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LETTER TO THE EDITOR

Does a glass of Coke boost the exposure to imatinib in gastrointestinal stromal tumour patients after gastrectomy?

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Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the digestive tract. In the advanced and metastatic setting, **imatinib** is the first line treatment [1]. Imatinib has been approved for GIST at a standard dose of 400 mg once daily [2]. Due to its oral route of administration, variable absorption can lead to variations in systemic exposure [3]. Changes in stomach pH due to gastric surgery or the use of acid reduction agents may influence absorption of certain oral drugs [4]. However, alterations in stomach pH is not expected to impact imatinib absorption since imatinib dissolves rapidly at a pH range of 1.0–6.8 [5].

Unexpectedly, decreased imatinib exposure has previously been reported in 18 GIST patients who underwent major gastrectomy [3]. Imatinib trough concentrations (C_{trough}) were significantly reduced compared to patients without gastric surgery (C_{trough} 942 ± 330 μg l^{-1} *vs.* 1.393 ± 659 μg l^{-1}) [3]. As a result, imatinib trough concentrations where below 1100 μg l^{-1} in patients with a major gastrectomy. This is important as trough concentrations below 1100 μg l^{-1} are associated with unfavourable treatment response [3]. It emphasizes the potential clinically relevant consequences of prior major gastrectomy for this group of patients [6].

The exact mechanism that explains reduced imatinib trough concentrations after major gastrectomy is unknown. Yoo *et al.* [3] suggest that decreased imatinib absorption is caused by an elevated gastric pH, which reduces the solubility of imatinib. As seen for other TKIs, exposure can be increased when the gastric pH is artificially lowered by concomitant use of an acidic beverage (e.g. cola) [7].

To investigate whether this proof of concept also applies to imatinib, a small study was performed to explore the effect of concomitant intake of imatinib with Coca-Cola on imatinib exposure in GIST patients with major gastrectomy. All patients gave informed consent before entering the study. This study was approved by the institutional ethics committee and registered at ClinicalTrials.gov nr: NCT02185937.

In this cross-over study in seven patients with previous gastrectomy, patients used 400 mg imatinib once daily taken with a glass of water. After reaching steady-state pharmacokinetics (day 7), a pharmacokinetic curve of imatinib was assessed at the following timepoints t = 0, 1, 2, 3, 4, 5, 6, 8 and 10 h after imatinib intake. Subsequently, imatinib 400 mg was concomitantly ingested with 150 ml of Coca-Cola classic (pH 2.4). Again, after reaching steady-state pharmacokinetics (day 14), the pharmacokinetic assessment was

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repeated. The order in which patients underwent both treatments was randomly assigned. Imatinib plasma concentrations were measured using a validated liquid chromatography tandem mass spectrometry method [8]. The area under the concentration–time curve (AUC), maximum observed plasma concentration, (C_{max}) and plasma concentration at t = 24 h (C_{trough}) were calculated using noncompartmental analyses in WinNonlin/Phoenix v6.3 (Pharsight Corporation).

The geometric mean (GM) of the AUC to 24 h including 95% confidence interval (CI) was 25 769 μg l^{-1}*h (CI 19 553–33 960) when imatinib was ingested with Coca-Cola; compared to 24 881 μg l^{-1}*h (CI 18 318–33 795) when imatinib was ingested with water. The GM of C_{trough} and C_{max} ingested with Coca-Cola was 789 μg l^{-1} (CI 594–1049) and 2224 μg l^{-1} (CI 1854–2670) compared to 662 μg l^{-1} (CI 487–901) and 2010 μg l^{-1} (CI 1662–2431) when ingested with water (Table 1). The GM-ratio including the 90% CI was 1.04 (CI 0.94–1.14) for AUC to 24 h, 1.10 (CI 1.0–0.22) for C_{max} and 1.19 (CI 1.0–1.42) for C_{trough} [9]. The small increase in imatinib exposure due to Coca-Cola intake appeared not to be clinically relevant as demonstrated by the GM-ratios. More importantly, the Coca-Cola intervention did not elevate trough concentrations above the defined threshold of 1100 μg l^{-1}. Therefore, it is not expected that ingesting imatinib with Coca-Cola in patients with major gastrectomy improves treatment outcome.

In accordance with previous research, mean trough concentrations observed in our study (662 ± 227 μg l^{-1}) were lower than trough concentrations in patients without gastrectomy (1393 ± 659 μg l^{-1}) [3]. This confirms the earlier observation that patients who underwent major gastrectomy had a significantly decreased imatinib exposure. Furthermore, we showed that imatinib exposure did not increase to normal levels when exposed to a more acidic environment. Therefore, increase of gastrointestinal pH after gastrectomy cannot be accounted for by the majorly reduced exposure of imatinib. In our study, we used 150 ml of Coca-Cola, which is a lower volume than used in previous studies in patients without gastrectomy. Since our patients had no or a significantly reduced stomach volume left the reduced volume of Coca-Cola used should be sufficient to induce adequate pH reduction.

The decreased imatinib absorption might be explained by absence of active transporters that are mainly present in the stomach. In a study in mice by Furmanski *et al.* [10], it was suggested that **ABCC4 transporters** facilitates **dasatinib** absorption. These transporters are resected when patient undergo major gastrectomy. Hypothetically, imatinib, like dasatinib absorption is facilitated by these transporters as well. This hypothesis, however, needs to be investigated more thoroughly.

In conclusion, we confirmed that patients after gastrectomy have a marked reduction in exposure to imatinib which may translate into worse clinical outcome. We could not demonstrate that reintroducing an acid environment led to increased exposure to imatinib. We therefore suggest that the remarkably low exposure of imatinib after major gastrectomy may be due to removal of gastric transporters. Finally, we advise to measure imatinib trough concentrations in all patients with major gastrectomies and personalize imatinib dosing accordingly to prevent ineffective treatment.

Table 1

Pharmacokinetic parameters imatinib

	Water	Cola
AUC_{0-24h}, μg h l^{-1}, GM (GM CV%)	24 881 (34.0)	25 769 (30.5)
C_{max}, μg l^{-1}, GM (GM CV%)	2010.1 (20.8)	2224.5 (19.9)
C_{trough}, mg l^{-1}, GM (GM CV%)	662.5 (34.2)	789.4 (31.5)
T_{max}, h, median (range)	2.0 (1–5)	2.0 (1–4)
$T_{1/2}$, h, median (range)	8.9 (5.3–21.2)	11.3 (4.6–12.7)

AUC_{0-24h}, area under the concentration–time curve to 24 h; GM, geometric mean; CV%, percentage of coefficient of variation defined by (standard deviation/mean) × 100; C_{max}, maximum observed plasma concentration; C_{trough}, plasma concentration at t = 24 h; T_{max}, time to maximum plasma concentration; $T_{1/2}$, elimination half-life.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [11], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [12].

Competing Interest

The authors declare no conflicts of interest. F.J.E.L., H.G., C. M.W. and D.M.K. have no relationships to disclose. I.M.E.D. holds a consulting or advisory role with Eisai and Lily. A.C. receives research funding from ViiV and Janssen Research. D. M.B. receives research funding from BMS, Viiv and Janssen. W.T.A.v.d.G receives research funding from Novartis and GSK, and holds a consulting or advisory role with Bayer. N. P.v.E receives research funding from Novartis, Jansen Cilag, Astellas and Astra-Zenica, and holds a consulting or advisory role with Astellas.

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Contributors

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all the raw study data and had final responsibility for the decision to submit for publication.

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