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# The impact of a 1-hour time interval between pazopanib and subsequent intake of gastric acid suppressants on pazopanib exposure

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## Abstract

Co-treatment with gastric acid suppressants (GAS) in patients taking anticancer drugs that exhibit pH-dependant absorption may lead to decreased drug exposure and may hamper drug efficacy. In our study, we investigated whether a 1-hour time interval between subsequent intake of pazopanib and GAS could mitigate this negative effect on drug exposure. We performed an observational study in which we collected the first steady-state pazopanib trough concentration ($C_{min}$) levels from patients treated with pazopanib 800 mg once daily (OD) taken fasted or pazopanib 600 mg OD taken with food. All patients were advised to take GAS 1 hour after pazopanib. Patients were grouped based on the use of GAS and the geometric (GM) $C_{min}$ levels were compared between groups for each dose regimen. Additionally, the percentage of patients with exposure below the target threshold of 20.5 mg/L and the effect of the type of PPI was explored. The GM $C_{min}$ levels were lower in GAS users vs non-GAS users for both the 800 and 600 mg cohorts (23.7 mg/L [95% confidence interval [CI]: 21.1-26.7] vs 28.2 mg/L [95% CI: 25.9-30.5], $P$ = .015 and 26.0 mg/L [95% CI: 22.4-

**Abbreviations:** ATPase, adenosine triphosphatase; $C_{min}$, trough concentration; CYP, cytochrome P450; GAS, gastric acid suppressants; GM, geometric mean; H2A, histamine-2-receptor antagonists; PFS, progression-free survival; PPI, proton pump inhibitor; RCC, renal cell carcinoma; STS, soft-tissue sarcoma; TDM, therapeutic drug monitoring; TKI, tyrosine kinase inhibitor

30.3] vs 33.5 mg/L [95% CI: 30.3-37.1], $P = .006$). Subtherapeutic exposure was more prevalent in GAS users vs non-GAS users (33.3% vs 19.5% and 29.6% vs 14%). Subanalysis showed lower GM pazopanib $C_{min}$ in patients who received omeprazole, while minimal difference was observed in those receiving pantoprazole compared to non-users. Our research showed that a 1-hour time interval between intake of pazopanib and GAS did not mitigate the negative effect of GAS on pazopanib exposure and may hamper pazopanib efficacy.

**KEYWORDS**
drug-drug interaction, gastric acid-suppressive agents, omeprazole, pantoprazole, pazopanib, pharmacokinetics

## 1 | INTRODUCTION

Pazopanib is an oral multitargeted tyrosine kinase inhibitor (TKI) registered as monotherapy for the treatment of advanced or metastatic renal cell carcinoma (RCC) and for patients with advanced soft-tissue sarcoma (STS) who received prior chemotherapy.[1-3] As for most oral targeting TKIs, the exposure of pazopanib is highly variable between patients (40%-70%) and the level of systemic exposure appears to be associated with its clinical effect.[4-10] For pazopanib, Suttle et al found an association between a pazopanib trough concentration ($C_{min}$) level of >20.5 mg/L and improved progression-free survival (PFS) in patients with advanced RCC.[11] This exposure-response target has been confirmed in a real-world patient cohort of patients with advanced RCC by Verheijen et al.[9] For patients with STS treated with pazopanib, the exposure-response relationship has not yet been confirmed, although a similar trend has been observed.[9]

The high interpatient variability of pazopanib can partly be explained by its slow and incomplete absorption which results in an oral bioavailability of approximately 21%.[12] Pazopanib is registered in a fixed dose of 800 mg once daily taken fasted. The oral route of administration puts pazopanib at high risk of drug absorption interactions. A favourable effect is that the intake of pazopanib with a high caloric meal increases its exposure up to ~2-fold.[13] In previous work from our research group, we demonstrated that the pazopanib dose can be reduced by 25% when taken with a continental breakfast.[14] Based on these results, our clinicians and patients prefer the prescription of 600 mg pazopanib taken with continental breakfast as starting dose. Conversely, a major disadvantage of pazopanib is that substances that increase intragastric pH are likely to reduce its exposure. Pazopanib requires a low intragastric pH for its absorption, as it is slightly soluble in aqueous solutions at pH 1 and practically insoluble above pH 4.[15]

Use of gastric acid suppressants (GAS) such as proton pump inhibitors (PPIs) or histamine-2-receptor antagonists (H2As) is common in patients with cancer.[16] For pazopanib, the influence of concomitant intake with esomeprazole has been investigated by Tan et al. Administration of esomeprazole 12 hours after fasted intake of pazopanib decreased mean pazopanib $C_{min}$ levels by 36%.[17] This decrease in exposure puts patients at risk for subtherapeutic exposure and thus possibly treatment failure.

**What's new?**

Use of gastric acid suppressants (GAS) is common in patients with cancer. However, absorption of pazopanib, an oral multitargeted tyrosine kinase, is pH-dependent, and concomitant therapy with GAS reduces its exposure and presumably its efficacy. Here, the authors evaluated whether a one-hour interval between the intake of pazopanib and then GAS could mitigate its negative effect on pazopanib exposure. It was found that, despite the optimized time-scheduled intake, co-treatment with GAS still resulted in a clinically relevant reduction in pazopanib exposure and may hamper pazopanib efficacy. Medical oncologists treating patients should try to avoid the combination of GAS and pazopanib.

