	760 (196–1900)	1140 (343–1797)	2489 (1590–4200)
p[a]	< 0.001	NS	< 0.001	< 0.001
Time of maximum plasma concentration of esomeprazole (min)				
SAH cohort	240 (60–492)	225 (90–480)	90 (30–240)	NA
Control cohort	120 (60–360)	240 (90–480)	120 (60–360)	NA
p	0.02	NS	0.027	
Esomeprazole AUC (mg × min/L)				
SAH cohort	25.3 (0.3–298)	45.5 (6.5–280)	24.8 (1.5–111)	252 (33.9–424)
Control cohort	208 (41.2–364)	146 (41.1–282)	208 (41.2–364)	254 (133–523)
p	< 0.001	NS	< 0.001	NS
5′-OH-esomeprazole AUC (mg × min/L)				
SAH cohort	1.3 (0.1–23.6)	3.7 (0.3–20.9)	2.0 (0.1–5.2)	6.3 (4.0–32.0)
Control cohort	10.7 (5.6–45.9)	12.0 (1.6–31.6)		18.6 (7.1–42.7)
p	< 0.001	0.002	< 0.001	0.001
5-O-Desmethyl esomeprazole AUC (mg × min/L)				
SAH cohort	0.3 (0.0–1.1)	0.6 (0.0–1.9)	0.3 (0.0–1.0)	0.9 (0.3–3.3)
Control cohort	1.7 (0.3–10.2)	1.1 (0.1–8.1)		1.1 (0.4–6.4)
p	< 0.001	NS	< 0.001	NS
Esomeprazole sulfone AUC (mg × min/L)				
SAH cohort	8.1 (0.2–138)	30.3 (0.2–87.4)	21 (0.6–127)	52.4 (17.3–191)
Control cohort	233 (15.9–569)	132 (8.9–324)		289 (122–508)
p	< 0.001	< 0.001	< 0.001	< 0.001
5′-OH-esomeprazole/esomeprazole AUC ratio reflecting CYP2C19 activity				
SAH cohort	0.07 (0.01–0.43)	0.04 (0.02–0.33)	0.08 (0.04–0.26)	0.04 (0.01–0.14)
Control cohort	0.06 (0.02–0.30)	0.08 (0.02–0.52)	NA	0.06 (0.03–0.18)
p	NS	NS	NS	NS
5-O-Desmethyl esomeprazole/esomeprazole AUC ratio reflecting CYP2C19 activity				
SAH cohort	0.01 (0.00–0.05)	0.00 (0.00–0.02)	0.01 (0.0–0.5)	0.00 (0.00–0.02)
Control cohort	0.01 (0.00–0.09)	0.01 (0.00–0.05)	NA	0.00 (0.00–0.02)
p	NS	NS	NS	NS
Esomeprazole sulfone/esomeprazole AUC ratio reflecting CYP3A4 activity				
SAH cohort	0.46 (002–1.20)	0.24 (0.07–1.59)	0.79 (0.21–2.0)	0.24 (0.04–1.46)
Control cohort	0.90 (0.38–1.84)	1.03 (0.38–1.92)	NA	1.02 (0.58–1.25)
p	0.002	< 0.001	NS	0.008

AUC = area under the concentration time curve, CYP2C19 = cytochrome P450 2C19, CYP3A4 = cytochrome P450 3A4, NA = not applicable, NS = not significant, p.o. = per os, SAH = subarachnoid hemorrhage.

[a]Significance of the between-group comparisons according to the Mann-Whitney *U* test (day 7 data of the subarachnoid hemorrhage cohort were compared with day 1 data of the control [elective surgery] cohort). No adjustment for multiple testing was performed here.

All data are presented as median and range.

SAH group on day 3 compared with day 1 (190 vs. 96 μg/L; $p = 0.036$), attributed to improvements in five patients (eFig. 1, http://links.lww.com/CCM/H615). In contrast, the control group showed a significant decrease in Cmax on the third study day (740 vs. 1140 μg/L; $p = 0.046$). By day 7, the median esomeprazole Cmax in the SAH group remained five times lower than the preoperative Cmax in the control group ($p < 0.001$).

Post-IV administration, the average Cmax was approximately 1.7 times higher in the control group than in the SAH group ($p < 0.001$, Table 1; and eFig. 1, http://links.lww.com/CCM/H615). However, there was no significant difference in the AUC following IV administration between the two groups (Table 2).

