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ORIGINAL ARTICLE

Influence of cardiopulmonary bypass on cefuroxime plasma concentration and pharmacokinetics in patients undergoing coronary surgery

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Abstract

OBJECTIVES: The aims of this study were to evaluate the influence of cardiopulmonary bypass (CPB) on the plasma concentrations and pharmacokinetics of cefuroxime and to assess whether the cefuroxime dose regimen (a 1.5 g dose, followed by 750 mg every 6 h for 24 h) is adequate for cardiac surgery antibiotic prophylaxis.

METHODS: A prospective, controlled, observational study compared patients undergoing coronary surgery with CPB (CPB group, $n = 10$) or off-pump surgery (off-pump group, $n = 9$). After each cefuroxime dose, blood samples were sequentially collected and analysed using high-efficiency chromatography. For demographic data and pharmacokinetic parameters, the authors used Fisher's exact test for nominal variables and Student's *t*-test and the Mann–Whitney *U*-test for parametric and non-parametric variables, respectively. Plasma concentrations were compared using ANOVA, and the percentage of patients with a remaining plasma concentration of >16 mg/l within 6 h after each bolus was quantified in tabular form.

RESULTS: After each cefuroxime bolus was administered, both groups presented a significant decrease in plasma concentration over time ($P < 0.001$), without differences between the groups. The mean CPB time of 59.7 ± 21.1 min did not change cefuroxime plasma concentrations or pharmacokinetics. The mean clearance ± SD (ml/kg/min) and median elimination half-life (h) of the CPB group versus the off-pump group were 1.7 ± 0.7 versus 1.6 ± 0.6 ($P = 0.67$), respectively, and 2.2 versus 2.3 ($P = 0.49$), respectively. Up to 3 h following the first bolus of 1.5 g, but not after 6 h, all patients had plasma concentrations >16 mg/l (CPB group = 20% and off-pump group = 44%). However, after all 750 mg boluses were administered, concentrations <16 mg/dl were reached within 3 h.

CONCLUSIONS: CPB does not influence cefuroxime plasma concentrations. The dosing regimen is adequate for the intraoperative period, but in the immediate postoperative period, it requires further review.

Keywords: Cefuroxime • Pharmacokinetics • Cardiac surgery • Cardiopulmonary bypass • HPLC

INTRODUCTION

In cardiac surgery, postoperative surgical site infection and mediastinitis are serious complications, with incidences ranging from 1.9 to 15%, especially for lower limb infections [1, 2]. The institution of cardiopulmonary bypass (CPB) in cardiac surgery, which promotes extensive haemodilution and physiological changes, has had profound effects on the plasma concentration of drugs and, therefore, on their therapeutic effectiveness, which presents an additional risk because these effects can alter antibiotic pharmacokinetics [3, 4].

Postoperative infections can increase morbidity, mortality and their associated costs in both man-hours and dollars spent; therefore, it is important to evaluate existing standards for the prevention and management of nosocomial infection and find optimal strategies for best practice implementation [5, 6]. When trying to prevent nosocomial infection, prophylactic intravenous antibiotics should be routinely administered to patients undergoing cardiac surgery [7]. The cephalosporin class of antimicrobials is currently the first choice for prophylaxis of infection from coronary operations, and the glycopeptides are selected for allergic patients or for centres with a high prevalence of methicillin-resistant *Staphylococcus aureus* [8, 9]. There has been a trend towards superior efficacy with cefuroxime compared with the other cephalosporins, but this difference has not reached statistical significance [7, 10, 11]. However, the prophylactic cefuroxime dose regimen previously studied (1.5 g bolus followed by 1.5 g every 12 h for 24 h) is not ideal because the washout of cefuroxime is completed before the 12th hour [12]. In β-lactam antibiotic prophylaxis, the time at which plasma concentrations remain above the minimal inhibitory concentration (MIC) is more important than the maximum concentrations that

are reached [12, 13], and it is necessary to consider the local bacteriological profile when choosing a cephalosporin.

Cefuroxime has a low toxicity and cost and good tissue penetration. Moreover, it has a good spectrum of activity against bacteria that often cause postoperative infections [7]. However, for patients undergoing cardiac surgery with CPB, there is no consensus on the ideal dose of cefuroxime to prevent infection [12, 14–21].