Previously, Mir et al reported a significantly shortened PFS and overall survival in patients with STS who were treated with GAS compared to patients not treated with GAS.[18] In contrast, in patients with advanced RCC, no statistical significant differences in PFS were observed between GAS- and non-GAS users in two real-world cohorts described by McAlister et al and Van de Sijpe et al.[19,20] However, these studies did not asses pazopanib $C_{min}$ levels which might have explained the apparent discrepancy in the observations. Furthermore, only McAlister et al reported the time of intake of GAS in relation to pazopanib administration.

Several strategies have been proposed to mitigate the interaction of TKIs with GAS. These include switching to short acting anti-acids, use of a once-daily regimen and application of a time interval between drug intakes according to the duration of pH elevation.[21] GAS do not elevate intragastric pH over the full 24-hour range and have a lag time before their onset of effect.[22-24] Therefore, the administration of the GAS 1 hour after intake of pazopanib allows pazopanib to be

dissolved at the lowest gastric pH. However, this intake strategy has not yet been evaluated clinically. Therefore, in our study, we investigated the influence of a 1-hour time interval between subsequent intake of pazopanib and GAS on pazopanib exposure taken with and without food.

## 2 | METHODS

### 2.1 | Patients

This observational study was performed using clinical data and pazopanib $C_{min}$ levels obtained from patients treated with pazopanib between March 2013 and March 2020. Patients had plasma pazopanib $C_{min}$ levels measured as part of routine patient care or as part of the DIET study, in which the effect of food on pazopanib pharmacokinetics was inverstigated.[14] To rule out potential influence from dose optimization, only the first measured steady-state $C_{min}$ level at dose of 800 mg taken fasted or 600 mg taken with food were included. Steady-state was defined as pazopanib treatment for more than seven consecutive days. For participants of the DIET study, both first measurements of 800 mg fasted and 600 mg taken with food were included. All patients were advised to take GAS 1 hour after pazopanib intake.

### 2.2 | Data collection

Baseline characteristics were retrospectively retrieved from the electronical health records or retrieved from the prospectively collected case report forms at the start of pazopanib treatment. Missing data at baseline were replaced by the closest value in time up to 21 days before start of treatment or assessed not available. For pazopanib treatment, start date, dose, time of intake, intake with or without food, concomitant use of PPI, H2A, antacids or interacting medicines were collected at start and at the time of first measured steady-state pazopanib $C_{min}$ level. For patients who were co-treated with a PPI or H2A, type, dose and frequency of this agent were documented. GAS use was defined as use of a PPI or H2A on the days before the first measured pazopanib $C_{min}$ level. As antacids only have a short duration of action of 30 to 60 minutes and only minimally affect intragastric pH when taken as recommended (2 hours after or 4 hours before pazopanib), users of antacids were considered not being treated with GAS. For evaluation of the time on treatment, the last day of pazopanib treatment and reason of treatment discontinuation were collected. Patients with gastrointestinal abnormalities and patients who used strong inducers or inhibitors of cytochrome p450 (CYP) 3A4 were excluded.

### 2.3 | Pazopanib quantification, sample collection and calculation of $C_{min}$

All blood samples were collected and handled as previously reported.[25] Pazopanib concentrations were measured using a validated high-performance liquid chromatography coupled with tandem mass spectrometry detection assay.[26] Patients who participated in the DIET study had their first pazopanib $C_{min}$ level measured at predefined moments.[14] For patients who were treated with pazopanib in routine care, no predefined sampling moments were set for measuring pazopanib plasma concentrations, although therapeutic drug monitoring (TDM) is standard of care in our clinic and the first measurement is usually performed 2 to 4 weeks after treatment initiation.[25] For each sample, the date and time of last intake of pazopanib and plasma sample collection were recorded. In case the sample was not collected 24 hours after intake, the $C_{min}$ was calculated by the approach described by Wang et al. This approach assumes a mono-exponential decline in plasma concentration and uses the interval between the last dose intake and the blood sample and the mean elimination half-life of pazopanib of 31 hours to calculate the $C_{min}$ level.[27]

### 2.4 | Statistical analysis

Analyses were performed for pazopanib $C_{min}$ levels both at 800 mg taken fasted and 600 mg taken with food. Patients were divided into two groups: patients who were treated with GAS or patients who were not treated with GAS. Patient characteristics and pazopanib plasma $C_{min}$ levels were described using descriptive statistics. For the primary outcome, geometric mean (GM) pazopanib $C_{min}$ levels were calculated per group and compared to an independent samples *t* test.

