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Serious central nervous system side effects of cephalosporins: A national analysis of serious reports registered in the French Pharmacovigilance Database

C. Lacroix[a], F. Kheloufi[a], F. Montastruc[b,c], Y. Bennis[d], V. Pizzoglio[e], J. Micallef[a,*]

[a] Centre Régional de Pharmacovigilance, Service de Pharmacologie Clinique et Pharmacovigilance, APHM, INSERM, Inst Neurosci Syst, Aix Marseille Univ, Marseille, France
[b] Centre Midi-Pyrénées de Pharmacovigilance, Pharmacoépidémiologie et d'Informations sur le Médicament, Centre Hospitalier Universitaire, Faculté de Médecine, Service de Pharmacologie Médicale et Clinique, Toulouse, France
[c] Unité clinique de Pharmacologie psychiatrique, Faculté de Médecine, Centre Hospitalier Universitaire, Toulouse, France
[d] Centre Régional de Pharmacovigilance, Centre Hospitalier Universitaire Amiens-Picardie, Amiens, France
[e] Centre Régional de Pharmacovigilance, Hospices Civils de Lyon, Lyon, France

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ABSTRACT

Introduction: Among antibiotics, Central Nervous System (CNS) adverse drug reactions (ADRs) are often under-suspected and overlooked. Cephalosporins are an important cause of drug-induced CNS ADRs but the characteristics of such ADR have not been fully explored. We aimed to characterize the profile of cephalosporins serious CNS ADRs.

Method: We performed an analysis of serious reports recorded in the French Pharmacovigilance database from 1987 to 2017.

Results: A total of 511 serious ADRs reports was analyzed. Patients had a mean age of 67.1 years and were mainly men (52.5%), with a mean creatinine clearance of 32.9 ml/min. The most involved molecules were cefepime (33.1%), ceftriaxone (29.7%), ceftazidime (19.6%), cefotaxime (9%) and cefazoline (2.9%), mostly administered intravenously (87.3%). A CNS history was observed in 25% of the reports ($n = 128$). Patients exhibited encephalopathy (30.3%), confusional state (19.4%), convulsion (15.1%), myoclonia (9.4%), status epilepticus (9.2%), coma (6.3%) and hallucination (4.3%). The mean time of onset was 7.7 days and the mean duration was 6 days. Cephalosporin plasma levels were recorded for 153 patients (29.9%) and 107 were above the standards including 62 (57.9%) related to renal impairment. Electroencephalograms were performed in 38.2% ($n = 195$) of the patients and 81% ($n = 158$) were abnormal.

Conclusion: This study characterizes an off-target CNS ADRs of several cephalosporins. Ceftriaxone represented a large part of our reports after cefepime and it would be relevant to warn healthcare professionals. Investigations (EEG, though plasma levels and renal function) can be precious tools for clinicians to make a prompt diagnosis and improve patients' outcomes.

1. Introduction

Antibiotics are widely prescribed both in the community and in the hospital sector. Antibiotics can be associated with many different adverse drug reactions (ADRs) well known to clinicians such as gastrointestinal discomfort. Nevertheless, Central Nervous System (CNS) serious ADRs which include neurological and psychiatric ADRs are an under-suspected and overlooked issue within β-lactam antibiotics [1–3]. In this antibiotic class, cephalosporins appear to be an important cause of CNS ADRs. In the literature, many case reports have been published concerning CNS ADRs with cephalosporins. Cefepime is the most reported antibiotic causing encephalopathy and non-convulsive status epilepticus [4–7]. ADRs reported with cefepime were mostly serious, i.e. they can lead to prolonged hospitalization or complications during hospitalization leading to life-threatening conditions or fatal outcomes [2,8]. As a result, CNS ADRs related to cefepime have been recently in the scope of medicine regulatory authorities. After several serious cases of non-convulsive status epilepticus reported to the Food

* Corresponding author: Centre Régional de Pharmacovigilance, Hôpital Sainte-Marguerite, 270, Boulevard de Sainte-Marguerite, 13274 Marseille CEDEX 09, France.
E-mail address: joelle.micallef@ap-hm.fr (J. Micallef).

