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ORIGINAL RESEARCH ARTICLE

Safety of the Geneva Cocktail, a Cytochrome P450 and P-Glycoprotein Phenotyping Cocktail, in Healthy Volunteers from Three Different Geographic Origins

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Abstract

Introduction and Objective Cytochrome P450 enzymes are the major drug-metabolizing enzymes in humans and the importance of drug transport proteins, in particular P-glycoprotein, in the variability of drug response has also been highlighted. Activity of cytochrome P450 enzymes and P-glycoprotein can vary widely between individuals and genotyping and/or phenotyping can help assess their activity. Several phenotyping cocktails have been developed. The Geneva cocktail is composed of a specific probe for six different cytochrome P450 enzymes and one for P-glycoprotein and was used in the context of a research aiming at exploring genotypes and phenotypes in distinct human populations (NCT02789527). The aim of the present study is to solely report the safety results of the Geneva cocktail in the healthy volunteers of these populations.

Materials and Methods The Geneva cocktail is composed of caffeine, bupropion, flurbiprofen, omeprazole, dextromethorphan, midazolam, and fexofenadine. The volunteers fasted and avoided drinking caffeine-containing beverages or food and grapefruit juice overnight before receiving the cocktail orally. They provided blood spots for the probes' concentrations at 2, 3, and 6 h after ingestion and were asked about adverse events.

Results A total of 265 healthy adult volunteers were included from Ethiopia, Oman, and the Czech Republic. The mean plasma concentrations at the 2-h sampling time of each probe drug in the total sample were: 1663 ng/mL for caffeine, 8 ng/mL for bupropion, 789 ng/mL for flurbiprofen, 6 ng/mL for dextromethorphan, 2 ng/mL for midazolam, 35 ng/mL for fexofenadine, and 103 ng/mL for omeprazole. Four adverse events were observed representing an occurrence of 1.5%. All these events were categorized as mild to moderate, non-serious, and resolved spontaneously. A causal link with the cocktail cannot be excluded because of the temporal relationship but is at most evaluated as possible according to the World Health Organization-Uppsala Monitoring Centre causal assessment system.

Conclusions In this research, healthy volunteers from three different human populations were phenotyped with the Geneva cocktail. Four adverse events were observed, confirming the safety of this cocktail that is given at lower than clinically relevant doses and therefore results in concentrations lower than those reported to cause adverse events.

1 Introduction

Cytochrome P450 enzymes (CYPs) are the major drug-metabolizing enzymes in humans and account for approximately 75% of the metabolism of marketed drugs. Five CYPs are involved in 95% of the reactions of this enzymatic system, namely, in decreasing order of importance, CYP3A4/5, 2C9, 2C19, 2D6, and 1A2. Not only do drugs depend on CYPs for their elimination but also, for a small number of them, for their bioactivation (for analgesics such as tramadol, codeine, and oxycodone, anti-platelet drugs

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Key Points

Cytochrome P450 and drug transport proteins, in particular P-glycoprotein, are of major importance in the variability of drug response in humans.

Phenotyping allows a real-life evaluation of the different cytochrome P450 enzyme and P-glycoprotein activity and this can be performed with phenotyping cocktails.

This study shows the safety of the Geneva cocktail after phenotyping of 265 health volunteers from different human populations.

such as clopidogrel, and antimalarial drugs such as artesunate) [1–3]. Furthermore, the importance of drug transport proteins, in particular P-glycoprotein (P-gp), on the variability to drug response has also been highlighted [4].

Activity of CYPs and P-gp can vary widely from one individual to another. Genetic polymorphism can affect the activity of CYPs and P-gp and this can be appraised by genotyping specific single nucleotide polymorphisms that predict the activity. However, environmental factors such as toxins, food, or other drugs can also influence the CYP and P-gp activity. The real-time in vivo activity of these enzymes can be determined by phenotyping the individual patient. This allows the assessment of the true activity of the patient's CYPs and P-gp, taking into account his/her genotype and environmental background at the same time.

Several phenotyping cocktails have been developed throughout the years [5]. The principle behind this approach is to simultaneously administer a number of specific probes allowing the assessment of the activity of different CYPs and transporters at the same time. The Geneva cocktail is composed of a specific probe for six different CYPs and one for P-gp and has been validated through clinical studies that showed its usefulness with no interference of each drug with any of the others [6, 7].