To identify potential differences in effect between the different types of GAS, an explorative sub-analysis was performed. In this analysis, the GM pazopanib $C_{min}$ levels of the two main subgroups of GAS were compared to the group of patients who were not treated with GAS, regarded as the reference group, using Dunnett's two-sided test to adjust for multiple comparisons. To explore the influence of use of GAS on treatment outcome, the median PFS between the two groups were analysed per tumour type by Kaplan-Meier method and compared statistically using the log rank test. Hazard ratios were estimated using univariate Cox-regression analyses. PFS was defined as the time on treatment until progression or death.

All statistical analyses were performed using IBM SPSS statistics for Windows version 25.0 (IBM Corp, Armonk, NY). Outcomes with *P* values <.05 were considered to be statistically significant.

## 3 | RESULTS

### 3.1 | Pazopanib 800 mg taken fasted

#### 3.1.1 | Patients

From March 2013 to March 2020, for 136 patients, using pazopanib 800 mg taken fasted, a steady-state pazopanib $C_{min}$ level was

**TABLE 1** Demographic and clinical characteristics of patients at baseline

| Baseline characteristic | | 800 mg taken fasted (n = 136) | | 600 mg taken with food (n = 83) | |
|---|---|---|---|---|---|
| | | Without GAS (n = 82) n (%) | With GAS (n = 54) n (%) | Without GAS (n = 57) n (%) | With GAS (n = 26) n (%) |
| Median age (range) (year) | | 61 (28-78) | 61.5 (45-85) | 61 (28-77) | 60 (45-85) |
| Sex | Male | 50 (61.0) | 40 (74.1) | 37 (64.9) | 18 (69.2) |
| Median BMI (range) (kg/m$^2$) | | 25.4 (17.2-52.4) | 25.9 (20.7-40.4) | 25.7 (18.7-52.4) | 24.3 (20.7-34.6) |
| Karnofsky performance score | | | | | |
| | 90-100 | 36 (43.9) | 13 (24.1) | 22 (38.6) | 7 (26.9) |
| | 80-89 | 35 (42.7) | 29 (53.7) | 29 (50.9) | 16 (61.5) |
| | <80 | 5 (6.1) | 9 (16.6) | 2 (3.5) | 3 (11.5) |
| Tumour type | | | | | |
| | RCC | 51 (62.2) | 45 (83.3) | 38 (66.7) | 23 (63.9) |
| | STS | 30 (36.6) | 9 (16.6) | 19 (33.3) | 3 (11.5) |
| | Other | 1 (1.2) | 0 | 0 | 0 |
| Histological subtype (RCC) | | | | | |
| | Clear cell | 28 (54.9) | 24 (53.3) | 16 (42.1) | 7 (26.9) |
| | Non clear cell | 23 (45.1) | 21 (46.7) | 22 (57.9) | 16 (69.5) |
| Previous systemic treatment | Yes | 42 (51.2) | 28 (51.9) | 30 (52.6) | 11 (42.3) |

Abbreviations: BMI, body mass index; GAS, gastric acid suppressants; RCC, renal cell carcinoma; STS, soft-tissue sarcoma.

measured. The majority of patients (n = 96) were treated for RCC, 39 patients were treated for soft tissue sarcoma and one for clear cell ovarium carcinoma. Out of these 136 patients, 82 (60.3%) patients did not use concomitant GAS, 50 (36.8%) patients used a PPI and 4 (2.9%) patients used an H2A. Of the PPI users, 26 patients used omeprazole, 3 esomeprazole, 19 pantoprazole, 1 rabeprazole and for 1 patient the type of PPI was unknown. Baseline characteristics were comparable between groups and are shown in Table 1.

### 3.1.2 | Pazopanib exposure with and without GAS

In patients treated with GAS, pazopanib GM $C_{min}$ was significantly lower compared to patients who were not treated with GAS (23.7 mg/L [95% CI: 21.1-26.7] vs 28.2 mg/L [95% CI: 25.9-30.5], $P$ = .015; Figure 1). This difference remained significant after excluding the four patients who used an H2A. In patients treated with GAS, 33.3% had a $C_{min}$ below the target threshold of 20.5 mg/L compared to 19.5% of the patients without GAS ($P$ = .07).

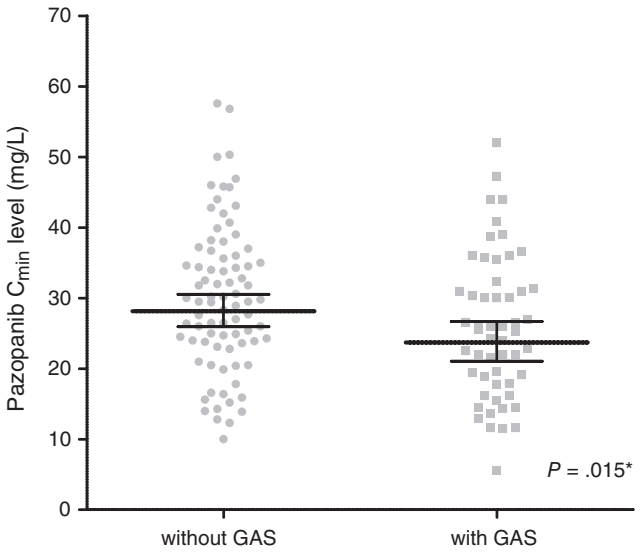


**FIGURE 1** Geometric mean (95% CI) scatter plots of the individual pazopanib trough concentration ($C_{min}$) levels for patients who were treated with pazopanib 800 mg taken fasted with and without gastric acid suppressants (GAS)

### 3.1.3 | Effect of the type of PPI

In an exploratory subgroup analysis, a lower GM pazopanib exposure was observed in patients treated with omeprazole (n = 26) (GM $C_{min}$ 22.8 mg/L [95% CI: 18.8-27.6]. $P$ = .038), while minimal reduction in pazopanib exposure was observed in those treated with pantoprazole (n = 19) (GM $C_{min}$ 26.6 mg/L [95% CI: 22.0-32.2], $P$ = .8) compared to patients who were not treated with GAS (Figure 2).