After oral dosing, on day 1, the median Tmax was approximately two times longer in the SAH group compared with the control group ($p = 0.02$; Table 2). However, considerable variability was observed in both groups. Tmax was still two-fold longer in the SAH group compared with the control group on day 1 (Table 2).

Bioavailability and Metabolites As Indicators of Cytochrome P450 Activity

The bioavailability of esomeprazole in the SAH group was markedly low, ranging from 10% to 20%. This low bioavailability did not show any improvement over time, remaining as low on the last study day as on the first day in the SAH cohort. In contrast, the control group consistently achieved higher AUC values on all study days (Table 2).

Consistent with these findings, bioavailability in the SAH group was significantly lower than in the control group on the first day of the study (8% vs. 59%; $p < 0.001$). By day 7, bioavailability in the SAH group increased only slightly to 18%. No significant differences in bioavailability were observed within the control group during the study period. Additionally, no significant correlations were found between patient age or body weight and any of the assessed pharmacokinetic parameters.

Primary esomeprazole metabolites were analyzed as indicators of the activities of the cytochrome P450 enzymes 2C19 and 3A4. Concentrations of OH-OM and DM-OM, reflecting hepatic CYP2C19 activity, were significantly lower in the SAH cohort than in the control group up to day 7 (Table 2). Plasma metabolic ratios did not significantly differ between the groups or study days (Table 2 and **Fig. 3**). In contrast, the concentrations and metabolic ratios of esomeprazole sulfone, which reflect the activity of both enteral and hepatic CYP3A4, were significantly lower in the SAH group compared with the control group (Table 2 and Fig. 3).

Impact of Erythromycin

Given our institutional practice of administering erythromycin to promote gastrointestinal motility in critically ill neurosurgical patients, its potential confounding effects were also examined. Erythromycin administration nominally resulted in a significantly shorter esomeprazole Tmax and approximately doubled the AUC compared with SAH patients who did not receive erythromycin (**eFig. 2**, http://links.lww.com/CCM/H615). These differences were not statistically significant, and the administration of erythromycin was not randomized but was based on the medical decisions of the attending physicians. However, significant inhibitory effects of erythromycin on CYP3A4 were evident from the IV data (eFig. 2, http://links.lww.com/CCM/H615).

DISCUSSION

Pharmacokinetic data for oral medications, typically based on healthy individuals, often do not account for the significantly impaired enteral drug absorption in critically ill patients (5, 6). Recent reviews have highlighted the need for a better understanding of oral bioavailability of drugs in this patient population (20).

Studies on gastrointestinal function in critically ill patients have consistently demonstrated notable impairments (21, 22). However, quantifying these dysfunctions is challenging (23–25). Several approaches including measurement of plasma citrulline levels (26, 27) and administration of lactulose and ^{2}H breath tests (28) have been employed to evaluate gastrointestinal function in critically ill patients. However, the impact of severe brain injury on gastrointestinal function, specifically the bioavailability of drugs administered via nasogastric tubes, remains unclear.

While the effect of aneurysmal SAH on cardiac and pulmonary function is well-studied (9–11), its impact on gastrointestinal function is less explored. Animal studies show that SAH leads to intestinal mucosal

