



Evolution of haemostatic parameters and risk of bleeding during treatment with cefazolin

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Received: 26 July 2018 / Accepted: 24 October 2018 / Published online: 10 November 2018
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Abstract

In 2017, five cases of severe haemorrhages during treatment with cefazolin occurred in France. The aim of this study was to assess the risk of haemorrhage related to treatment with cefazolin by evaluating haemostatic parameters and bleeding events. A retrospective study was conducted from January 2016 to December 2017. Two populations were analysed: (i) overall population, which included all patients treated with cefazolin during this period and (ii) coagulation study population, which included all patients treated with cefazolin with available coagulation parameters (activated partial thromboplastin time (aPTT) and international normalised ratio (INR) at baseline and at the end of treatment or EoT). Values of either aPTT or INR at baseline and at EoT were compared. Cases of severe haemorrhages were reported and correlated with values of aPTT and INR. Overall, 132 patients received cefazolin and 59/132 (45%) were included in the coagulation study group. A significant increase of median aPTT was observed from baseline to EoT (39.5 and 44.3 sec; $p = 0.004$, respectively). Overall, severe haemorrhage occurred in 7/132 (5%) patients. Coagulation parameters were available in three of them, and no correlation was observed between bleeding events and aPTT increase. This study showed that bleeding is probably more frequent than ever reported before during cefazolin treatment. The significant increase of aPTT observed during cefazolin treatment was not correlated with risk of haemorrhage. Further studies are needed to explore the possible physio-pathological pathways behind the modification of haemostatic parameters and risk of haemorrhage.

Keywords Cefazolin · Haemorrhage · Activated partial thromboplastin time · Coagulation · Bleeding · International normalised ratio

Introduction

Cefazolin is a first-generation cephalosporin largely used worldwide, especially in surgical prophylaxis [1] but also in treatment of methicillin-sensitive bacterial sepsis because of its effectiveness, low cost and good safety profile [2–4]. Hypoprothrombinemia is a rare but severe side effect of cefazolin which can lead to severe and, sometimes, fatal bleeding [5–13]. This side effect is also

common during treatment with other cephalosporins, such as cefoperazone, and it is due to presence in the molecular structure of a heterocyclic thiol, 2-methyl-1, 3, 4-thiadiazole-5-thiol (MTD), which can inhibit the γ -carboxylation of glutamic acid, a vitamin K-dependent reaction, required for the formation of active clotting factors [14]. Because of the risk of hypoprothrombinemia, the package insert of cefazolin already contains a warning about risk of coagulation disorders and suggests a posology's adaptation according to dosage of international normalised ratio (INR) in patients with coagulopathy, namely vitamin K deficiency [15].

In 2017, five cases of severe haemorrhages associated with hypoprothrombinaemia during high-dose cefazolin treatment were described in France [5, 6]. Consequently, the committee for drug vigilance of the *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (French National Agency for Drug Safety) recommended a strict monitoring of INR and a quick supplementation in vitamin K in case of severe hypoprothrombinaemia during treatment with cefazolin [16]. However, to our knowledge, neither clinical trials nor cohort studies have investigated the risk

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of coagulopathy and haemorrhage associated with cefazolin treatment.

The aim of this study was to evaluate the risk of haemorrhage during cefazolin treatment by assessing the evolution of haemostatic parameters and the occurrence of severe haemorrhages.

Materials and methods

A retrospective cohort study was conducted at a Clinical Hospital of 350 beds located in the *Ile-de-France* region in France. All patients treated with cefazolin from January 1, 2016 to December 31, 2017 were included, except patients who met the following exclusion criteria: (i) duration of treatment with cefazolin ≤ 24 h and (ii) paediatric age.

Two populations were analysed: (i) overall population, which included patients with or without INR and thromboplastin time (aPTT) dosage at baseline and/or at end of treatment (EoT), (ii) coagulation study population, which included patients already contained in overall population with available dosage of aPTT and INR at baseline and at EoT.