### 3.1.4 | Effect of GAS use on treatment outcome

For the exploratory analysis on PFS, follow-up data were available for 94 of 96 patients with advanced RCC, of which 44 (46.8%) were treated with GAS concomitantly. A total of 51 patients stopped pazopanib treatment due to disease progression or death; 24 patients of them used GAS concomitantly. An overview of reasons for

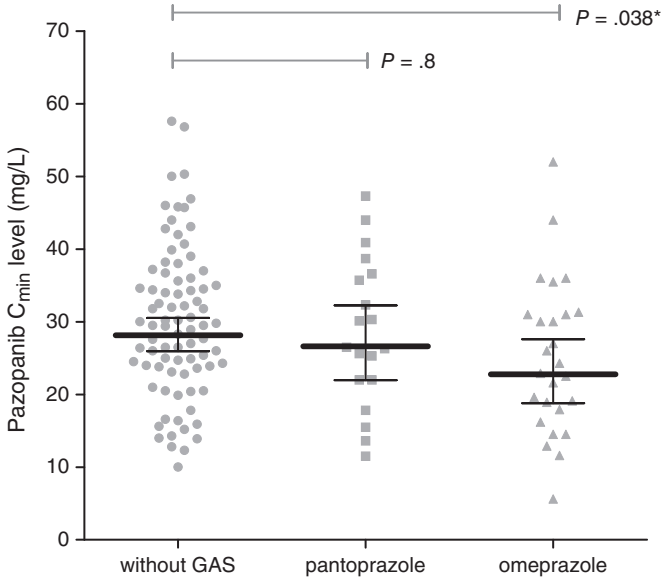


**FIGURE 2** Geometric mean (95% CI) scatter plots of the individual pazopanib trough concentration ($C_{min}$) levels for patients who were treated with pazopanib 800 mg taken fasted without gastric acid suppressants (GAS), with omeprazole and with pantoprazole respectively

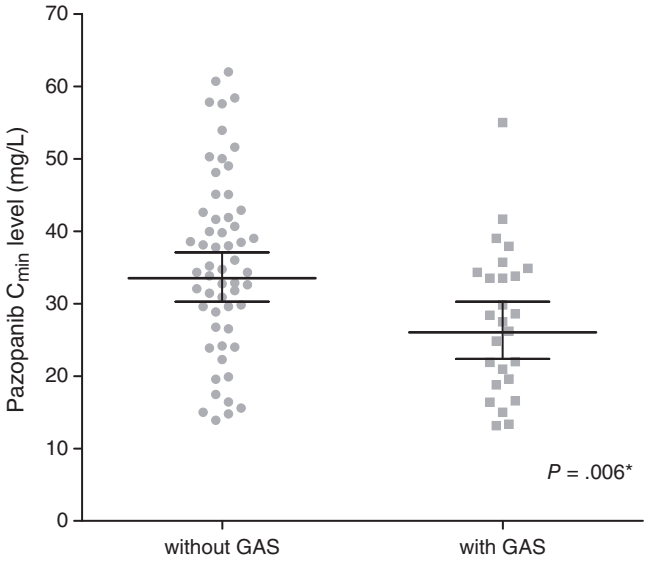


**FIGURE 3** Geometric mean (95% CI) scatter plots of the individual pazopanib trough concentration ($C_{min}$) levels for patients who were treated with pazopanib 600 mg taken fed with and without gastric acid suppressants (GAS)

treatment discontinuation is listed in Table S1. No significant difference in PFS was observed for patients who were treated with and without GAS (11 vs 12 months, HR 1.13, 95% CI: 0.64-1.78, $P$ = .7; Figure S1).

Of the 38 patients with STS, follow-up data were available for 34 patients of which 8 (23.5%) were treated with GAS. A total of 25 patients stopped pazopanib treatment due to disease progression or death, of which 7 patients used GAS. The reasons for treatment discontinuation are listed in Table S1. Median PFS was shortened for patients who were treated with GAS compared to those without (17 vs 32 weeks, HR 3.89, 95% CI: 1.44-10.55, $P$ = .008; Figure S2).