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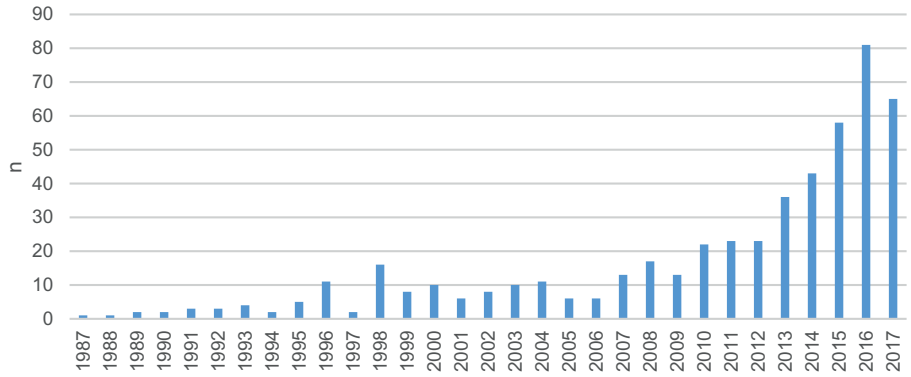

Fig. 1. Number of serious reports of CNS ADRs related to cephalosporins registered by year in the French Pharmacovigilance Database over the last 30 years.

and Drug Administration (FDA), a safety communication was performed and a warning was added to the label of cefepime [9]. However, less is known concerning the potential of CNS ADRs with other cephalosporins, and characteristics of CNS ADRs occurring in the overall class of β-lactams is scarce. Indeed, only a few case reports have described CNS ADRs related to medicines other than cefepime [10–13]. Most of the other published data evaluated one or two cephalosporins and only a few include pharmacokinetic data such as plasma levels that could be an important parameter in clinical practice in order to react as soon as possible and manage the ADR. In addition, ADRs are not always correctly identified or documented in these studies. Many case reports demonstrate that electroencephalograms (EEG) show epileptic activity and typical waves with cephalosporin-induced encephalopathy [14–17]. Also, little is known about psychiatric adverse effects that can misidentified in clinical practice. No study based on a large database (as pharmacovigilance one) have been performed to evaluate, at a population level, the characteristics of cephalosporins and CNS ADRs. Because early diagnosis is important to avoid serious consequences, we aimed to characterize and focus on these serious ADRs using data from the French Pharmacovigilance Database in order to provide accurate elements for clinicians and improve appropriate management.

2. Methods

The French pharmacovigilance network consists in 31 Regional Pharmacovigilance Centres that collect and analyze spontaneous reports of ADRs. Reporting of serious and/or unexpected ADRs has been compulsory for physicians, dentists and midwives since 1984 and for pharmacists since 1995. Also, nurses (since 1995) and patients, families and associations (since 2011) can contribute on a voluntary basis. ADR reports received at a Regional Pharmacovigilance Centre are thoroughly assessed for causality, expectedness and seriousness of the ADR. To make sure the information in the French Pharmacovigilance Database is reliable and medically validated, each spontaneous report submitted to a given Regional Pharmacovigilance Centre undergoes a pharmacological, clinical and biological assessment process by a trained assessor of the Regional Pharmacovigilance Centre. It is then recorded in the French Pharmacovigilance Database and transmitted to the national agency of medicines via the French Pharmacovigilance Database, a common computerized database using Medical Dictionary for Regulatory Activities (MedDRA) terminology for ADRs coding [18]. Each report is coded by the same trained assessor using MedDRA dictionary in order to copy exactly the ADRs reported without extrapolation. Numerous pharmaco epidemiological studies have shown the validity and high quality of the French Pharmacovigilance Database including to assess CNS-drug induced effects [19–21].

All serious reports of a CNS (neurological and/or psychiatric) ADR involving a cephalosporin (Anatomical Therapeutic Chemical: J01DA, J01DB, J01 DC, J01DD, J01DE, J01DF, J01DI) and registered in the French Pharmacovigilance Database until December 31st 2017 were extracted. According to the recommendations of the International Committee on Harmonization, serious ADRs were defined as a fatal or life-threatening ADR, an ADR requiring hospitalization or prolongation of ongoing hospitalization, resulting in persistent or significant disability, other medically important conditions or congenital abnormality or birth defect [22].