The MIC of cefuroxime ranges from 1 to 4 mg/l for the principal bacteria that are involved in surgical site infections. Maintenance concentrations of four times greater than the MIC are recommended as an alternative to protect patients against infections that are caused by more resistant bacterial strains. The presence of the drug at this concentration allows for adequate prophylaxis during cardiac surgery [13, 15].

The main goals of this study were to evaluate whether CPB influences the plasma concentrations and pharmacokinetics of cefuroxime and whether the dosing regimen of a 1.5 g bolus at the induction of anaesthesia, followed by three boluses of 750 mg every 6 h (total dose = 3.75 g), is adequate to maintain plasma concentrations >16 mg/l for the first 24 h after the beginning of surgery.

METHODS

Patients and clinical procedure

After approval from the Hospital Ethics Committee (identifier: 123/06), registration on ClinicalTrials.gov (identifier: NCT 01228825) and obtaining written informed consent from each individual, 20 patients who were scheduled for coronary artery bypass graft surgery (CABG) were enrolled in the study. The exclusion criteria included age over 75 years old, a body mass index (BMI) of >35 kg/m^2, a left ventricle ejection fraction <35%, previous nephrectomy, serum creatinine ≥1.4 mg/dl, prothrombin activity lower than 80% and use of oral anticoagulants or allergies to cefuroxime.

The patients were allocated to two groups: CABG with CPB (CPB group, $n = 10$) and without CPB (off-pump group, $n = 9$). The choice of the groups was performed in an independent manner because the decision to utilize CPB depended on the position of the anastomosed arteries and the choice of the surgical team. Cefuroxime (Zinacef^{R,} Lot: 6043, GlaxoSmithKline Brazil, Ltd, Rio de Janeiro, Brazil) was administered intravenously in a bolus dose of 1.5 g at the induction of anaesthesia at least 30 min before the chest incision, followed by three boluses of 750 mg every 6 h for 24 h (total dose = 3.75 g).

CPB without concentrators or ultra-filtrating devices was performed using an extracorporeal circuit and a membrane oxygenator, primed with lactated Ringer's solution (Oxim II-34 Ultra membrane oxygenator Edwards Lifesciences, Irvine, CA, USA). After the initiation of CPB, the patients were cooled, and the core temperature was maintained at 28–34°C until the end of coronary grafting. After rewarming to 37°C, the patients were weaned from CPB. When necessary, vasoactive drugs were infused by the attending anaesthesiologist.

Analytical procedure

After the first bolus of cefuroxime, blood samples were drawn from a radial catheter every 15 min of the first hour and at 2, 3 and 6 h. Extra samples were also collected at periods considered as having high risk for bacterial contamination: at chest incision, at the beginning of CPB (or the beginning of anastomosis for the off-pump group), after protamine infusion and at chest suture. For the additional bolus, samples were collected after 30 min and at 1, 3 and 6 h.

The blood samples were centrifuged at 3000 rpm for 20 min, and plasma was frozen and stored at −20°C until analysis. The HPLC method was used to determine plasma cefuroxime concentrations and was validated before the protocol [12, 22].

The kinetic disposition of cefuroxime was evaluated by applying the open monocompartmental model, which is based on plasma drug concentrations multiplied by time ($C \times T$), after the last bolus of cefuroxime. PK Solutions software, version 2.0, by Monocompartment Pharmacokinetics Data Analysis (Ashland, OH, USA), was used to perform this modelling.

The groups were also compared according to the length of surgery, the number of grafts, temperature, blood pressure, haematocrit, total diuresis, crystalloid volume and the quantity of red blood cells received.

To calculate the sample size, it was assumed that CPB could change cefuroxime plasma concentrations by 20%, with a 10% standard deviation (SD); there was one control for each case. An unpaired Student's t-test was used with 80% power and an α error of 5%, which resulted in a minimum sample size of six cases and six controls, with 10 degrees of freedom.

All data were tested for normality using the Shapiro–Wilk test. For demographic data and pharmacokinetic parameters, the authors used Fisher's exact test for nominal variables and Student's t-test and the Mann–Whitney U-test for parametric and non-parametric variables, respectively. ANOVA was used to evaluate the haematocrit values and for the comparison of cefuroxime plasma concentrations after the logarithmic transformation of non-parametric variables to parametric variables. Time was a covariate when necessary (e.g. samples collected at periods of high risk for bacterial contamination).