## 3.2 | Pazopanib 600 mg taken with food

### 3.2.1 | Patients

For 83 patients, using 600 mg pazopanib taken with food, a steady-state pazopanib $C_{min}$ level was available, of whom 61 had RCC and 22 had STS. Out of these 83 patients, 26 (31.3%) patients did use GAS concomitantly, 25 patients used a PPI and 1 patient used an H2A. Of the PPI users, 13 patients used omeprazole, 11 pantoprazole and 1 rabeprazole. Additional baseline characteristics are shown in Table 1.

### 3.2.2 | Pazopanib exposure

In the patients treated with GAS the GM of the pazopanib $C_{min}$ was 26.0 mg/L (95% CI: 22.4-30.3) compared to 33.5 mg/L (95% CI: 30.3-37.1) ($P$ = .006) in patients who were not treated with GAS concomitantly (Figure 3).

In patients treated with GAS, 26.9% had a $C_{min}$ below the target threshold compared to 14.0% of the patients without GAS ($P$ = .16).

### 3.2.3 | Effect of type of PPI

Exploratory sub-analysis on the effect of the type of PPI on pazopanib exposure showed a pronounced effect for omeprazole use (n = 13) (GM $C_{min}$ 22.9 mg/L [95% CI: 18.7-27.9], $P$ = .003), whereas a minimal effect for pantoprazole use (n = 11) was observed (GM $C_{min}$ 29.5 mg/L [95% CI: 22.4-38.7], $P$ = .5) compared to non-GAS use (Figure 4).

There was a partial overlap in patients treated with pazopanib 800 mg taken fasted and 600 mg taken fed due to the DIET study patients who had a pazopanib $C_{min}$ level measured at both 800 and 600 mg. Therefore, a sensitivity analysis was performed excluding these overlapping observations. After exclusion of the DIET study patients, 11 patients remained, of which 4 patients used pantoprazole, 2 used omeprazole and 5 did not use GAS. For patients who were treated with omeprazole, a similar trend was observed as reported for the whole group (Supplementary Figure 3).

## 4 | DISCUSSION

Our study shows that despite using a 1-hour time interval between dosing, co-treatment with GAS still resulted in reduced pazopanib exposure. Although the average pazopanib $C_{min}$ level was above the target threshold of 20.5 mg/L, a larger proportion of patients co-treated with GAS showed sub-therapeutic pazopanib $C_{min}$ levels (33.3% vs 19.5%), suggesting that

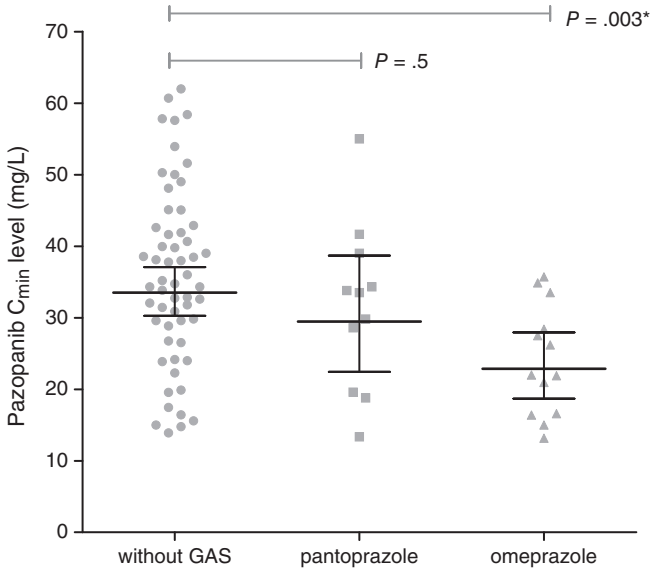


**FIGURE 4** Geometric mean (95% CI) scatter plots of the individual pazopanib trough concentration ($C_{min}$) levels for patients who were treated with pazopanib 600 mg taken fed without gastric acid suppressants (GAS), with omeprazole and with pantoprazole respectively

this drug interaction remains clinically relevant despite the time-scheduled intake, and could negatively affect patient outcome.

In patients treated with 600 mg pazopanib taken with food, the difference in pazopanib exposure between patients who were treated with GAS and those without GAS was even more pronounced compared to patients treated with 800 mg pazopanib taken fasted (GM $C_{min}$ 26.0 vs 33.5 mg/L compared to 23.7 vs 28.2 mg/L). This is an unexpected finding, as we assumed that food intake would somewhat diminish the negative effect of GAS on pazopanib absorption due to enhanced solubility in a lipophilic environment. However, the bottleneck of pazopanib absorption is thought to lie within its poor dissolution at higher pH values.[15,28] In patients without GAS, meal-stimulated gastric acid release after intake of pazopanib with food may provide suitable intragastric pH for pazopanib dissolution. However, in patients who are co-treated with GAS, inhibition of the meal-stimulated gastric acid release by GAS may have hampered pazopanib absorption.[29]

Interestingly, in the explorative sub-analysis, this negative effect of GAS on pazopanib $C_{min}$ seemed to be the strongest for patients who used omeprazole, whereas the effect of pantoprazole was limited compared to patients who were not treated with GAS. This difference may be explained by the different pharmacological characteristics of these drugs.