Data about cefazolin treatments, patients' characteristics and laboratory analyses were gathered from local software used in daily clinical practice (Sillage v15.5.1.22 and CGM Lab channel 1.20.33686). Laboratory tests included haematological analysis, coagulation parameters, serum chemistry tests, measures of renal function, including estimated glomerular filtration rate (eGFR), and serum albumin measurement, either only at baseline or at baseline and EoT. INR was preferred to prothrombin time (PT) because it is more frequently used in clinical practice. Modification of diet in renal disease (MDRD) formula was used to calculate eGFR.

To establish whether a patient received cefazolin overtreatment or not, cefazolin dose pro kilo (expressed as mg/kg/day) was calculated and compared to the theoretical optimal dose of cefazolin according to the eGFR. Theoretical optimal dose of cefazolin was 80–100 mg/kg/day for patients with eGFR \geq

60 ml/min/1.73m²; 50–60 mg/kg/day for patients with eGFR from 25 to 59 ml/min/1.73m²; 25–30 mg/kg/day for patients with eGFR < 25 ml/min/1.73m²; or in dialysis [17]. Haemorrhage was defined as any bleeding event reported in medical records. Severe haemorrhage was defined as any bleeding event which led to a clinical instability requiring transfer to intensive care unit (ICU). They were included only when severe bleeding events occurred at least 24 h after the start of treatment with cefazolin and not more than 24 h after the end of treatment with cefazolin. Cefazolin's blood concentration was not systematically dosed but it was obtained only when physician suspected that haemorrhage was related to cefazolin's overdose.

For statistical analysis, Mann-Whitney/Wilcoxon two-sample test was used for quantitative variables while Fisher's exact test was used for qualitative variables. Quantitative variables were presented in the text as median value.

Differences in main features of two populations (overall and coagulation study) were tested. In overall population, the association of clinical and laboratory features with bleeding occurrence was assessed by the mentioned tests above. In coagulation study population, changes of coagulation parameters (aPTT, INR and platelets counts) from baseline to EoT were analysed through the same tests. Results were stratified according to cefazolin overdose, cefazolin treatment duration and use anticoagulant treatment. Association of clinical and laboratory features with significant increase of aPTT (Δ aPTT > 25 sec) in coagulation study population was investigated.

Results

A total of 182 patients received cefazolin during the study period but only 132/182 (73%) received cefazolin for more than 24 h (overall population). Among these patients, 59/132 (45%) had an available coagulation parameters at beginning and EoT and were included in the coagulation study (Fig. 1).