ADRs were analyzed according to System Organ Class (SOC) and Preferred terms levels of MedDRA classification. SOCs “Neurologic affection” and/or “Psychiatric affection” were selected for the analysis. General information concerning patients' characteristics were collected. When available, history of CNS disease was extracted. For each report, information about co-prescriptions (other antibiotics or drugs known to be involved in CNS ADRs), electroencephalograms and measurements of plasma levels of cephalosporins performed during the CNS ADRs were collected when available and were compared to standards [23–26]. The daily dose reported was the dose of cephalosporins at the time of the CNS onset. The creatinine clearance was estimated by the Cockcroft-Gault formula and renal impairment defined when creatinine clearance was under 60 ml/min.

3. Results

3.1. General characteristics of serious case reports

A total of 511 serious reports were identified in the French Pharmacovigilance Database representing 755 CNS ADRs analyzed in our study (Fig. 1). Reports involving men accounted for 52.5%. Mean age was 67.1 (SD: 20.6) and 62.4% of the reports concerned patients over 65 (mean age: 79.1). The ADR resulted in a hospitalization or prolonged hospitalization in 71.2% (n = 364) of the cases while fatal and life-threatening ADRs were reported in respectively 6.1% (n = 31) and 11.9% (n = 61) of the cases. A persistent or significant disability/incapacity was observed in 5 reports.

Creatinine clearance was registered for 195 reports with a mean of 32.9 ml/min (SD: 25.1). Among these 195 creatinine clearances, we observed 87.7% of renal impairment. A documented history of CNS diseases was found in 128 reports (25%) and 32 of them had several CNS diseases. The most frequent ones were depression (23.1%), alcoholism (20.3%), epilepsy (16.4%), cognitive disorders (10.2%), and anxious-depressive syndrome (8.6%) (Table 1).

3.2. Characteristics of cephalosporins involved in the ADR

We identified 20 different cephalosporins involved in CNS ADRs, mainly cefepime (n = 169, 33.1%), ceftriaxone (n = 152, 29.7%), ceftazidime (n = 100, 19.6%), cefotaxime (n = 46, 9%) and cefazoline (n = 15, 2.9%) (Fig. 2). An association of two or more cephalosporins was found in 8 reports. Cephalosporins were administered

Table 1
Demographic and clinical characteristics of patients.

Patients' characteristics
Male, n = 268 (52.5%)
Female, n = 242 (47.5%)
Mean age (years), 67.1 (SD:20.6)
Age > 65 years old, n = 319 (62.4%)
Mean weight (kg), 69.8 (SD:22.3)
CNS history, n = 128 (25%)

Kg kilograms, CNS central nervous system, SD Standard Deviation.

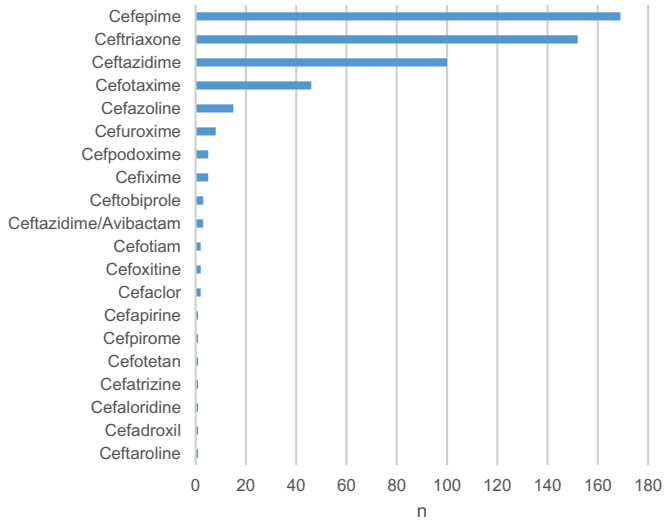

Fig. 2. Number of serious cases reports of CNS ADRs registered per cephalosporin in the French Pharmacovigilance Database.
ADRs Adverse Drug Reactions, CNS Central Nervous System.

intravenously in 399 reports (87.3%), orally in 31 reports (6.8%), through intramuscular injections in 19 reports (4.2%), sub-cutaneous injections in 14 reports (3.1%) and intraperitoneal injection in 1 report. Table 2 shows the mean daily dose of the five most involved molecules, the comparison with the maximum dose in the summary of Products characteristics (SmPC) and the number of patients with renal impairment.

3.3. Co-prescriptions

For 254 patients (49.7%), we found a concomitant exposition to other antibiotics (38.2% of quinolones and 18.9% of β-lactams). For 150 patients (29.4%), we found a concomitant exposition to other drugs that can have an effect on the CNS.