Pantoprazole has a slower inhibition rate of the gastric H+/K+ adenosine triphosphatase (ATPase) compared to omeprazole. In porcine gastric vessels, it took omeprazole 30 minutes to fully inhibit the H+, K+ ATPase, whereas for pantoprazole only 50% inhibition was reached at 45 minutes.[30] The faster rate of inhibition by omeprazole may be a plausible explanation for the observed effect on pazopanib $C_{min}$ as pazopanib may have had less time to dissolve at low pH.

Another difference between pantoprazole and omeprazole is their duration of action. However, as omeprazole 20 mg only showed a marginally longer duration of pH elevation >4 compared to pantoprazole 40 mg (49.16% vs 41.94% of the day), this difference is less likely to explain the observed differences on pazopanib $C_{min}$ levels.[22]

Omeprazole and pantoprazole are both metabolised by CYP2C19 and to a lesser extent by CYP3A.[31] However, omeprazole is also an inhibitor of CYP2C19 and thus inhibits its own metabolism leading to non-linear pharmacokinetics.[32] The accumulation of omeprazole may have resulted in a longer duration of acid inhibition. Furthermore, omeprazole is a dose-dependent inducer of CYP1A2, whereas pantoprazole does not affect CYP1A2.[33,34] Although CYP1A2 has a minor role in pazopanib metabolism, induction of CYP1A2 may have contributed to the lower pazopanib exposure.[15] In summary, multiple pharmacological differences may have contributed to the observed differences in effect on pazopanib exposure, but the exact underlying mechanism remains unclear.

Previously, Mir et al described a significant shortened PFS in patients with STS treated with pazopanib and GAS.[18] In our study, pazopanib $C_{min}$ levels in patients treated with GAS were significantly lower, which could explain the observed difference in outcome. Likewise, we also observed a shortened PFS in the small group of patients with STS in our analysis. However, it is important to note that STS is a highly heterogeneous disease and the observed difference may also have been caused by differences in response between differences in disease subtypes.

In contrast, we did not observe a difference in PFS for patients with RCC who were treated with and without GAS. This finding is in line with previous reports by McAlister and Van de Sijpe, who showed no significant difference in PFS between patients treated with and without GAS.[19,20] The percentage of non-GAS patients with subtherapeutic exposure at first measured $C_{min}$ was comparable to previously reported percentages of pazopanib underexposure (16.4%-19.6%).[9,11] However, in the participating hospitals in our study pazopanib dose optimization based on measured $C_{min}$ levels is standard of care. This strategy enables to timely identify patients with subtherapeutic pazopanib levels and perform interventions to help these patients achieve adequate exposure. Consequently, the lack of observed difference in PFS in our cohort could be attributed by this strategy.

The present study has a number of limitations, inherent to its real-world and retrospective setting. First, no a priori sample size calculation was performed as the study was not initially designed for this analysis. A cross-over design would have been a more ideal design given the high interpatient variability of pazopanib. Nevertheless, the sample size and design is comparable to two previous studies performed on this topic.[19,20] Also, the FDA guideline on clinical drug interaction studies states that positive findings from retrospective evaluations can provide valuable insights for clinical practice as we demonstrated in our study.[35] Another potential limitation of our study is that there may have been differences between the registered and the actual time of pazopanib intake and sample collection. However, since TDM monitoring is well embedded in our clinic, these differences are likely to be small and of limited influence. An important limitation is that there was no formal check if the intake advice was communicated by the oncologist or pharmacist and adhered to by the

patient. Therefore, there might have been slight differences in the time of intake of the GAS. In addition, PPIs are also available without prescription in drugstores. Although registration of over-the-counter drug use is standard of care in the Netherlands while screening for drug interactions, the use of undocumented GAS cannot be completely excluded. This potential under-reporting of GAS use, however, would have only diluted the observed differences in exposure. Furthermore, we were not able to assess the influence of the dose of the PPIs, as for some patients these details were missing. Last of all, genetic variations in CYP2C19 are known to contribute to variability in gastric acid inhibition by PPIs, particularly at low doses.[36] However, genotyping was not performed in our study. Approximately 5% of the Dutch population has the CYP2C19*17/*17 genotype and these patients may need up to a 5-fold higher PPI dose to achieve sufficient gastric acid suppression.[37-39] Therefore, including CYP2C19 genotype in future studies may be warranted.

To the best of knowledge, this is the first study that quantified the influence of GAS on pazopanib exposure in a real-world setting. The clinical consequence of reduced exposure could not be fully assessed, as dose-optimization is standard of care in our clinic. However, the negative effect of GAS on pazopanib exposure despite application of a 1-hour time interval between intake remains clinically relevant, especially for clinicians without access to TDM services. When possible, the use of GAS should be avoided in patients taking pazopanib. In patients who still require co-treatment with GAS, application of a 1-hour time interval between pazopanib and GAS in combination with TDM appears a feasible strategy to optimise pazopanib exposure. Alternatively, if possible switching to another TKI with comparable effectiveness which is less dependent of a low intragastric pH for their absorption, for example, sunitinib for RCC,[40] may also be an option. The observed difference between omeprazole and pantoprazole is an interesting finding that warrants prospective validation and elucidation of the underlying mechanism. Currently, we are investigating whether switching omeprazole for pantoprazole in patients with subtherapeutic exposure helps to achieve adequate pazopanib exposure.