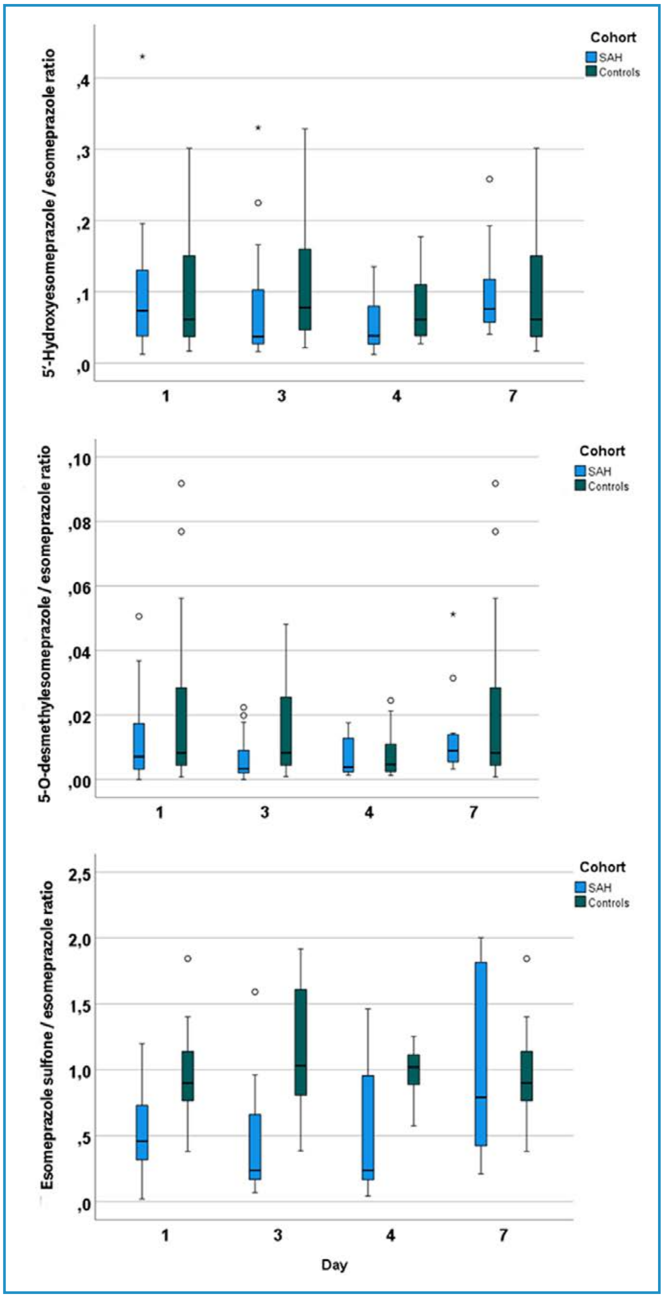

Figure 3. Three primary metabolites of esomeprazole were analyzed as indicators of cytochrome P450 2C19 (5′-OH-esomeprazole and 5-O-desmethyl esomeprazole) and cytochrome P450 3A4 (esomeprazole sulfone) activity. Data are normalized for differences in bioavailability by the ratios of the respective metabolites over the parent drug. *Blue boxes* show the subarachnoid hemorrhage (SAH) group and *green* the control group. Medians are the *horizontal lines* in the *boxes* that show the 25th and 75th quartiles. *Outliers* are shown by *open circles* and *far outliers* by *asterisks*. There were no significant differences between the groups and study days concerning CYP2C19 activity. However, the esomeprazole sulfone formation was substantially lower in the SAH cohort indicating very low CYP3A enzyme activity.

damage, including shedding and apoptosis of epithelial cells, villi disarrangement, mucosal atrophy, and inflammatory infiltration (29). In the clinical setting gastrointestinal dysfunctions such as bleeding, gastric reflux, and decreased peristalsis have been reported in patients with SAH (16). Other studies observed impaired upper gastrointestinal tract motility (30) or reported deteriorating splanchnic tissue perfusion after acute SAH (31). Soppi et al (12) and Abboud et al (13) reported very low AUC values for enteral nimodipine in SAH patients. Enteral application resulted in negligible serum concentrations for up to 12 days post-hemorrhage (13). However, as a probe drug for intestinal absorption nimodipine is not optimal, it has a low and variable bioavailability (around 10%), a very high first pass metabolism, and as a calcium antagonist, it may decrease intestinal motility. Therefore, here we chose esomeprazole, which is clinically used in critically ill patients and is absorbed primarily in the duodenum (15, 32, 33). Esomeprazole is uncharged and relatively lipophilic; thus, it does not dependent on specific transport systems for absorption. Nevertheless, there is no single probe drug completely reflecting all aspects in the present context. While PPIs are widely used in the critically ill, they may also have adverse effects and potentially increase mortality (34). Although a larger observational study has recently reported that SAH patients have a similar risk of approximately 5% to develop severe gastrointestinal bleeding as other intensive care patients the application of PPIs may result in a relevant risk reduction (16). However, to determine the risk-benefit ratio of PPIs, further studies are needed.

Our study found that esomeprazole absorption in SAH patients was five to ten times lower than in age and body weight-matched controls. The SAH group exhibited significantly lower Cmax, AUC, and bioavailability after enteral administration, with increased Tmax and lagtime, compared with the elective surgery group. The most reasonable explanation for the much lower Cmax after IV dosing in the SAH group is a higher volume of distribution. Patients with SAH received more IV fluids (around 4 L a day; Table 1) compared with the elective surgery patients with a normal fluid intake of approximately 2 L a day, although this was not measured. Overall, no significant pharmacokinetic improvements were observed even a week after ictus. Although mechanisms remain unclear, our data suggest inadequate intestinal drug absorption in high-grade SAH patients.