This Geneva cocktail was used in the context of a study aimed at exploring the variability of the ADME (Administration, Distribution, Metabolism, Excretion) genotypes and phenotypes in distinct human populations (Mouterde et al., GWAS of phenotypes associated with the Geneva cocktail of drugs in four human populations, in preparation). For further information on this specific study, see clinicaltrials.gov (NCT02789527). The aim of this present article was to solely report the safety of the Geneva cocktail in the healthy volunteers of these populations.

2 Materials and Methods

The protocol of this study was approved by the Ethics Commission of the Canton of Geneva, Geneva (Switzerland), the Institutional Review Board of Charles University, Faculty of Sciences, Prague (Czech Republic), the National Research Ethics Review Committee and the Food, Medicine and Healthcare Administration and Control Authority of Ethiopia, Addis Ababa (Ethiopia), and the Medical Research and Ethics Committee of Sultan Qaboos University, Muscat (Sultanate of Oman).

The Geneva cocktail is composed of a combination of substances (caffeine, bupropion, flurbiprofen, dextromethorphan, midazolam, and fexofenadine) in a single capsule and an additional tablet of omeprazole. The best sampling time to determine the metabolic ratio of all CYP probes together was shown to be at 2 h [7].

Healthy unrelated individuals, aged between 18 and 50 years, recruited among students and staff in the academic institutions involved (Addis Ababa University, Sultan Qaboos University, and Charles University in Prague), with two parents and at least three grandparents born to the population and who provided written informed consent were included in this study. Exclusion criteria were pregnant or breastfeeding women, women who considered that being pregnant was a possibility, and volunteers allergic to one of the compounds included in the cocktail.

The volunteers were asked to fast and avoid drinking caffeine-containing beverages or food and grapefruit juice overnight. They entered the sampling site early in the morning where they received the cocktail orally (time 0) in a dosage shown in Table 1 (the same table also shows the enzymatic target), and waited 30 min in the presence of the monitoring clinician. They received a breakfast 30 min after taking the cocktail (but continued to avoid any caffeine-containing beverages or food and grapefruit juice for the whole trial duration) and left the sampling site. They returned to the sampling site three times during the day (at times +2, +3, and +6 h after cocktail administration), each time informing the clinician about adverse events (AE) [see monitoring below], and standardized volume blood spots, as described previously [6], were taken from the volunteers for phenotype analysis at +2, +3, and +6 h after having received the cocktail. Monitoring was thus performed through individual interviews of the volunteers by the clinician monitoring the trial each day. Volunteers could report any AE for the duration of the trial (between 10 and 22 days per site), and action undertaken for such an event could lead to in-depth medical consultation or hospitalization (each of which did not happen). For each volunteer, a clinician had to complete both an AE form and a serious AE (SAE) form associated with the CRF, that included: the starting date and time of the AE,

Table 1 Formula of the "Geneva cocktail" and comparison with usually prescribed therapeutic dosages

Probe	Enzymatic target	Dosage (mg)	Usual therapeutic dosage
Caffeine	CYP1A2	50	100 mg in a usual cup of coffee
Bupropion	CYP2B6	20	150–300 mg/day
Flurbiprofen	CYP2C9	10	150–200 mg/day
Omeprazole	CYP2C19	10	40–80 mg/day
Dextromethorphan	CYP2D6	10	75–100 mg/day
Midazolam	CYP3A4	1	7.5–15 mg/day
Fexofenadine	P-glycoprotein	25	120–180 mg/day

CYP cytochrome P450

a description of its nature, a statement of its severity (mild, moderate, severe, life threatening, or death), if it was a SAE (SAE was considered if it resulted in any of the following: death, life threatening, volunteer hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or medically important), in which case the SAE form also had to be completely informed (which did not happen).

Clinicians monitoring the study had to assess the causal link with the cocktail of the study (excluded, not excluded, adverse drug reaction [ADR], or not assessable), and if the causal link was not excluded, assess the degree of causality according to the World Health Organization-Uppsala Monitoring Centre causality assessment system (certain, probable, possible, unlikely, unclassifiable), where an AE is deemed "possible" when there is a reasonable time relationship to drug intake [8]. Finally, a clinician had to report on the issue of the AE (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown). If observed, SAEs were to be documented similarly.