Fig. 1 Study flowchart

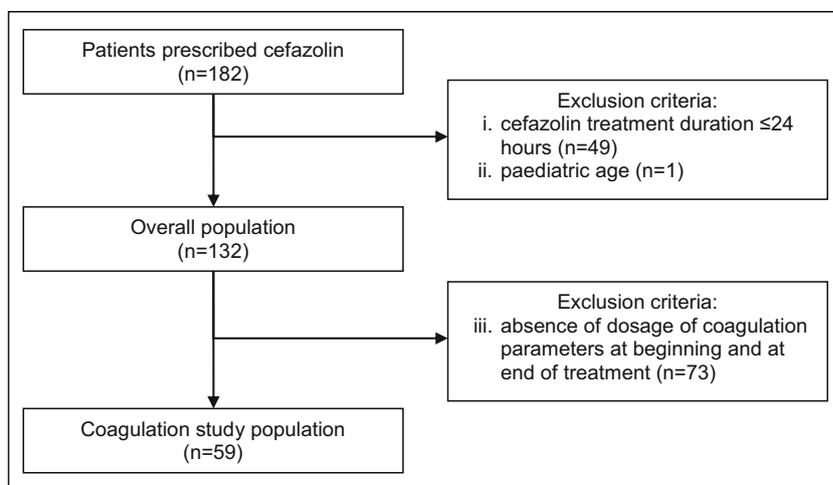


Table 1 Patients' characteristics

Parameter	Overall (<i>n</i> = 132)	Coagulation study (<i>n</i> = 59)
Age, years (range)	70 (18–102)	72 (36–93)
Gender		
Male (%)	78 (59)	35 (59)
Female (%)	54 (41)	24 (41)
BMI		
Normal weight (%)	45 (34)	19 (32)
Overweight (%)	41 (31)	22 (37)
Obesity class 1 (%)	26 (20)	8 (14)
Obesity class 2 (%)	4 (3)	4 (7)
Obesity class 3 (%)	14 (11)	5 (8)
Underweight (%)	2 (1)	1 (2)
Hospital unit		
Infectious diseases (%)	102 (77)	47 (80)
General medicine (%)	15 (12)	7 (12)
Orthopaedic surgery (%)	7 (5)	2 (3)
Emergency (%)	1 (1)	0 (0)
Other medical units (%)	7 (5)	3 (5)
Other surgical units (%)	0 (0)	0 (0)
Diagnosis		
Cutaneous infection (%)	44 (33)	15 (25)
Osteoarthritis (%)	14 (11)	9 (15)
Sepsis (%)	35 (27)	18 (31)
Osteomyelitis (%)	12 (9)	4 (7)
Necrosis (%)	16 (12)	7 (12)
Others (%)	11 (8)	6 (10)
Coagulopathy		
Liver cirrhosis (%)	12 (9)	5 (8)
Other coagulopathies (%)	0 (0)	0 (0)
None (%)	120 (91)	54 (92)
Anticoagulants		
Anti-platelets (%)	26 (19)	11 (19)
LMWH (%)	75 (57)	34 (63)
Anti-vitamin K (%)	5 (4)	5 (3)
Other anticoagulants (%)	5 (4)	3 (5)
None (%)	21 (16)	6 (10)
Posology, g/day (range)	8 (1–12)	8 (1–10)
Treatment duration, days (range)	6 (2–28)	6 (2–21)
aPTT, sec (range)	40.7 (30.6–88.9)	39.5 (30.6–88.9)
INR (range)	1.22 (0.9–4.33)	1.22 (0.9–3.96)
eGFR, ml/min/1.73m ² , (range)	70 (9–189)	70 (13–159)
Haemoglobin, g/dl (range)	10.8 (7.0–15.5)	10.8 (7.6–15.3)
Platelets, <i>n</i> × 10 ³ /μl (range)	247.5 (52–725)	272 (52–573)
Leukocytes, cel × 10 ³ /μl (range)	11.9 (3.3–29.1)	11.9 (4.8–29.1)
Neutrophils, cel × 10 ³ /μl (range)	7.0 (1.7–26.7)	9.7 (2.5–26.7)
CRP, cel × 10 ³ /μl (range)	89 (2.9–379)	116 (2.9–295)
AST, IU/l (range)	23 (7–155)	25 (9–155)
ALT, IU/l (range)	22 (6–142)	21 (6–101)
Bilirubin, mg/dl (range)	8 (2–132)	8 (2–132)

Table 1 (continued)

Parameter	Overall (<i>n</i> = 132)	Coagulation study (<i>n</i> = 59)
Albumin, g/l (range)	30 (17–42)	28 (17–39)
Sodium, mmol/l (range)	138 (133–161)	137 (3.9–161)
Potassium, mmol/l (range)	3.9 (2.8–5.5)	3.9 (2.9–5.5)

ALT, alanine aminotransferase; *aPTT*, activated partial thromboplastin time; *AST*, aspartate aminotransferase; *BMI*, body mass index; *CRP*, C-reactive protein; *eGFR*, estimated glomerular filtration rate; *LMWH*, low molecular weight heparins; *INR*, international normalised ratio