Furthermore, the negative interaction with GAS may also be of major importance for other TKIs that require low intragastric pH for optimal absorption, such as gefitinib, erlotinib and dasatinib.[23]

## 5 | CONCLUSION

In our study, we found that application of a 1-hour time interval between pazopanib and GAS intake still results in a significantly lower pazopanib exposure. Medical oncologists treating patients should try to avoid the combination of GAS and pazopanib. If use of GAS is unavoidable, the use of pantoprazole might be preferred over omeprazole, with a 1-hour interval between intake as the best known option so far.

### CONFLICT OF INTEREST

All mentioned relationships are outside the submitted work. Frank G. A. Jansman has been on an advisory board for Amgen and Servier. Paul Hamberg has been on an advisory board for Bristol-Meyers Squibb, Ipsen, Novartis, Esai, Sanofi, Jansen and Pfizer. Winette T. A. van der Graaf received a research grant from Novartis, has been on an advisory board for Bayer, and has been a consultant for Springworks. Ingrid M. E. Desar received a research grant from Novartis. Nielka P. van Erp has received research grants from Novartis, Astellas, Janssen-Cilag, Pfizer, Ipsen, has been on an advisory board for Pfizer, and received honoraria from Bayer and Sanofi. Carla M. L. van Herpen has received research grants form AstraZeneca, Bristol-Meyers Squibb, Merck Sharp and Dohme, Merck, Ipsen, Sanofi, and Novartis, has been on an advisory board for Bayer, Bristol-Meyers Squibb, Ipsen, Merck Sharp and Dohme and Regeneron. The other authors declared no potential conflicts of interest (Stefanie D. Krens, Floor J. E. Lubberman, Marthe van Egmond, David M. Burger, Walter L. Vervenne, Hans Gelderblom).

### DATA AVAILABILITY STATEMENT

The datasets generated and analysed for the current study are available from the corresponding author on reasonable request.

### ETHICS STATEMENT

Our study was performed in accordance with the Declaration of Helsinki (October 2013) and was approved by the Institutional Review Board from the Radboudumc (December 2018; 2018-4617). With consent of our Institutional Review Board and according to Dutch law on medical research (WMO, article 1) no-ethical approval is required when using anonymous data from routine diagnostic databases, as was done for part of the data analysed in our study. The DIET study was registered at ClinicalTrials.gov (NCT02138526).

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### REFERENCES

1. Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther*. 2007;6(7):2012-2021.
2. FDA. Drug label votrient FDA; 2009.
3. EMA. Votrient summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/votrient-epar-product-information_en.pdf. Accessed June 30, 2020.
4. Houk BE, Bello CL, Poland B, Rosen LS, Demetri GD, Motzer RJ. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/pharmacodynamic meta-analysis. *Cancer Chemother Pharmacol*. 2010;66(2):357-371.
5. Rini BI, Melichar B, Ueda T, et al. Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. *Lancet Oncol*. 2013;14(12):1233-1242.
6. Fukudo M, Ito T, Mizuno T, et al. Exposure-toxicity relationship of sorafenib in Japanese patients with renal cell carcinoma and hepatocellular carcinoma. *Clin Pharmacokinet*. 2014;53(2):185-196.
7. Demetri GD, Wang Y, Wehrle E, et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *J Clin Oncol*. 2009;27(19):3141-3147.
8. Hurwitz HI, Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. *Clin Cancer Res*. 2009;15(12):4220-4227.
9. Verheijen RB, Swart LE, Beijnen JH, Schellens JHM, Huitema ADR, Steeghs N. Exposure-survival analyses of pazopanib in renal cell carcinoma and soft tissue sarcoma patients: opportunities for dose optimization. *Cancer Chemother Pharmacol*. 2017;80:1171-1178.