3.4. Type of ADRs reported

A total of 967 ADRs was reported including 755 psychiatric and/or neurologic ADRs (78.1%), representing 1.89 ADR/report and 1.48 CNS ADR/report. A neurologic ADR was found in 439 reports and a psychiatric was found in 141 reports. A concomitant psychiatric and neurologic ADR was found in 70 reports. As shown in Fig. 3, the most frequently reported serious ADR were neurologic ADR including mainly encephalopathy (34.1%), convulsion (27%), myoclonia (9.4%), and psychiatric ADR including mainly confusional state (19.4%) and hallucination (6.7%).

The mean time of onset of CNS ADRs was 7.7 days (SD: 11.3) after starting a cephalosporin. Mean duration of the ADR was 6 days (SD: 7.4).

3.5. Explorations

3.5.1. Plasma levels

Cephalosporin plasma levels were available for 153 patients (29.9%): 86 cefepime (56.2%) including 56 above the standards (65.1%) (40–60 mg/l), 41 ceftazidime (26.8%) including 31 above the standards (75.6%) (40–80 mg/l), 18 ceftriaxone (11.8%) including 16 above the standards (88.9%) (10–30 mg/l), 4 cefotaxime (2.6%) including 1 above the standards (25%) (20–60 mg/l) and 4 cefazoline (2.6%) including 3 above the standards (75%) (40–80 mg/l). Among reports with plasma levels above the standards, 57.9% where related to a renal impairment (Table 3).

3.5.2. Electroencephalogram

Results of an electroencephalogram were available in 195 reports (38.2%) and were abnormal for 81%. In 107 reports, encephalopathy was suspected through the electroencephalogram. Electroencephalograms specific findings are shown in Table 4.

4. Discussion

To our knowledge, this is the first pharmacovigilance study that investigated cephalosporins and CNS ADRs at a population level through a large pharmacovigilance database. Indeed, more than 500 serious reports have been recorded in the French Pharmacovigilance Database for thirty years which represents a total of 755 CNS ADRs occurring after a median time to onset of 8 days. A substantial part of these ADRs lead to serious complications, with life-threatening conditions and fatal outcome representing 18% in our study. Our study may confirm that the elderly are more prone to CNS ADRs as the mean age of patients in our study was 67.7 [3,27]. Signs of encephalopathy (confusional state, hallucination, and coma) and/or signs of convulsive state (convulsion, myoclonia, status epilepticus) were the main ADRs reported. Psychiatric ADRs were also reported in our study though they are not well described in the literature and often included in the neurologic ADRs pattern.

Our results show that various cephalosporins other than cefepime can induce CNS ADRs in real practice despite scarce data. Among uncommon medicines inducing CNS ADRs, cefuroxime was also a cephalosporin found in our study showing that CNS ADRs can also occur during oral therapy and is not limited to parenteral cephalosporin.

Table 2
Mean daily doses of the main cephalosporins involved in CNS ADRs, number of patients with doses above to the maximum dose of Summary of Product Characteristics and number of patients suffering from renal impairment.

Cephalosporins	Mean daily dose, g/day (range)	n (%)	Number of patients with Dose > Maximal dose of SmPC	Number of patients with Renal impairment and Dose > Maximal dose of SmPC
Cefepime	4.6 (0.3–30)	131 (77.5%)	1 (0.8%)	1 (100%)
Ceftriaxone	1.7 (0.5–6)	98 (64.5%)	3 (3.1%)	–
Ceftazidime	4.7 (0.05–16)	71 (71%)	7 (9.9%)	5 (71.4%)
Cefotaxime	4.2 (0.27–12)	37 (80.4%)	0	–
Cefazoline	4.1 (0.8–8)	9 (60%)	3 (33.3%)	–

ADRs Adverse Drug Reactions, CNS Central Nervous System, SmPC Summary of Products Characteristics.