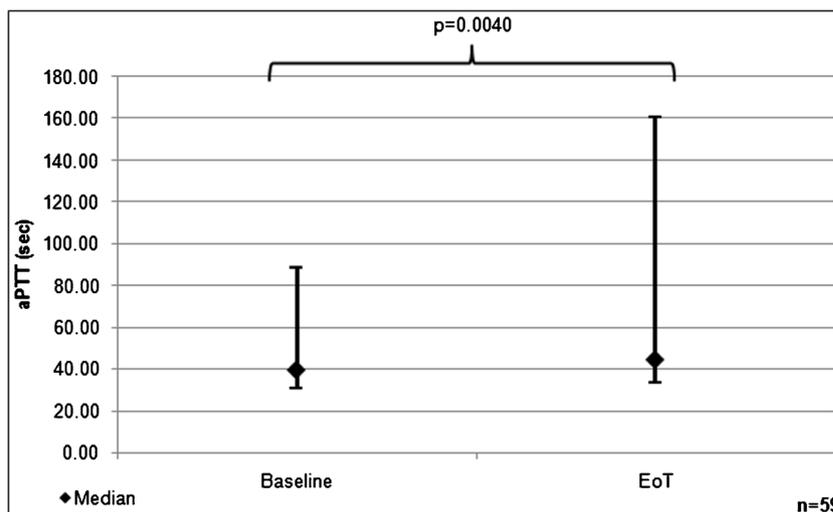
In the overall population, median duration of antibiotic treatment was 6 days and median posology was 94 mg/kg/day. Among coagulation study population, 13/59 (22%) patients received low molecular weight heparins (LMWH) at high-dose regimen and 2/59 (3%) received an anti-vitamin K. Main characteristics of overall population and coagulation study population are summarised in Table 1.

No difference was observed between overall and coagulation study populations in term of use of anticoagulation treatment ($p = 0.36$), median age ($p = 0.78$), aPTT ($p = 0.94$), INR ($p = 0.91$) and platelets count ($p = 0.25$) at baseline. Similarly, no difference was found between the two populations in frequency of haemorrhage during treatment with cefazolin ($p = 0.95$).

In coagulation study population, median aPTT was significantly higher at EoT than at baseline (39.5 vs 44.3 sec; $p = 0.004$; Fig. 2) but no significant differences were found in median INR ($p = 0.50$) and platelet counts ($p = 0.08$) at the same time points. No differences were found in median Δ aPTT, when patients were stratified according to the use of anticoagulant treatment ($p = 0.75$) and in median aPTT, when patients were stratified according to treatment duration (> 7 days or > 10 days) and cefazolin overtreatment ($p = 0.23$; $p = 0.74$; $p = 0.59$ respectively). A significant increase of aPTT (> 25 sec) was associated only with advanced age ($p = 0.002$) and impaired renal function ($p = 0.03$) (Table 2).

In the overall population, bleeding occurred in 7/132 (5%) patients. Among them, 3/7 (43%) experienced cutaneous bleeding and 4/7 (57%) experienced digestive bleeding (2/4, 50% were cirrhotic). Severity of bleeding required patient's transfer to ICU in 3/7 (43%) cases. Overall, 5/7 (71%) cases required transfusion. One cirrhotic patient died of rupture of gastro-oesophageal varices. In 4/7 (57%) cases, bleeding occurred within the first 8 days of cefazolin treatment. Dosage of cefazolin haematic concentration at bleeding's occurrence was available only in one case. In this patient, cefazolin's residual blood concentration was higher than normal range (66 ml/l, range 20–30 ml/l). Only haemoglobin and platelets were associated with bleeding events in overall population (Table 3) ($p = 0.005$ and $p = 0.02$, respectively). In coagulation study, bleeding events (3/59; 5%) were not correlated with aPTT increase ($p = 0.11$).

Fig. 2 Evolution of activated partial thromboplastin time during treatment with cefazolin



Discussion

For the first time, we evaluated the consequences of cefazolin treatment on coagulation parameters in a cohort study. Indeed, until now, case reports and case series described bleeding and PT prolongation but did not calculate the risk of coagulation disorders during cefazolin treatment [5–12]. Accounting for almost 60 patients, this is the largest study which explored the problem of cefazolin-related coagulopathy, giving an estimation of bleeding risk in a real-life cohort.

The most important result of our study was the significant increase of aPTT observed during cefazolin treatment, which no other author had ever reported before. In animal studies, cefazolin showed a good coagulation safety profile without effects on

platelet aggregation, bleeding time, PT and aPTT [18]. In humans, aPTT increase is not usual during treatment with other cephalosporins, even though it has been occasionally reported [19–21]. We conducted an exploratory analysis which showed that there was no clinical impact of aPTT increase because it was not associated with the risk of bleeding or with cefazolin overdose. However, our results contrast with the scarce data available in literature and need to be verified in a larger study.