3 Results

A total of 265 healthy adult volunteers were included from Ethiopia, Oman, and the Czech Republic. The 104 Ethiopian volunteers had four grandparents who were born in the country, and spoke one of 17 official Ethiopian languages as a mother tongue. Among the 61 Omani volunteers, all had their four grandparents born in the country or, for a few of them, in Omani communities in Tanzania and Zanzibar, and spoke Arabic as a mother tongue. The 100 Czech volunteers had at least three grandparents born in the country or in Slovakia, and spoke Czech or Slovak as a mother tongue.

Demographic characteristics of these populations are shown in Table 2.

Regarding allergic medical history, no volunteer reported a known allergy to the drugs included in the Geneva cocktail and a total of 27 volunteers reported allergies, mainly seasonal allergic rhinitis.

A total of four AEs were observed: three in the Ethiopian, one in the Omani, and none in the Czech/Slovakian volunteers representing an occurrence of AEs in 1.5% of volunteers (Table 3).

The three AEs observed among the Ethiopian volunteers were dizziness, lack of concentration and headache for the first event, numbness of both hands for the second, and nausea and abdominal heaviness for the third. The Omani volunteer experienced a localized erythematous macular non-pruritic rash on both thighs, which was associated neither with any hemodynamic instability nor with signs of upper airway obstruction.

All these events were categorised as mild to moderate, non-serious, and resolved spontaneously. None of the volunteers who experienced an AE required any specific medical care other than reassurance of the volunteer. A causal link with the cocktail could not be excluded because of the temporal relationship but was at most evaluated as possible according to the World Health Organization-Uppsala Monitoring Centre causality assessment system [8].

The mean plasma concentrations at the 2-h sampling time of each probe drug in the total sample were: 1663 ng/mL for caffeine, 8 ng/mL for bupropion, 789 ng/mL for flurbiprofen, 6 ng/mL for dextromethorphan, 2 ng/mL for midazolam, 35 ng/mL for fexofenadine, and 103 ng/mL for omeprazole (Table 4 and Fig. 1). For the maximum plasmatic concentrations at the 2-h sampling time, see Table 4. The four volunteers who experienced an AE were not at the extreme values of these concentrations (Table 5).

4 Discussion

The Geneva cocktail was successfully used to phenotype the healthy volunteers included in this trial that explored the variability of genotypes and phenotypes in three human populations. No SAE was observed in these 265 healthy volunteers and this confirmed the good tolerance of the Geneva cocktail already observed in other studies using this cocktail that included either healthy volunteers or patients. Indeed, a study aiming at validating the incorporation of flurbiprofen

Table 2 Characteristics of the healthy volunteers

Characteristics	Ethiopia	Sultanate of Oman	Czech Republic
Sample size (female/male)	104 (31/73)	61 (43/18)	100 (68/32)
Proportion female	0.30	0.70	0.68
Age, years[a]			
Mean (SD)	21.7 (2.19)	27.8 (7.18)	25.4 (4.80)
Median (min–max)	21.5 (18.6–33.0)	25.1 (19.1–52.9)	24.1 (16.4–44.9)
Mean female (SD)	21.3 (1.81)	25.3 (4.92)	24.8 (3.91)
Median female (min–max)	21.3 (18.6–27.8)	23.5 (19.1–43.9)	24.0 (20.0–42.1)
Mean male (SD)	21.8 (2.30)	33.5 (8.20)	26.5 (6.05)
Median male (min–max)	21.5 (18.7–33.0)	31.7 (22.6–52.9)	24.4 (16.4–44.9)
Self-declared height, cm			
Mean (SD)	170.3 (8.40)	160.9 (9.27)[b]	172.0 (9.39)
Median (min–max)	171.0 (150–195)	159.5 (126–189)[b]	170.5 (150–195)
Mean female (SD)	162.3 (6.83)	157.8 (8.77)[b]	167.5 (6.45)
Median female (min–max)	162.0 (150–178)	157.0 (126–189)[b]	169.0 (150–178)
Mean male (SD)	173.6 (6.48)	168.2 (5.57)	181.5 (7.36)
Median male (min–max)	173.0 (155–195)	168.5 (154–175)	183.0 (168–195)
Self-declared weight, kg			
Mean (SD)	60.8 (9.11)	60.5 (12.78)	66.8 (13.87)
Median (min–max)	60.0 (41–85)	60.0 (41–96)	64.5 (39–140)
Mean female (SD)	55.3 (8.05)	55.3 (8.92)	61.8 (10.34)
Median female (min–max)	54.0 (41–75)	53.0 (41–79)	60.0 (39–100)
Mean male (SD)	63.2 (8.43)	73.0 (11.73)	77.4 (14.31)
Median male (min–max)	63.0 (45–85)	70.0 (53–96)	75.5 (56–140)
Proportion of women taking contraceptive pill	0	0	0.426
Proportion smoke (female/male)	0.01 (0/0.01[c])	0	0.25 (0.25[d]/0.25[e])
Proportion alcohol (female/male)	0.26 (0.06[c]/0.34[f])	0	0.97 (0.97 [g]/0.97 [h])
Proportion khat (female/male)	0.01 (0/0.01)	0	0
Proportion AE (female/male)	0.03 (0.03/0.03)	0.02 (0.02/0)	0