For each group, the percentage of patients with remaining plasma concentrations >16 mg/l within 6 h after each bolus was illustrated in tabular form.

RESULTS

One patient in the off-pump group was excluded because the installation of CPB was necessary during the procedure. Table 1 shows the baseline characteristics of the patients and the preoperative and surgical data for both groups. The mean length of CPB was 59.7 ± 21.1 min, which took into account that this group was submitted to a minimum haematocrit and to lower temperatures than the off-pump group. The lowest values of mean arterial pressure in the CPB group were observed immediately after the beginning of bypass, but they normalized within a few seconds. The CPB group also had a greater number of grafts, with no difference in surgical time. No patient presented with surgical site infection until discharge from the hospital, and the patients had been in the intensive care unit for a maximum period of 3 days without complications.

After each dose of cefuroxime, both groups presented first an increase and then a significant decrease in drug plasma concentrations over time ($P < 0.001$), without a significant difference between groups (Fig. 1).

Table 1: Comparison of baseline characteristics and preoperative and intraoperative data of CPB and off-pump groups

Variable	CPB group ($n = 10$)		Off-pump group ($n = 9$)		P-value
	Mean (SD) or median	95% CI or Q1, Q3	Mean (SD) or median	95% CI or Q1, Q3	
Baseline characteristics					
Age (years)*	59.3 (9.1)	52.8–6.8	59.6 (6.9)	54.2–64.9	0.95
Weight (kg)*	68.4 (8.3)	62.5–74.3	76.6 (11.3)	69.9–85.2	0.09
Height (m)*	1.6 (0.1)	1.6–1.7	1.7 (0.1)	1.6–1.8	0.28
BMI (kg/m^2) *	25.6 (2.8)	23.6–27.6	27.3 (3.1)	24.8–29.7	0.24
Gender (number)**					
Male	6		5		0.99
Female	4		4		
Preoperative data					
Urea (mg/dl)*	29.8 (7.7)	24.3–35.3	34.3 (6.2)	29.6–39.1	0.18
Creatinine (mg/dl)*	0.9 (0.17)	0.8–1.1	1.0 (0.1)	0.9–1.1	0.10
Calculated creatinine clearance (ml/min)*	89.2 (26.8)	70.0–108.3	80.8 (17.3)	67.5–94.2	0.44
Glycaemia (mg/dl)*	105.6 (26.9)	86.4–124.8	115.1 (27.1)	94.3–135.9	0.45
Prothrombin activity (%)***	95	83.1, 100.0	81.8	77.0, 100.0	0.62
Intraoperative data					
Length of surgery (min)***	129.9	116, 142	130	127, 133	0.46
Haematocrit (%)****					<0.001
Initial	40.3 (3.8)	37.4–43.1	37.8 (3.9)	34.8–40.8	0.19
Minimum	23.4 (3.2)	21.0–25.9	28.7 (5.6)	24.4–33.0	0.03
Final	27.3 (2.5)	25.4–29.3	31.3 (6.0)	26.7–35.8	0.09
Red blood transfusion (units)***	1	1, 2	1	0, 2	1.0
Number of grafts***	4	3, 5	2	1, 3	0.002
Minimum blood pressure (mmHg)***	39.5	32.5–46.5	57.8	52.7–62.9	<0.001
Minimum temperature (°C)***	30	29, 31	35	34, 35	<0.001
Diuresis (ml)***	725	600, 900	700	600, 800	0.62
Volume replacement (ml)*	3542 (748.6)	2576–4327	3611 (546.5)	3191–4035	0.29

Parametric variables: mean (SD) and 95% CI used as summary measures, comparisons by Student's t-test (*) or ANOVA (****). Nominal variable: Fischer's exact test (**). Non-parametric variables: median and 1°, 3° inter-quartile, comparisons by the Mann–Whitney test (***), $P < 0.05$.