In our study, no differences in median Δ aPTT was found between patients with or without anticoagulation treatment, suggesting that increase of aPTT was not influenced by the use of anticoagulants, in particular, LMWH which have been taken by 34/59 (63%) patients. Indeed, we did not measure systemically cefazolin blood concentrations but no difference

Table 2 Factors associated with aPTT increase > 25 sec ($n = 59$)

Parameter or outcome	aPTT increase \leq 25 sec ($n = 41$)	aPTT increase > 25 sec ($n = 18$)	<i>p</i> value
Age, years (range)	65 (55–77)	82 (75–92)	0.002
Male gender (%)	25 (61)	10 (55)	0.4
BMI (range)	26.8 (23–30)	26.7 (24–30)	0.9
Coagulopathy (%)	3 (7)	2 (11)	0.4
Anticoagulant treatment (%)	28 (68)	14 (77)	0.3
Cefazolin overdose (%)	24 (58)	10 (55)	1
Antibiotic treatment duration > 8 days (%)	10 (24)	5 (28)	0.7
Cefazolin posology, g/days (range)	8 (6–8)	6 (6–8)	0.1
Bleeding (%)	3 (7)	0 (0)	0.3
eGFR < 60 ml/min/1.73m ² (range)	11 (27)	10 (55)	0.03
Haemoglobin, g/dl (range)	10.6 (9.3–12.9)	11.7 (9.6–12.4)	0.7
Platelets, $n \times 10^3/\mu\text{l}$ (range)	330 (250–386)	263 (198–372)	0.3
Leukocytes, $n \times 10^3/\mu\text{l}$ (range)	11.9 (7.8–14.3)	11.8 (8.1–14.2)	0.7
CRP, mg/dl (range)	113 (69–186)	136 (56–162)	0.8
Albumin, g/l (range)	28 (22–32)	31 (27–36)	0.2

aPTT, activated partial thromboplastin time; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate

Table 3 Factors associated with bleeding ($n = 132$)

Parameter or outcome	No bleeding ($n = 125$)	Yes bleeding ($n = 7$)	p value
Age, years (range)	69.8 (18–102)	71.8 (36–93)	0.8
Male gender (%)	75 (60)	3 (43)	0.3
BMI (range)	27 (23–31)	25 (24–28)	0.7
Coagulopathy (%)	10 (8)	2 (29)	0.1
Anticoagulant treatment (%)	106 (84)	5 (71)	0.3
Antibiotic treatment duration >8 days (%)	28 (22)	4 (57)	0.1
Cefazolin posology, g/days (range)	8 (6–8)	6 (6–8)	0.2
eGFR < 60 ml/min/1.73 m ² (range)	71 (49–104)	53 (31–116)	0.4
Haemoglobin, g/dl (range)	9.4 (9.4–10.9)	11.9 (10.1–13.3)	0.005
Platelets, $n \times 10^3/\mu\text{l}$ (range)	383 (295–544)	241 (179–725)	0.02
Leukocytes, $n \times 10^3/\mu\text{l}$ (range)	10.8 (9.1–14.2)	10.7 (7.1–14.2)	0.4
CRP, mg/dl (range)	184 (13–205)	84 (35–162)	0.4
Albumin, g/l (range)	25 (23–27)	31 (25–35)	0.1
aPTT at start of treatment, sec (range)*	40.0 (30.6–88.9)	45.1 (39.6–48.6)	0.4
aPTT at end of treatment, sec (range)**	43.8 (16.1–85.8)	39.0 (37.1–48.1)	0.4

*Available for 83/125 (66%) patients without bleeding and 6/7 (86%) patients with bleeding

**Available for 56/125 (45%) patients without bleeding and 3/7 (43%) patients with bleeding

aPTT, activated partial thromboplastin time; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate

was found according to cefazolin dose. This fact make a cefazolin concentration-dependent increase of aPTT unlikely, contrasting with data reported for other antibiotics, such as telavancin [22].