AE adverse event, *max* maximum, *min* minimum, *SD* standard deviation

[a]In days divided by 365.25

[b]One missing value (one female volunteer did not know her height), statistics computed on 60 volunteers (42 women, 18 men)

[c]Occasionally

[d]Of which 0.09 on a daily basis, 0.16 occasionally

[e]Of which 0.19 on a daily basis, 0.06 occasionally

[f]Of which 0.32 only occasionally (on a monthly or yearly basis)

[g]Of which 0.90 only occasionally (on a monthly or yearly basis)

[h]Of which 0.90 only occasionally (on a monthly or yearly basis)

in the cocktail in 12 healthy male volunteers revealed no AEs [9] (data on file). Another study that evaluated the usefulness and effectiveness of a dry blood spot sampling carried out on ten healthy volunteers showed no AEs after administration of the cocktail alone [7]. A third study that evaluated the incorporation of fexofenadine and bupropion in the cocktail with the dried blood spot sampling method in 30 healthy volunteers who completed four sessions showed no AEs [6]. A study aiming at investigating the association between CYP and P-gp activities and plasma antidepressant concentration in patients also showed the cocktail to be safe [10]. Moreover, the Geneva cocktail has been routinely used in patients for more than 10 years with the occurrence of only two non-serious mild AEs (both transient dizziness and nausea). Part of this collective was described in a retrospective study that aimed to assess whether an AE or abnormal therapeutic drug monitoring was attributable to abnormal CYP activity in a psychiatric setting [11].

Adverse drug reactions can occur with most drugs. Dose-dependent ADRs, type A, are the most common category

Table 3 Characteristics of the observed adverse events

Adverse event	Population	Sex	Age, years	Delay of onset after ingestion	Severity	Seriousness	Causal link as assessed by investigator	Issue at end of follow-up (1 day)
Dizziness, lack of concentration and headache	Ethiopian	M	21	Before ingestion	Mild	No	Excluded	Recovering/resolving
Numbness of both hands	Ethiopian	F	20	45 min	Mild	No	Not excluded	Recovered/resolved
Nausea and abdominal heaviness	Ethiopian	M	20	15 min	Mild	No	Not excluded	Recovering/resolving
Erythematous macular non-pruritic rash on both thighs	Omani	F	22	3 h and 20 min	Mild	No	Not excluded	Recovered/resolved