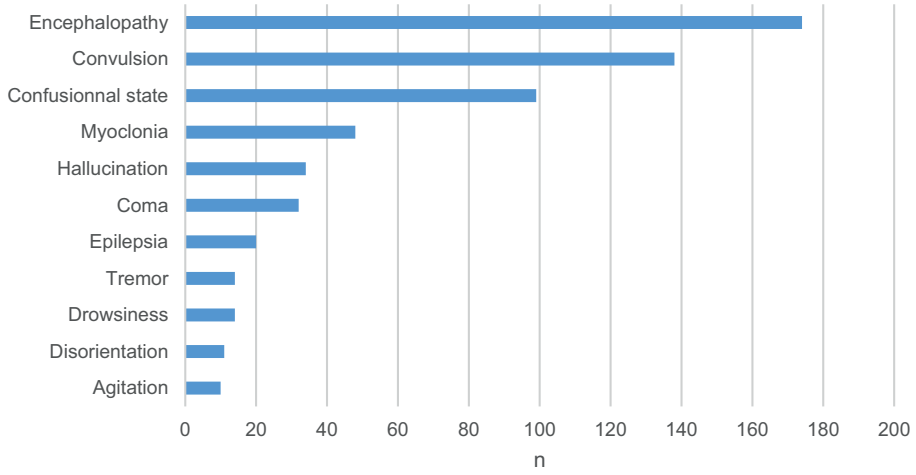

Fig. 3. Main results of ADRs registered from reports concerning cephalosporins and CNS ADRs in the French Pharmacovigilance Database.
ADRs Adverse Drug Reactions, CNS Central Nervous System.

However, cefepime was the most involved drug with a total of 169 reports which mirrors the literature with about 150 case reports published [4,5,14–16,28–33]. Ceftriaxone with 152 reports and ceftazidime with 100 reports were also an important part of CNS ADRs inducing drugs in our study as well as other cephalosporins such as cefotaxime with 46 reports or cefazoline with 15 reports to a lesser extent [12]. Ceftazidime is known to provide CNS ADRs with about 30 case reports published [6,13,34–36] but ceftriaxone is under-recognized throughout literature compared to our results, with only a dozen or so case reports published [10,37–40]. Ceftriaxone may be involved in CNS mechanisms in animal studies mediating the glutamate transporter GLT-1. In fact, by increasing GLT-1 expression, ceftriaxone may inhibit the development of opioid-induced hyperalgesia in mice [41]. Moreover via the upregulation of GLT-1 expression, ceftriaxone seems to be involved in attenuating drug-seeking behavior for example with alcohol or cocaine [42–44]. Pathophysiology of CNS ADRs is not well known though an increase in glutamatergic excitation seems to be involved in the pathophysiology of beta-lactams-induced neurological ADRs [45], as well as a decrease in γ-aminobutyric acid (GABA, a major inhibitory neurotransmitter in the CNS) via the competitive concentration-dependent inhibition of the GABA-A receptor complex. A release of endotoxins and cytokines, an increase in excitatory ability related to *N*-methyl-D-aspartate receptors and α-amino-3-hydroxy-5-methyl-isoxazolepropionate receptors are also among other hypothesis [34]. An important point is that the SmPCs of ceftriaxone doesn't recommend any dose adaptation to the renal function. One of the feature common to all cephalosporins was that most of patients received doses below the maximum dose labelled in the SmPC showing that CNS ADRs can occur whatever the dose, and that the use of cephalosporin doses over recommended doses is not a necessary condition to the onset of CNS ADRs. However, the use of higher doses and a probable high exposure appears to be a risk factor as a substantial part of patients had a renal impairment and 57.9% of patients with doses above the maximum dose indicated in the SmPC had renal impairment. This is in line with previous medicine regulatory authorities' investigations such as the one from the FDA's adverse event reporting system database that recorded 59 cases of non-convulsive status epilepticus mainly in older patients with renal impairment in between 1996 and 2012. This study lead to a safety communication reminding clinicians to adjust the dose of cefepime in patients with renal impairment [9]. In France, a warning concerning cefepime and the risk of neurological severe ADR when daily doses are not respected for renal insufficient patient was published in 2014 [46] and again in 2018 [47]. Nevertheless, the French medicine agency warned healthcare professionals about the risk of complications during hospitalization including life-threatening conditions and fatal outcomes even in patients with a normal renal function. The elderly were also targeted in this communication because they represent a vulnerable population for who the risk of CNS ADRs is higher. Like patients in intensive care, they can display a concomitant medical condition or multiple concomitant therapies.

Previous CNS diseases also appear to be an individual risk factor [8,34]. In our study, a substantial number of reports concerned patients with a concomitant medical condition including 25% of the patients experimented a CNS history in our population including more than a half over 65 years. According to several studies, antibiotics [3,27] such

Table 4
Electroencephalograms activity finding: Number of patients for each electroencephalographic specificity.