The only factors associated with a significant increase of aPTT (> 25 s) during treatment with cefazolin were advanced age and impaired renal function. These results suggests that in elderly patients and patients affected by chronic kidney disease, a strict surveillance of aPTT should be pursued, especially in case of a contemporary administration of cefazolin for a long scheduled duration (e.g. endocarditis) and other drugs with a prolongation effect on aPTT.

Differently from reported cases, we did not find INR increase. This fact is surprising because until now, all data pointed to an interference on vitamin K reactions by the MTD included in cefazolin molecule, documented by severe hypoprothrombinemia [5–12]. On the other hand, our data show that increase of INR is not usual during cefazolin treatment, and mechanisms of cefazolin interference on coagulation cascade are far from being explained.

In this study, a clinically significant bleeding occurred in 7/132 (5%) patients. To the best of our knowledge, this represents the first estimate of the absolute risk of bleeding during cefazolin treatment. Moreover, other studies, which were designed to explore frequency of adverse drug events related to cefazolin use did not report severe bleeding events, meaning that this specific side effect has been until now scarcely investigated and, probably, underestimated [23–33].

It is possible that other factors influence the total risk of bleeding during cefazolin treatment. We found an association

of bleeding events with low platelet level and, surprisingly, with a higher level of haemoglobin. More interestingly, frequency of bleeding was not different between patients with or without aPTT increase, and no association was found with aPTT level at baseline or at the EoT. Thus, it is possible that clinical impact of aPTT increase observed during cefazolin treatment is less significant than INR increase observed during cephalosporin treatment which, conversely, is associated with an increased risk of bleeding [13, 34].

Several conditions can lead to haemostatic abnormalities. We can assume that an acquired deficit of coagulation occurs, especially in the intrinsic pathway which is normally explored by aPTT. Haemophilia A, a disease characterised by a factor VIII deficit, is classically associated with immunological diseases, cancers and other malignant blood diseases; however, acquired haemophilic syndrome related to bacterial sepsis or viral infections was reported in literature, as well as to the use of certain antibiotics, such as penicillins and chloramphenicol, especially when antibiotics were associated to factor VIII inhibitors [35, 36]. Deficit of factor X is typically associated to amyloidosis but was also observed during treatments with certain drugs, such as valproic acid, acrinidin derivatives and antimycotics [37, 38]. In our opinion, further studies should be conducted to verify and explain an aPTT increase, exploring more deeply the involved mechanisms, for example by measuring coagulation factors of the intrinsic pathway, such as factors V, VIII, IX and X. Also, further studies should verify whether or not the aPTT increase under cefazolin treatment is transient, like aPTT increase during oritavancin treatment [39].

Considering the study design (cohort study), some confounding factors could have affected our results because our study had several limitations: (i) the small study sample limited statistical analysis; (ii) many patients included in the study had received anticoagulant drugs, and it is not possible to exclude an interference on aPTT dosage; and (iii) there was no control group to assess the absolute risk of coagulation abnormalities and bleeding.

This study showed that treatment with cefazolin is associated with increase of aPTT of which clinical relevance is probably negligible in case of administration of cefazolin in patients without other risk factors for severe bleeding. However, a careful evaluation of the risk of haemorrhage before the prescription of cefazolin should be envisaged in each patient to avoid the introduction of a molecule which could contribute to increase the overall risk of bleeding in patients already at risk of haemorrhage. This conduct seems particularly reasonable in case of long duration therapies (e.g. endocarditis) in aged patients and those affected by chronic kidney disease. Moreover, a cautious conduct is advisable because the risk of severe bleeding during treatment with cefazolin has not been well defined, and possibly, it has been underestimated until now.

This study showed that bleeding during treatment with cefazolin is probably more frequent than ever reported before, even though the absolute risk of haemorrhage still needs to be assessed. Furthermore, an increase of aPTT was observed and this result needs to be verified in further studies which should also explore possible physio-pathological pathways behind the modification of haemostatic parameters during treatment with cefazolin.

Compliance with ethical standard

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

Informed consent Because this study did not require neither further laboratory analysis nor different clinical acts than daily clinical routine, a written consent form was not proposed to any eligible patients.

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