F female, *M* male

Table 4 Plasma concentrations of the micrococktail components at 2 h

	ng/mL	Caffeine	Bupropion	Flurbiprofen	Omeprazole	Dextromethorphan	Midazolam	Fexofenadine
Ethiopia	Median	1202	7.7	777	73.2	3.8	1.5	12
	Mean	1272	8.2	816	92.2	6.2	1.6	24
	SD	463	3.2	264	77.3	5.9	0.8	15
	Min	421	1.1	353	0.4	0.4	0.2	7
	Max	3165	18.9	1520	394.0	29.2	5.9	89
Sultanate of Oman	Median	1589	4.0	906	45.2	2.7	1.3	49
	Mean	1656	4.2	886	81.1	5.0	1.7	57
	SD	612	1.8	255	9918.0	8.8	1.6	30
	Min	28	0.7	396	1.2	0.3	0.2	17
	Max	3966	10.7	1490	482.0	62.9	12.1	187
Czech Republic	Median	1921	7.8	695	48.9	3.5	1.0	29
	Mean	2073	8.8	701	128.3	5.5	1.2	32
	SD	1171	4.2	227	205.3	6.0	0.6	17
	Min	287	0.5	139	0.8	0.1	0.2	5
	Max	6726	24.8	1290	1330.0	26.4	3.7	114
Total	Median	1426	6.8	752	54.5	3.3	1.2	29
	Mean	1663	7.5	789	103.2	5.7	1.5	35
	SD	898	3.8	258	144.1	6.7	1.0	24
	Min	28	0.5	139	0.4	0.1	0.2	5
	Max	6726	24.8	1520	1330.0	62.9	12.1	187

max maximum, *min* minimum, *SD* standard deviation

of ADRs accounting for approximately 80% of ADRs. The type A ADRs are characterized by a dose-dependent increase in the pharmacological effect of the drug and are normally reversible when the dose is reduced or the drug is withdrawn. As mentioned in Table 1, the Geneva cocktail is typically a very low single-dose cocktail, with each probe at a dosage well under the usual therapeutic dose. Moreover, plasma concentrations in healthy volunteers having taken the Geneva cocktail showed pharmacokinetic parameters (area under the concentration–time curve and maximum concentration) that are not expected to have any therapeutic effect or toxic dose-dependent effect [7] and this was confirmed in the present study.

Looking one by one at the probes in the Geneva cocktail, the data available confirmed that the dosages given should not induce any AE. Use of caffeine, although not a therapeutic drug, can be associated with AEs such as tachycardia, nervousness, or insomnia. Recommendations exist as to the