10. Benoist GE, van der Meulen E, Lubberman FJE, et al. Analytical challenges in quantifying abiraterone with LC-MS/MS in human plasma. *Biomed Chromatogr*. 2017;31(11):e3986.
11. Suttle AB, Ball HA, Molimard M, et al. Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. *Br J Cancer*. 2014;111(10):1909-1916.
12. Deng Y, Sychterz C, Suttle AB, et al. Bioavailability, metabolism and disposition of oral pazopanib in patients with advanced cancer. *Xenobiotica*. 2013;43(5):443-453.
13. Heath EI, Chiorean EG, Sweeney CJ, et al. A phase I study of the pharmacokinetic and safety profiles of oral pazopanib with a high-fat or low-fat meal in patients with advanced solid tumors. *Clin Pharmacol Ther*. 2010;88(6):818-823.
14. Lubberman FJE, Gelderblom H, Hamberg P, et al. The effect of using pazopanib with food vs. fasted on pharmacokinetics, patient safety, and preference (DIET study). *Clin Pharmacol Ther*. 2019;106(5):1076-1082.
15. FDA. Vorient (pazopanib hydrochloride) tablets: clinical pharmacology biopharmaceutics review(s); 2010. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000_ClinPharmR.pdf. Accessed June 30, 2020.
16. Smelick GS, Heffron TP, Chu L, et al. Prevalence of acid-reducing agents (ARA) in cancer populations and ARA drug-drug interaction potential for molecular targeted agents in clinical development. *Mol Pharm*. 2013;10(11):4055-4062.
17. Tan AR, Gibbon DG, Stein MN, et al. Effects of ketoconazole and esomeprazole on the pharmacokinetics of pazopanib in patients with solid tumors. *Cancer Chemother Pharmacol*. 2013;71(6):1635-1643.
18. Mir O, Touati N, Lia M, et al. Impact of concomitant administration of gastric acid-suppressive agents and pazopanib on outcomes in soft-tissue sarcoma patients treated within the EORTC 62043/62072 trials. *Clin Cancer Res*. 2019;25(5):1479-1485.
19. McAlister RK, Aston J, Pollack M, Du L, Koyama T, Chism DD. Effect of concomitant pH-elevating medications with pazopanib on progression-free survival and overall survival in patients with metastatic renal cell carcinoma. *Oncologist*. 2018;23(6):686-692.
20. Van De Sijpe G, Beuselinck B, Van Nieuwenhuyse T, et al. Impact of concomitant acid suppressive therapy on pazopanib efficacy and dose reductions in patients with metastatic renal cell carcinoma. *Eur J Clin Pharmacol*. 2020;76(9):1273–1280.
21. Albiges L, Powles T, Staehler M, et al. Updated European Association of Urology Guidelines on renal cell carcinoma: immune checkpoint inhibition is the new backbone in first-line treatment of metastatic clear-cell renal cell carcinoma. *Eur Urol*. 2019;76(2):151-156.
22. Miner P Jr, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. *Am J Gastroenterol*. 2003;98(12):2616-2620.
23. van Leeuwen RWF, Jansman FGA, Hunfeld NG, et al. Tyrosine kinase inhibitors and proton pump inhibitors: an evaluation of treatment options. *Clin Pharmacokinet*. 2017;56(7):683-688.
24. Bisson C, St-Laurent M, Michaud JT, LeBel M. Pharmacokinetics and pharmacodynamics of ranitidine and famotidine in healthy elderly subjects: a double-blind, placebo-controlled comparison. *Pharmacotherapy*. 1993;13(1):3-9.
25. Lankheet NAG, Desar IME, Mulder SF, et al. Optimizing the dose in cancer patients treated with imatinib, sunitinib and pazopanib. *Br J Clin Pharmacol*. 2017;83:2195-2204.
26. van Erp NP, de Wit D, Guchelaar HJ, Gelderblom H, Hessing TJ, Hartigh J. A validated assay for the simultaneous quantification of six tyrosine kinase inhibitors and two active metabolites in human serum using liquid chromatography coupled with tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2013;937:33-43.
27. Wang Y, Chia YL, Nedelman J, Schran H, Mahon FX, Molimard M. A therapeutic drug monitoring algorithm for refining the imatinib trough level obtained at different sampling times. *Ther Drug Monit*. 2009;31(5):579-584.
28. Herbrink M, Groenland SL, Huitema ADR, et al. Solubility and bioavailability improvement of pazopanib hydrochloride. *Int J Pharm*. 2018;544(1):181-190.
29. Koziolek M, Alcaro S, Augustijns P, et al. The mechanisms of pharmacokinetic food-drug interactions - a perspective from the UNGAP group. *Eur J Pharm Sci*. 2019;134:31-59.
30. Besancon M, Simon A, Sachs G, Shin JM. Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. *J Biol Chem*. 1997;272(36):22438-22446.
31. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs*. 2003;63(24):2739-2754.
32. Li XQ, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos*. 2004;32(8):821-827.
33. Rost KL, Brösicke H, Brockmöller J, Scheffler M, Helge H, Roots I. Increase of cytochrome P450IA2 activity by omeprazole: evidence by the 13C-[N-3-methyl]-caffeine breath test in poor and extensive metabolizers of S-mephenytoin. *Clin Pharmacol Ther*. 1992;52(2):170-180.
34. Wedemeyer RS, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. *Drug Saf*. 2014;37(4):201-211.
35. FDA. Clinical drug interaction studies - cytochrome P450 enzyme- and transporter-mediated drug interactions guidance for industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions. Accessed November 16, 2020.
36. Hunfeld NG, Mathot RA, Touw DJ, et al. Effect of CYP2C19*2 and *17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. *Br J Clin Pharmacol*. 2008;65(5):752-760.
37. Sim SC, Risinger C, Dahl ML, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther*. 2006;79(1):103-113.
38. KNMP. Guidelines of the Dutch Pharmacogenetic Working Group. https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica/pharmacogenetics-1. Accessed July 17, 2020.
39. Scott SA, Sangkuhl K, Stein CM, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther*. 2013;94(3):317-323.
40. FDA. Sutent clinical pharmacology and biopharmaceutics review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021938_S000_Sutent_BioPharmR.pdf. Accessed November 10, 2006.


## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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