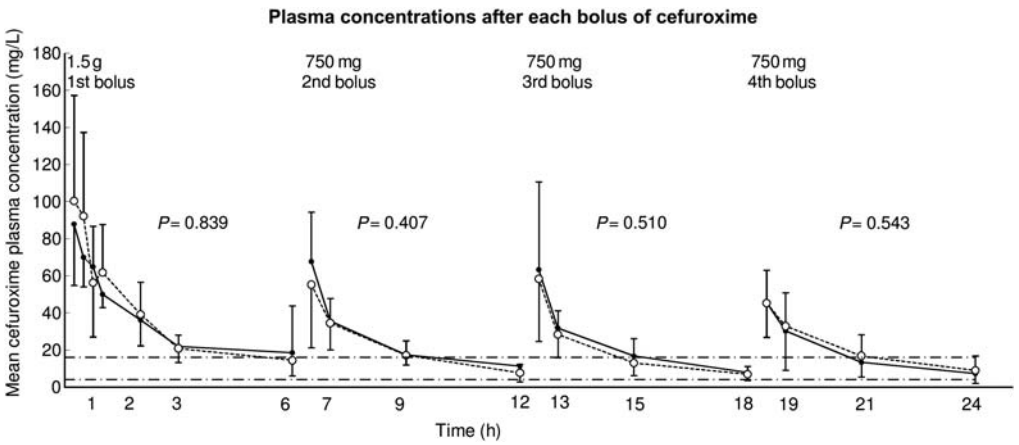

Figure 1: Plasma curve decay for the concentrations of cefuroxime in a 24-h period. The values are reported as the mean ± 1 SD. Filled circles: CPB group; open circles and dashed line: off-pump group. Comparisons by ANOVA, $P < 0.05$.

Table 2 shows the mean concentrations and the 95% CI of both groups during critical moments of antimicrobial prophylaxis, which were comparable between the groups ($P = 0.218$). The results of the pharmacokinetic data of cefuroxime after the last bolus of cefuroxime showed no differences between the groups (Table 3).

Evaluating the dosing regimen, Fig. 1 shows that the mean cefuroxime plasma concentrations were greater than four times the MIC until 3 h after each bolus, except for the third bolus in the off-pump group and the fourth bolus in the CPB group; for the first cefuroxime dose (1.5 g), all patients had plasma concentrations that were more than four times the MIC until 3 h after the bolus. However, immediately before the second dose, only 20% of the patients from the CPB group and 44% of the patients from the off-pump group presented concentrations greater than this desired value. After each bolus of 750 mg, both groups reached cefuroxime plasma concentrations that were less than four times the MIC before 3 h had passed (Table 4).

DISCUSSION

The results showed that CPB with an average time of 59.7 ± 21.1 min and a minimal mean temperature of 29.9 ± 1.3°C did not influence plasma concentrations or cefuroxime kinetics, and an extra bolus of cefuroxime after CPB was unnecessary. The dosing regimen used in our study guaranteed plasma concentrations that were more than four times the MIC during the intraoperative period, but during all other intervals between doses, the dosing regimen should be reviewed.

CPB can promote a drop in drug plasma concentrations due to haemodilution, changes in the volume of distribution, a redistribution of blood flow to peripheral tissue, vasodilatation, inflammatory activity, drug sequestration by the CPB circuit and lungs, and decreased protein binding, especially in procedures that last longer than 400 min. Therefore, some authors have justified using an extra bolus of antibiotic at the end of CPB to avoid inadequate serum antibiotic levels at the time of clot formation [3, 4, 20]. We found that cefuroxime plasma concentrations decreased during the first minutes of CPB, which was similar to the findings of these authors, but this decrease promptly recovered in the next few minutes (Table 2).

Our study and others showed that CPB did not exert influence on water-soluble cephalosporins, especially if the patients were submitted to moderate hypothermia or if the CPB lasted <120 min [12, 17, 18, 23]. The rate of elimination of the water-soluble cephalosporins is dependent on renal function, which is changed by CPB [4, 12, 17, 23]. Hypothermia, hypotension, changes from pulsatile to non-pulsatile flow and changes in protein binding can reduce the plasma clearance, prolong the biological half-life and elevate plasma concentrations, making the extra dose unnecessary [18]. However, plasma concentrations or pharmacokinetics of vancomycin, a water-soluble glycopeptide antibiotic 90% excreted unchanged by the kidney, are not influenced by the use of profound hypothermic circulatory arrest [24].