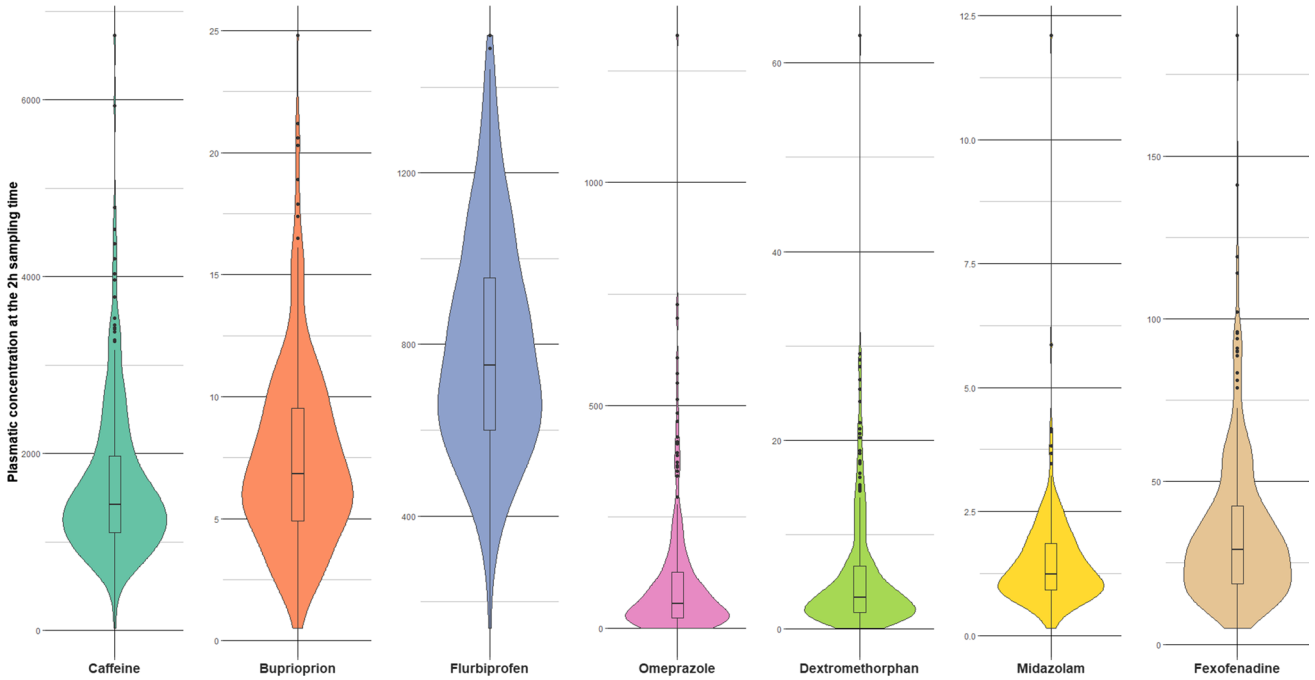

Fig. 1 Plasma concentration of each probe at the 2-h sampling time

Table 5 Plasma concentrations of each probe at the 2-h sampling time for the four volunteers that had an adverse event

Volunteer (sex, age, years)	Caffeine (ng/mL)	Bupropion (ng/mL)	Flurbiprofen (ng/mL)	Omeprazole (ng/mL)	Dextromethorphan (ng/mL)	Midazolam (ng/mL)	Fexofenadine (ng/mL)
Ethiopian (M, 21)	1234	11.7	846	176.0	18.9	1.3	17
Ethiopian (F, 20)	1202	8.1	1180	75.4	7.3	1.2	56
Ethiopian (M, 20)	1447	11.7	872	62.9	3.2	0.6	25
Omani (F, 22)	1469	5.8	695	1.2	2.4	1.6	52

F female, *M* male

maximum tolerated daily dose of caffeine and a recent systematic review has thoroughly evaluated this aspect. The authors concluded that the available evidence supports that the intake of a daily dose of 400 mg of caffeine, eight-fold the dose incorporated in the Geneva cocktail, in healthy adults was not associated with any AEs [12].

Regarding bupropion, a French review showed an increased risk of seizures could occur with an increasing dose of bupropion in patients taking 300–450 mg/day [13]. The US Food and Drug Administration labeling for bupropion recommends a maximum daily dose of 450 mg to reduce the risk of seizures [14]. Doses between 300 and 450 mg of bupropion correspond to plasma concentrations of 4-hydroxybupropion of 1000 ± 509 ng/mL and 1246 ± 492 ng/mL, respectively [15]. The maximum plasma concentration reached in our study was approximately 40–50 times lower than those that trigger potential seizures.

A pharmacokinetic study with a sustained-release form of 200 mg of flurbiprofen induced several adverse reactions in the participants included. However, mean plasma concentrations were around 10 µg/mL, seven-fold higher than the maximum concentration at the 2-h sampling time reached in our study [16].

A study conducted with dextromethorphan showed that slurred speech, light-headedness, and fatigue were commonly reported at doses higher than 10 mg/kg/day [17]. The mean weight of our volunteers was between 60.8 and 66.8 kg depending on the population (Table 2). These AEs would therefore occur around 600 mg, a dose 60-fold higher than the dose given to our volunteers.

A recent study evaluated the relationship between the pharmacokinetics and the pharmacodynamics of midazolam, using a sedation scale range from 1 (anxious or restless or both) to 6 (no response to the stimulus). This study showed that for a score of 3–5, the EC50 value was 68.7 ng/mL and

that for a score of 6, the EC50 value was of 117.1 ng/mL [18]. Another study that used both the saccadic eye movement and the electroencephalographic effect as pharmacodynamic measurements showed that the median effective concentration for the saccadic eye movement was 40 ± 7 ng/mL and that this value was 77 ± 15 ng/mL for the electroencephalographic effect [19]. The plasma concentrations of midazolam that show an effect in these two studies were 12- to 34-fold higher than after the intake of the Geneva cocktail.

For fexofenadine, in healthy volunteers taking as much as 690 mg twice a day during 28.5 days, no difference in sedation relative to placebo was reported and a single dose of fexofenadine hydrochloric acid up to 800 mg during 28.5 days resulted in a cardiac safety profile similar to that of placebo [20]. Administration of fexofenadine 240 mg/day did not worsen driving performance [20]. The maximum concentration for a dose of 180 mg of fexofenadine corresponds to 330–735 ng/mL, this being two- to four-fold higher than the maximum concentration reached at the 2-h sampling time in this study [21].