In a similar study on patients recovering from cardiogenic shock (35), we found significant but less severe impairment in esomeprazole absorption compared with SAH patients (**eFig. 3**, http://links.lww.com/CCM/H615). This suggests that neurointestinal mechanisms may be more relevant than cardiovascular shock. However, there remain legitimate questions about to which degree these observations are attributable to critical illness vs. being unique for patients with brain injury. Furthermore, it remains unclear if impaired drug absorption is more pronounced in patients with SAH compared with other neurocritical care patients.

This study demonstrates that esomeprazole can serve as a probe drug for intestinal absorption and assessing the activities of the CYP2C19 and CYP3A4 enzymes. When using drugs like nimodipine or esomeprazole as indicators of intestinal absorption, we cannot fully differentiate between intestinal absorption, cytochrome P450 mediated metabolism in the gut wall, and first-pass metabolism in the liver. Poor liver function can increase blood concentrations of these drugs, counteracting poor absorption. In intensive care patients, poor liver function may be due to hypoperfusion and ischemia, systemic inflammation, and drug-drug interactions.

In the patients studied here, there was no evidence of relevant hepatic ischemia. However, we found that CYP3A4 activity was significantly reduced in the initial days after SAH, a finding that was only partially attributable to erythromycin comedication in some patients. Conversely, CYP2C19 activity was similar between the SAH and control groups (Table 2). Importantly, none of our patients exhibited significant hepatic impairment. Serum bilirubin (Table 1) and INR as indicators of the hepatic drug elimination capacity were normal in all patients. Generally, impaired liver function might have affected the 5′-OH-esomeprazole/esomeprazole ratio (36), but that was not found here.

Concerning pharmacokinetics of the parent drug esomeprazole, it is very unlikely that this was modified by renal function because the fraction of esomeprazole eliminated unchanged via the urine is very low. Also, our data did not indicate an effect of augmented renal function (37) in the SAH group on esomeprazole clearance since AUCs after IV application were almost identical in both groups (Table 2). However, the primary metabolites are eliminated by secondary hepatic metabolism and renal elimination. Thus, enhanced renal elimination of esomeprazole metabolites may partially have contributed to the low values of esomeprazole sulfone as indicator of CYP3A4 activity. Here, we did not collect urine but it might be considered in future studies.

While esomeprazole pharmacokinetics are influenced by CYP2C19 polymorphism, this effect is less pronounced than with racemic omeprazole. As summarized by Ogilvie et al (18), about 30% of esomeprazole is metabolized via CYP3A4, the remaining via CYP2C19. However, after the first dose, the fraction metabolized via CYP3A4 becomes even larger because esomeprazole is known to inhibit its own metabolism. This was further supported by our observation that the ratios of the two CYP2C19-generated metabolites were less than ten-fold smaller than the esomeprazole-sulfone/esomeprazole ratio (Table 2).

The study is limited by the variability in patient comorbidities and medications. The impact of erythromycin on esomeprazole absorption (38) should be interpreted cautiously due to the small sample size and lack of randomization. Similarly, the effect of nimodipine on intestinal motility warrants further investigation. Despite these limitations, such "real-world studies" provide valuable insights into medical practice, complementing highly controlled studies on selected patient groups.

In conclusion, our findings suggest that drug absorption is significantly impaired in the first week following high-grade SAH due to a variety of factors. Given this, administering vital drugs with a low therapeutic index via enteral routes during this period is not advisable. The evidence using esomeprazole as a probe drug may represent many other drugs, but further studies are needed, especially for drugs relying on specific absorption transport systems like most antibiotics, nucleosides, or amino acid derivatives.

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Dr. Abboud designed and supervised the study. Dr. Stenzig performed the power analysis. Drs. Kranawetter, Brockmöller, and Abboud drafted the article. Ms. Sindern, Ms. Hapke, and Dr. Harnisch collected samples and clinical data. Dr. Brockmöller and Ms. Bruns performed pharmacological analyses. Dr. Brockmöller and Ms. Sindern performed statistical analysis and interpreted the data. Drs. Moerer, Mielke, Rohde, Brockmöller, and Abboud critically revised the article.

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The study was approved by the local ethics committee (application number: 10/01/19).

Informed consent was obtained from each patient or their next of kin.

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