Despite the various conclusions of different dosing regimens, previous studies have found no concrete justification for the administration of an extra bolus based on the use of CPB [12, 17, 18, 20, 23], and the results of this study indicated that antibiotic prophylaxis should be performed at fixed intervals according to the pharmacokinetics of the antibiotic, rather than according to the use of CPB.

Cefuroxime, as reported before [12, 17], showed linear pharmacokinetics; in addition, we did not find differences either in pharmacokinetic parameters between groups or in cefuroxime plasma concentrations after each antibiotic bolus, and during critical moments for antibiotic prophylaxis, we observed that more patients in the off-pump group had cefuroxime plasma concentrations >16 mg/dl at 6 h after the first dose (Table 4). The sample size was calculated considering cefuroxime plasma concentrations, and it could have been underpowered to detect differences in pharmacokinetic parameters. The kinetic disposition of cefuroxime was evaluated only after the last dose of cefuroxime, when the effect of CPB could have been less evident, but differences in the pharmacokinetic parameters were not found when other authors compared cefuroxime pharmacokinetic parameters after each bolus, only in patients who were not submitted to CPB [17].

There are many schemes for antibiotic prophylaxis in patients undergoing cardiac surgery with CPB, with variations in the intervals between doses and/or in the duration of prophylaxis [12, 14–19, 21]. However, plasma concentrations of at least four times the MIC must be reached and maintained throughout the intraoperative period, which encompasses the greatest risk for bacterial contamination, for effective antibiotic prophylaxis [13].

As demonstrated by Nascimento *et al.* [12], a dosing regimen of 1.5 g every 12 h for 24 h is ineffective for guaranteeing plasma concentrations greater than four times the MIC.

In the present study (cefuroxime dose regimen of a 1.5 g bolus and then 750 mg every 6 h for 24 h), all patients had plasma concentrations greater than four times the MIC until 3 h after the first bolus of 1.5 g. Considering that the length of surgery was <3 h in both groups and that, during critical periods

Table 2: Cefuroxime plasma concentrations (mg/l) during critical periods for antibiotic prophylaxis

Blood samples	CPB group		Off-pump group	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Chest incision	63.1 (19.9)	45.4–80.7	76.6 (57.7)	19.3–133.9
Beginning CPB/ anastomosis	27.4 (7.5)	20.8–34.0	57.7 (34.0)	23.9–91.5
After protamine	30.0 (6.5)	24.3–35.8	38.5 (24.7)	13.9–63.0
Chest suture	25.7 (7.0)	19.5–32.0	25.8 (19.3)	6.7–45.0

Mean (SD) and 95% CI used as summary measures.

Table 3: Pharmacokinetic parameters and statistical analysis between CPB and off-pump groups

Variable	CPB group		Off-pump group		*P*-value
	Mean (SD) or median	95% CI or Q1, Q3	Mean (SD) or median	95% CI or Q1, Q3	
Minimum concentration (mg/l)*	6.1	4, 7.7	5.7	4.6, 9.1	0.77
AUC 18–24 h (mg h/l)*	118.7	89.4, 141.4	120.7	91.3, 128.9	0.97
Elimination half-life (h)*	2.2	1.9, 2.5	2.3	2.1, 3.4	0.49
Elimination constant (h^{-1})**	0.3 (0.1)	0.3–0.4	0.3 (0.1)	0.2–0.4	0.35
Volume of distribution (l/kg)**	0.3 (0.1)	0.2–0.4	0.4 (0.2)	0.2–0.5	0.70
Clearance (ml/kg/min)**	1.7 (0.7)	1.2–2.2	1.6 (0.6)	1.1–2.0	0.67

Non-parametric variables: median and 1°, 3° inter-quartile, comparisons by the Mann–Whitney test (*). Parametric variables: mean and 95% CI used as summary measures, comparisons by Student's *t*-test (**), $P < 0.05$.