Omeprazole is not known for SAEs at therapeutic doses during short-term treatments even though a recent review assessed the AEs reported in studies of different designs (e.g., clinical trials, cohort studies) and occurring at normal doses [22]. The usual maximum concentration observed after a single dose of omeprazole shows a large inter-individual variability range, for example, from 300 to 640 ng/mL after a single 40-mg dose of encapsulated enteric-coated granules [23]. The maximum concentration reached at the 2-h sampling time for omeprazole in our study was 1330 ng/mL for a 10-mg dose, being even higher than predicted for a single dose but still in expected concentrations after a therapeutic dose without any ADR reported.

This study has a few limitations. As per most healthy volunteer studies, most of the information collected was self-reported by the volunteer, notably if she/he had fasted, smoked or taken any caffeine-containing beverage or food, and if she/he had taken any medication. The drugs included in the Geneva cocktail are normally available only on prescription, limiting the self-intake of these drugs. However, omeprazole is an over-the-counter drug in some countries, notably in the Czech Republic, and this could therefore explain the high plasma concentration that was observed in a single volunteer from that country. Additionally, for nearly every probe, outliers with higher plasma concentrations were observed, perhaps owing to a slow metabolizer genotype. However, none of these volunteers experienced an AE confirming the safety of the Geneva cocktail in all genotypic populations.

5 Conclusions

In the context of this research, 265 healthy volunteers from three different human populations were phenotyped with the Geneva cocktail. Four AEs were observed, all of them were mild to moderate, non-serious, and resolved spontaneously. Causality was at most deemed as "possible" according to the World Health Organization-Uppsala Monitoring Centre causality assessment system but only because of the temporal relationship. These results are in line with the low dosage and therefore lower drug concentrations than those reported to induce AEs. This research including more than 250 healthy volunteers confirmed the safety and good tolerance with low drug concentrations obtained of each substrate after ingestion of the Geneva cocktail.

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Declarations

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Conflicts of interest/competing interests Victoria Rollason, Médéric Mouterde, Youssef Daali, Martina Čížková, Edita Priehodová, Iva Kulichová, Helena Posová, Jitka Petanová, Anwar Mulugeta, Eyasu Makonnen, Abir Al-Habsi, Robin Davidson, Khalid K. Al-Balushi, Khalid Al-Thihli, Marie Cerná, Said Al-Yahyaee, Viktor Černý, Getnet Yimer, Estella S. Poloni, and Jules Desmeules have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval The protocol of this study was approved by the Ethics Commission of the Canton of Geneva, Geneva (Switzerland), the Faculty of Sciences, Institutional Review Board of Charles University, Prague (Czech Republic), the National Research Ethics Review Committee and the Food, Medicine and Healthcare Administration and Control Authority of Ethiopia, Addis Ababa (Ethiopia), and the Medical Research and Ethics Committee of Sultan Qaboos University, Muscat (Sultanate of Oman). All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to Participate Written informed consent from all subjects was obtained prior to performing any study procedures.

Consent for Publication Not applicable.

Availability of Data and Material The datasets analyzed during the current study are not publicly available because of an ongoing analysis of phenotype and genotype association, but are available from the corresponding authors on reasonable request.

Code Availability Not applicable.

Author Contributions VR, MM, YD, MČ, EP, IK, HP, JP, AM, EM, AA-H, RD, KKA-B, KA-T, MC, SA-Y, VČ, GY, ESP, and JD made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work. VR, MM, YD, MČ, EM, KKA-B, KA-T, MC, SA-Y, VČ, GY, ESP, and JD drafted the work or revised

it critically for important intellectual content. VR, MM, YD, MČ, EP, IK, HP, JP, AM, EM, AA-H, RD, KKA-B, KA-T, MC, SA-Y, VČ, GY, ESP, and JD approved the version to be published. VR, MM, YD, MČ, EP, IK, HP, JP, AM, EM, AA-H, RD, KKA-B, KA-T, MC, SA-Y, VČ, GY, ESP, and JD agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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