Electroencephalographic finding	n (%)
Epileptic activity	55 (28.2%)
Slow waves discharges	51 (26.2%)
Triphasic waves	15 (7.7%)
Delta activity	8 (4.1%)
Biphasic waves	6 (3.1%)
Theta activity	3 (1.5%)

Table 3
Level of exposure to cephalosporins: Number of patients with plasma levels measurement, median plasma levels, number of plasma levels above the standards and number of patients with plasma levels above the standards related to a renal impairment.

Molecule	Plasma levels standards (mg/l)	Number of patients with plasma levels (n, %)	Median plasma levels (mg/l)	Number of plasma levels above the standards (n, %)	Number of patients with plasma levels above the standards and a renal impairment (n, %)
Cefepime	40–60	86 (52.7%)	96.5	56 (65.1%)	35 (62.5%)
Ceftazidime	40–80	41 (41%)	104	31 (75.6%)	14 (45.2%)
Ceftriaxone	10–30	18 (11.8%)	81.4	16 (88.9%)	8 (50%)
Cefotaxime	20–60	4 (8.7%)	11.4	1 (25%)	1 (100%)
Cefazoline	40–80	4 (26.7%)	210.5	3 (75%)	2 (66.7%)

as other β-lactams [34] or quinolones [48] are known to provide the same types of side effects. Benzodiazepines, anti-psychotics, anti-depressants and anxiolytics, anti-epileptics, opioid antalgics are known to induce CNS ADRs and were often found in the reports [1]. Exposure to such medicine could have led to a difficult assessment of causality of cephalosporin but it is unlikely that these they represent cofounding factors. Each case reported to the pharmacovigilance centre undergoes a pharmacological, clinical and biological assessment by experimented and trained clinicians which makes causality very likely. This highlights the fact that clinicians should think of an iatrogenic etiology when they deal with a neurologic or psychiatric condition in a patient treated with multiple medications including cephalosporins. When available, they should rely on the expertise of a pharmacovigilance centre who can help clinicians in causality determination or guide them in complementary explorations.

Indeed, additional explorations such as EEG appear to be important as they can guide to a prompt and accurate diagnosis of ADR. Previous studies highlighted specific signs on EEG such as triphasic waves, delta, theta activity and epileptic activity that can help to identify cephalosporin-induced neurological ADR [14–17]. Therapeutic drug monitoring is also among additional paraclinical explorations that can quickly give an idea of cephalosporin exposure and can be a substantial help for clinicians. However, data from case reports or from retrospective studies doesn't always include plasma levels explorations, and the relationship between the level of exposure to cephalosporin and the onset of CNS ADRs is not fully established. A retrospective cohort study managed by Huwyler and al. showed that neurotoxicity related to cefepime occurred at plasma levels > 35 mg/l which is under the standards [49]. In our study, CNS disorders occurred at a plasma levels within the therapeutic range while 69.9% of patients with available plasma levels had levels over the therapeutic range. As a result, prospective studies are needed to properly identify and quantify the determinants of the onset of CNS disorders related to cephalosporins such as renal function, plasma levels of cephalosporins and EEG. Even though cefepime has been in the spotlight of international medical regulatory authorities, it would also be relevant to deeply investigate other cephalosporins as there is a gap in knowledge concerning molecules other than cefepime. This would help to better understand the off-target effects of the medicines that are not well known by healthcare professionals as well as define to what extent the safety message applies to other cephalosporins.

5. Conclusion

This study shows that the off-target CNS ADRs of various cephalosporins can be life threatening and lead to a fatal outcome. Many factors may increase the susceptibility of patients to develop CNS ADRs such as age > 65 years old, renal impairment, previous CNS diseases, other medications. Investigations such as EEG, cephalosporin plasma levels and renal function monitoring can be precious tools for clinicians to make a prompt diagnosis and improve patients' outcomes or prevent the onset of CNS ADRs. Cefepime appears to be the most reported substance but other cephalosporins such as ceftriaxone can significantly cause CNS ADRs which justify the importance for clinicians to report CNS ADRs related to all cephalosporins. As ceftriaxone is widely used both in the community and in the hospital sector, it would be relevant to warn healthcare professionals about the potential risk of CNS ADRs which seems to be under-estimated and under-suspected.

Conflicts of interest

Clémence Lacroix, Farid Kheloufi, François Montastruc, Youssef Bennis, Véronique Pizzoglio and Joëlle Micallef declare that they have no conflict of interest.

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