Table 4: Percentage of patients with cefuroxime plasma concentrations >16 mg/l

Cefuroxime bolus	Percentage of patients (%) with cefuroxime plasma concentrations ≥16 mg/l				
	0 h	0.5 h	1 h	3 h	6 h
1st bolus: 1.5 g					
CPB group	100	100	100	90	20
Off-pump group	100	100	100	66	44
2nd bolus: 750 mg					
CPB group	100	100	100	60	30
Off-pump group	100	100	100	44	11
3rd bolus: 750 mg					
CPB group	100	100	90	40	10
Off-pump group	100	100	77	33	11
4th bolus: 750 mg					
CPB group	100	80	60	30	0
Off-pump group	100	100	88	33	22

First bolus: 0–6 h (1.5 g cefuroxime); second bolus: 6–12 h (750 mg cefuroxime); third bolus: 12–18 h (750 mg cefuroxime); fourth bolus: 18–24 h (750 mg cefuroxime).

of antibiotic prophylaxis, all mean plasma concentration were also >16 mg/dl, there was no need for an extra dose after CPB, and this antibiotic regimen was adequate for the intraoperative period. However, the doses of 750 mg of cefuroxime used for the second, third and fourth boluses were not sufficient to guarantee the desirable plasma concentrations until the sixth hour. Considering the real possibility of complicated and long-length cases of cardiac surgery, using or not using CPB, the second dose might not be sufficient to maintain plasma concentrations >16 mg/dl until chest closure. Although recent trends have favoured only intraoperative coverage, the data are not yet conclusive for patients undergoing cardiac surgery, so single-dose prophylaxis could be used in circumstances the surgeon considers optimal for patient care (Class IIa, Level B) [14], but it is also necessary to consider the surgical time.

Regarding the length of the dosing regimen, there is evidence indicating that antibiotic prophylaxis of 48 h is as effective as a 24-h regimen (Class IIa, Level B) [14], but an inadequate drug type and/or dosage regimen can create antibiotic-resistant microorganisms [7]. The 24-h dosing regimen that was used in this study showed that the mean cefuroxime plasma concentration was greater than four times the MIC until 3 h after each bolus, except for the third bolus in the off-pump group and the fourth bolus in the CPB group, but they were all greater than the MIC, without differences between the groups (Fig. 1). Moreover, 6 h after each bolus, the number of patients with cefuroxime plasma concentrations greater than four times the MIC was very low, indicating the need to shorten the dose interval (Table 4).

The observed mean cefuroxime half-lives were ∼2.2 and 2.3 h for the CPB and off-pump groups, respectively (Table 3). A shortening of the interval between doses from 6 to 4 h, instead of the use of larger doses at longer intervals, could be a more effective dosing regimen for patients undergoing cardiac surgery with CPB lasting <2 h.

It is important to consider that when we propose changes to the interval between doses, we are elevating the total dose of cefuroxime; however, this dose is the same as that recommended by American Heart Association's and American College of Cardiology's AHA/ACC 2004 guideline [25], in an inadequate dose regimen demonstrated by Nascimento *et al*. [12], and the economic impact of prolonged hospitalization, morbidity and mortality related to deep sternal wound infection is much more important than the small variation in cost due to the shortening of the interval [6]. However, it is necessary to compare in a randomized study this new, proposed dose regimen with that tested in this study, with patients submitted to CPB only, calculating the sample size also to find the incidence of adverse effects with the increased total dose.

Cefuroxime is a water-soluble antibiotic, with good tissue penetration and rapid distribution from plasma to tissue and without accumulation in fat tissues [18]. Its elimination is dependent on renal function with a minimal dose-limiting toxicity, so there are no recommendations to administer cefuroxime by weight in adults [13, 14, 20]. It is necessary to emphasize that the exclusion criteria excluded patients with a BMI of >35 kg/m^2, serum creatinine ≥1.4 mg/dl or previous nephrectomy.

Although this study focused on cefuroxime plasma concentrations, it is necessary to report that no patient presented with a surgical site infection. This finding can be justified by our sample size and our allocation criteria, which excluded patients with high-risk factors for infections (e.g. being elderly, obesity, diabetes mellitus, renal insufficiency).

In conclusion, CPB did not influence cefuroxime plasma concentrations, and a 1.5 g bolus of cefuroxime at anaesthesia induction guaranteed plasma concentrations greater than four times the MIC during the intraoperative period, which shows that the extra bolus after CPB is unnecessary. However, the proposed dose regimen was not satisfactory for the postoperative period and might not be sufficient for prolonged surgeries. The dosing regimen for prophylaxis in patients undergoing coronary surgery should be re-evaluated, using an interval between doses of <6 h.

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